Pulmonary Hypertension Associated with Respiratory Disease

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Todd M. Kolb and Paul M. Hassoun

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Abstract

Pulmonary hypertension is a common complication of many chronic respiratory diseases. The mechanisms contributing to the development of pulmonary hypertension in this context are multiple and go beyond chronic hypoxic vasoconstriction. Outcomes are universally worsened when pulmonary hypertension complicates chronic respiratory disease. Treatment strategies target the underlying disease, as pulmonary vasodilator therapy has proven largely ineffective in trials to date. This chapter summarizes current understanding of the epidemiology, pathophysiology, and treatment of pulmonary hypertension as it relates to a spectrum of chronic respiratory diseases.

Abbreviations

6MWD	6-min walking distance
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
CPFE	Combined pulmonary fibrosis and emphysema
CTD	Connective tissue disease
D_{LCO}	Diffusing capacity of the lung for carbon monoxide
ERA	Endothelin receptor antagonist
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
HP	Hypersensitivity pneumonitis

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IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
LAM	Lymphangioleiomyomatosis
LTOT	Long-term oxygen therapy
LV	Left ventricle
LVRS	Lung volume reduction surgery
NF	Neurofibromatosis
NO	Nitric oxide
NSIP	Nonspecific interstitial pneumonia
NYHA	New York Heart Association
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PaO_2	Arterial partial pressure of oxygen
PASP	Pulmonary artery systolic pressure
PDE5	Phosphodiesterase-5
PH	Pulmonary hypertension
PLCH	Pulmonary Langerhans cell histiocytosis
PM/DM	Polymyositis/dermatomyositis
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
RV	Right ventricle
RVSP	Right ventricular systolic pressure
SLE	Systemic lupus erythematosus
SS	Sjogren's syndrome
SSc	Systemic sclerosis
TAPSE	Tricuspid annular plane systolic excursion
TGF-β RII	Transforming growth factor beta receptor II
TGF-β	Transforming growth factor beta
TSC	Tuberous sclerosis
UIP	Usual interstitial pneumonia
V/Q	Ventilation/perfusion
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

Introduction

Elevated pressure in the pulmonary circulation can complicate a diverse group of respiratory diseases. When measured mean pulmonary arterial (PA) pressure reaches or exceeds 25 mmHg, the respiratory disease has been complicated by pulmonary hypertension (PH). In this context, the term PH does not refer to a specific pathological diagnosis, but instead describes the sequelae of a spectrum of pulmonary (and cardiac) pathologies. As might be expected from a diverse group of diseases, varied mechanisms contribute to PH, including loss of vascular surface area, increased pressure in the pulmonary venous circulation, mechanical obstruction of the pulmonary vessels, or hypoxia-mediated pulmonary vasoconstriction. The latter concept is covered extensively in a separate chapter (▶ Chap. 162, "Hypoxic Pulmonary Hypertension") and will not be addressed in detail here. However, it is important to remember that chronic hypoxia is a nearly universal complication of the described disorders, and its effects are likely to exacerbate the mechanisms contributing to pulmonary pressure elevation described below. The present chapter will attempt to address a broad spectrum of respiratory disorders causing PH and will use prototypical examples to describe current understanding of PH in these disorders. Diagnosis, pathogenesis, and management of PH will be discussed.

Importance of PH in Respiratory Disease

Chronic respiratory disease is a common cause of PH, present in 25.9 % of all US patients who died from PH between 2000 and 2002 (Hyduk et al. 2005). Alternatively, the prevalence of PH in respiratory disease is quite variable, and precise estimates have been constrained by limited population-based hemodynamic data and variability in the parameters and methods used to define PH. In general, PH appears to be more common in advanced respiratory disease, regardless of the underlying diagnosis. For example, PH prevalence increases with disease severity in idiopathic pulmonary fibrosis (IPF), from 8.1 % at initial evaluation (Hamada et al. 2007) to 30–40 % at the time of transplant evaluation or referral to tertiary care (Lettieri et al. 2006; Nathan et al. 2007). Moreover, early identification of PH can be challenging in patients with chronic respiratory disease. The cardinal symptoms of PH, namely, increased dyspnea and reduced exercise capacity, are generally associated with the

underlying respiratory disorder. Physical examination findings may not be present until severe right ventricular (RV) pressure overload or failure has developed, and the sensitivity of early noninvasive screening modalities may be limited by the underlying pulmonary disease. Transthoracic echocardiography is perhaps the best initial noninvasive study to screen for PH in chronic lung disease, and provides useful two-dimensional estimates of RV chamber size, wall thickness, systolic pressure (RVSP), and left heart function during initial assessment. However, image analysis may be limited by hyperinflation or parenchymal lung abnormalities. Notably, a well-defined tricuspid regurgitant jet (necessary for RVSP estimation) was present in only 20 % of chronic lung disease patients in one recent study (Burgess and Bright-Thomas 2002). Not surprisingly, the correlation between estimated RVSP and pulmonary pressures measured by right heart catheterization is poor in advanced lung disease (Arcasoy et al. 2003). In a study of patients with advanced COPD referred for lung volume reduction surgery, echocardiographic RVSP estimates detected PH with a sensitivity of only 60 % and specificity of 74 % (Fisher et al. 2007). Tricuspid annular plane systolic excursion (TAPSE) appears to be an accurate measure of RV function in PH patients, including those with PH secondary to chronic respiratory disease (Forfia et al. 2006). Newer techniques, including three-dimensional echocardiography, tissue Doppler ultrasonography, and ultrasound strain imaging, may increase our abilities to noninvasively screen for PH in patients with chronic lung disease and have been recently reviewed (Mertens and Friedberg 2010).

Pulmonary function testing may be useful in predicting PH when respiratory symptoms worsen. Isolated reductions in D_{LCO} have been associated with PH in IPF, sarcoidosis, and systemic sclerosis (SSc) (Steen et al. 1992; Nadrous et al. 2005; Nunes et al. 2006). However, a reduced D_{LCO} is not predictive of elevated PA pressure in COPD patients (Gartman et al. 2012). Objective measures of diminished exercise capacity may reveal a diagnosis of PH in chronic lung disease. There is a modest negative correlation between six-minute walking distance (6MWD) and estimated systolic pulmonary arterial (PA) pressure in COPD patients (Gartman et al. 2012), and significant reductions in 6MWD have been reported in IPF patients with moderate to severe PH (Leuchte et al. 2004). Cardiopulmonary exercise testing (CPET) may be more useful in the detection of increased PA pressure in patients with chronic respiratory disease (Arena et al. 2011). Increased dead space ventilation, reduced ventilatory efficiency, and reductions in end-tidal CO_2 measurements with exercise have been associated with PH in COPD and ILD (Holverda et al. 2008; Vonbank et al. 2008; Glaser et al. 2009).

Regardless of the underlying respiratory diagnosis, the development of PH is universally associated with worsened outcomes. In COPD, even modest increases in mean PA pressure (greater than 20 mmHg) have been correlated with reduced survival (Oswald-Mammosser et al. 1995; Weitzenblum et al. 1981). Patients with advanced IPF complicated by PH had a 1-year mortality of 28 %, while those without PH had 5.5 % 1-year mortality (Lettieri et al. 2006). In sarcoidosis, PH is an independent predictor of mortality (Shorr et al. 2003), and the hazard ratio for death in patients with PH was estimated to be 10.4 when compared to patients without PH (Baughman et al. 2010). In patients with systemic sclerosis (SSc)-associated interstitial lung disease complicated by PH, there was a fivefold increased risk of death when compared to SSc patients with pulmonary arterial hypertension (PAH), despite the notoriously poor survival in this population (Mathai et al. 2009).

Despite its apparently high prevalence and universal association with increased morbidity and mortality, current guidelines generally recommend against routine administration of PH-specific (pulmonary vasodilator) therapy for PH associated with chronic respiratory diseases. There is, in general, a lack of evidence demonstrating clinical benefit, and in some cases the use of pulmonary vasodilators has led to worsened ventilation/perfusion (V/Q) matching and worsening respiratory symptoms. However, not all PH associated with chronic respiratory diseases should be approached from the same perspective,

and in some cases the PH appears to be "out of proportion" to the severity of the underlying lung disease. Conceptually, this may be due to direct involvement of the underlying disease on the pulmonary vasculature or to exaggerated pulmonary vascular remodeling and/or vasoconstriction in response to the underlying parenchymal disease. The general consensus among experts in the field is that patients with "out of proportion" PH may be considered for a carefully monitored trial of pulmonary vasodilator therapy.

Pathophysiology of PH Development in Respiratory Disease

The pathophysiology of PH in chronic respiratory disease is complex and multifactorial. Multiple mechanisms contribute to impede the generally low resistance to flow through the pulmonary circulation. Through varied mechanisms, chronic respiratory diseases have direct and indirect pathogenic effects on the pulmonary circulation (Fig. 1). These complex interactions can be conceptually simplified into alterations that result in a) increased pulmonary vascular resistance (PVR) and b) dysfunctional heart-lung interactions.

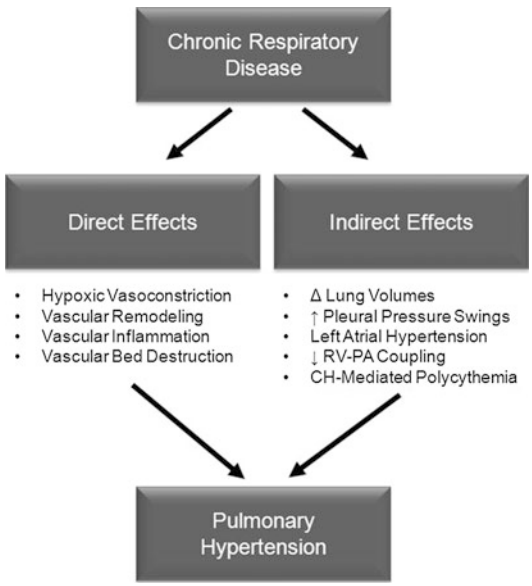

Fig. 1 Mechanisms of pulmonary hypertension development in chronic respiratory disease. *RV* right ventricle, *PA* pulmonary artery, *CH* chronic hypoxia

Direct Effects on the Pulmonary Circulation

Increased PVR is the primary precipitant of PH in chronic respiratory disease. As one might anticipate, the mechanisms contributing to increase PVR are varied, and specific mechanisms may contribute differentially in each disorder. In general, narrowing of the pulmonary vasculature from hypoxic pulmonary vasoconstriction contributes to increase PVR in most of these disorders. The mechanisms will not be addressed in detail here, though a brief accounting is warranted. Alveolar hypoxia induces rapid vasoconstriction of small, precapillary pulmonary arteries to preserve V/Q matching and minimize arterial oxygen desaturation. The mechanisms of hypoxic pulmonary vasoconstriction have been reviewed (Archer and Michelakis 2002) and involve alterations in potassium and calcium flux in smooth muscle cells, resulting in contraction and increased vascular tone. Pulmonary vasoconstriction can be further exacerbated by hypercapnia and acidemia in COPD (Enson et al.1964) or by increased sympathetic activity driven by intermittent hypoxemia (as in obstructive sleep apnea) (Sajkov and McEvoy 2009). However, mechanisms beyond hypoxic vasoconstriction clearly exist, as correlations between PA pressure and systemic oxygenation have not been robust (Girgis and Mathai 2007). While these observations may reflect individual differences in the capacity for hypoxic pulmonary vasoconstriction, other mechanisms appear to play a significant role.

Most prominently, pulmonary vascular remodeling is a critical determinant of PVR in patients with chronic respiratory disease. This remodeling includes, to varying degrees, all layers of the pulmonary vasculature (intima, media, and adventitia). Pathological remodeling in chronic hypoxia (both human disease and animal models) is characterized by neo-muscularization of arterioles, medial hypertrophy of small muscular arteries, and intimal thickening and fibroelastosis

(Penaloza and Arias-Stella 2007). These pathological changes are the hallmark of PH associated with chronic respiratory diseases, with lesser degrees of intimal and adventitial remodeling observed. However, the remodeling effects associated with chronic hypoxia are insufficient to describe all pulmonary vascular remodeling associated with chronic respiratory disease. Endothelial cell dysfunction, EC apoptosis, and increased proliferation of multiple cell types (endothelial, smooth muscle, and fibroblasts) appear to play prominent roles in the vascular remodeling process (Budhiraja et al. 2004; Farkas and Kolb 2011). In addition, thromboembolic lesions can further impede pulmonary vascular flow and frequently complicate chronic lung diseases like COPD (Tillie-Leblond et al. 2006; Rizkallah et al. 2009), sarcoidosis (Minai et al. 2010), and IPF (Panos et al. 1990).

Inflammation contributes prominently to the pathogenesis of many respiratory diseases, and inflammation of the pulmonary vasculature is another mechanism contributing to the increase PVR in many of these disorders. In PAH, inflammatory cell infiltrates (including macrophages, dendritic cells, and lymphocytes) have been described surrounding characteristic plexiform lesions (Tuder et al. 1994), and alterations in circulating levels of various cytokines, chemokines, and growth factors have been reported (Hassoun et al. 2009). Similar inflammatory processes appear to be relevant in PH associated with chronic respiratory disease. In COPD, inflammatory infiltrates composed primarily of activated T-lymphocytes have been described in the adventitia of muscular pulmonary arteries (Peinado et al. 1999), and increased expression of growth factors (vascular endothelial growth factor, VEGF; transforming growth factor-β, TGF-β) and their receptors (TGF-β RII) been measured in remodeled pulmonary arteries (Santos et al. 2003; Vignola et al. 1997; Beghe et al. 2006). Perivascular fibrosis and vascular inflammation have been described in the pulmonary arteries and veins of patients with chronic sarcoidosis (Diaz-Guzman et al. 2008; Rosen et al. 1977; Takemura et al. 1991). In IPF, elevated TGF-β levels are presumed to contribute to both endothelial cell apoptosis and smooth muscle cell hypertrophy, thereby significantly influencing pulmonary vascular remodeling (Farkas et al. 2011).

Finally, when functional lung parenchyma is lost through tissue destruction (e.g., emphysema) or fibrosis (e.g., IPF), associated vascular beds are also lost, contributing to a reduction in the overall vascular surface area. Although extensive parenchymal destruction necessary for this mechanism to increase PVR independently, it must be remembered that parenchymal and vascular loss occurs in conjunction with hypoxic pulmonary vasoconstriction, vascular remodeling, and vascular inflammation, and these additive mechanisms are all likely to contribute to PH development in chronic respiratory disease.

Indirect Effects on the Pulmonary Circulation

Chronic respiratory disease can also influence the development of PH through indirect (nonvascular) effects on the pulmonary circulation. Associated changes in lung volume (hyperinflation and underinflation) may contribute to increase PVR. Obstructive lung disease, frequently complicated by air trapping and hyperinflation, may promote classical "zone 1" physiology (alveolar pressure exceeds pulmonary capillary pressure, resulting in capillary collapse). Less commonly, widespread atelectasis (e.g., chronic hypoventilation) may result in low lung volumes and de-recruitment of associated pulmonary capillaries (Forfia et al. 2013). Lung hyperinflation may also increase right atrial pressure, leading to reduced venous return and subsequent reductions in RV preload (Forfia et al. 2013). In COPD patients, hyperinflation has been directly correlated with reduced atrial chamber size, global RV dysfunction, and reduced left ventricular (LV) filling (Watz et al. 2010). In addition, highly negative pleural pressures may be necessary to facilitate ventilation in advanced respiratory disease. These highly negative pleural pressures reduce intrathoracic pressure and increase LV wall stress during ejection (Buda et al. 1979), potentially resulting in left atrial hypertension

and increased pulmonary venous pressures. Indeed, many risk factors for left heart dysfunction (diastolic or systolic) are frequently present as comorbidities in patients with chronic respiratory disease, especially those associated with cigarette smoking. Similarly, intrinsic RV dysfunction (though rare in most chronic respiratory diseases) may further exacerbate the clinical consequences of increased PVR through worsened coupling of RV contractility with the pulmonary circulation. Increased blood viscosity due to chronic hypoxia-induced polycythemia may also contribute to increased PVR in chronic respiratory disease.

PH in Specific Respiratory Diseases

As outlined above, PH may arise from diverse mechanisms in chronic respiratory disease, though the consequences of PH development are universally unfavorable. The following sections will describe current understanding of PH in the context of specific respiratory disorders, including pathogenesis, outcomes, and treatment. Although it is not possible to cover all respiratory diseases that have been reported to be associated with PH, the paragraphs below highlight diagnoses that are a) commonly encountered and b) more frequently associated with PH in the medical literature. Since most clinical trials of PH-specific therapies have focused on patients without underlying respiratory diseases, much of the available evidence is limited to small trials and case series.

Interstitial Lung Diseases

The term ILD is used to describe a diverse group of disorders characterized pathologically by an accumulation of cells or fibrotic tissue in the interstitial spaces of the lung parenchyma. Pulmonary inflammation and/or fibrosis represents the final common pathway for lung damage (Danoff et al. 2007). Greater than 150 disorders have been associated with the development of ILD, and PH has been described in many of these. A conceptual framework for consideration of the varied spectrum of ILD has been proposed (Fig. 2) (Danoff et al. 2007). Using this framework, the present chapter will focus on idiopathic, connective tissue disease-associated granulomatous and heritable ILDs, as most investigation into associated PH has been focused on these diagnoses.

Idiopathic ILD

This group of disorders has been described as the idiopathic interstitial pneumonias (IIP) in major consensus guidelines (ATS/ERS 2002). Idiopathic pulmonary fibrosis (IPF) is the prototypical diagnosis in this class and is characterized radiographically by patchy reticular opacities, generally with peripheral and basilar distribution, and often association with volume loss, traction bronchiectasis, and honeycombing (Fig. 3). Histologically, IPF is defined by a pattern described as usual interstitial pneumonia (UIP), characterized by patchy areas of architectural destruction, fibrosis (often with honeycombing), and scattered fibroblastic foci (ATS/ERS 2002). Similarly, the pulmonary vasculature displays heterogeneous abnormalities in IPF. Vessel density is reduced in areas of fibroblastic foci and honeycombing (Colombat et al. 2007), while increased vascularity has been described in non-fibrotic areas (Ebina et al. 2004; Cosgrove et al. 2004; Simler et al. 2004). Abnormal vascular morphology has been described in areas where capillary surface area is relatively preserved (Colombat et al. 2007). Expression of angiogenic and angiostatic mediators appears to be altered in IPF lungs (Ebina et al. 2004; Cosgrove et al. 2004), and similar molecular changes have been directly linked to increased endothelial cell apoptosis and PH development in animal models (Farkas et al. 2009). In addition, increased expression of a number of inflammatory mediators (interleukin-6, TGF-β, endothelin-1) has been demonstrated in the pulmonary vasculature of IPF patients with PH (Rubens et al. 2001; Yamakami et al. 1997; Lesur et al. 1994).

Pulmonary hypertension prevalence increases with IPF severity, from 8.1 % at initial evaluation (Hamada et al. 2007) to 30–40 % at the time of transplant evaluation or referral to tertiary care (Lettieri et al. 2006; Nathan et al. 2007). In one study, 86 % of IPF patients had PH by RHC at the

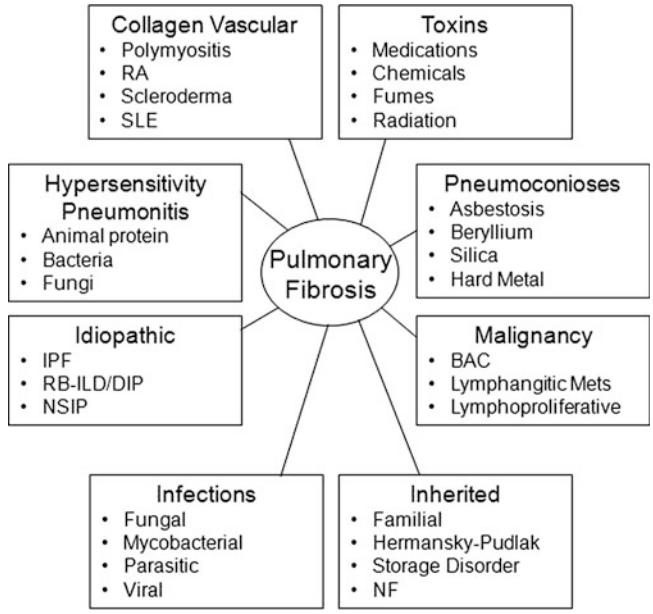

Fig. 2 Conceptual framework for considering the varied causes of pulmonary fibrosis and interstitial lung disease. The included diagnoses are not inclusive of all respiratory disorders associated with interstitial lung disease. *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *BAC* bronchoalveolar carcinoma, *NF* neurofibromatosis, *IPF* idiopathic pulmonary fibrosis, *RB-ILD* respiratory bronchiolitis-interstitial lung disease, *DIP* desquamative interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia (Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Danoff SK, Terry PB, and Horton MR, A clinician's guide to the diagnosis and treatment of interstitial lung diseases, Southern Medical Journal, Vol. 100)

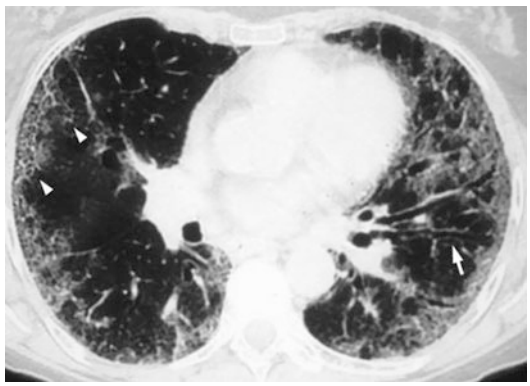

Fig. 3 Chest CT findings of idiopathic pulmonary fibrosis. *White arrowheads* denote peripheral reticular opacities, while *white arrow* denotes traction bronchiectasis (Image courtesy of Dr. Stanley Siegelman, Department of Radiology, Johns Hopkins University)

time of lung transplantation (Nathan et al. 2008). Although the prevalence is much higher in advanced disease, early IPF can be complicated by PH, with a reported prevalence of approximately 10 % IPF patients with an average FVC ~ 70 % in one study (Raghu et al. 2013). Interestingly, 5 % of this cohort also had an elevated pulmonary artery wedge pressure, reinforcing the importance of comorbid diagnoses in PH development. In general, PH associated with IPF is mild, and approximately half of patients have a mean PA pressure of less than or equal to 30 mmHg (Lettieri et al. 2006). However, in advanced disease, severely elevated PA pressures (mean >40 mmHg) were noted in 2–9 % of IPF patients awaiting lung transplant (Lettieri et al. 2006; Shorr et al. 2007).

Development of PH is uniformly associated with increased morbidity and mortality in IPF patients. Patients with advanced IPF complicated by PH had a 1-year mortality of 28 %, while those without PH had 5.5 % 1-year mortality (Lettieri et al. 2006). Even modest increases in PA pressure are predictive of reduced long-term survival in IPF patients (Hamada et al. 2007). In terms of morbidity, IPF patients with PH have been

shown to have reduced oxygenation and exercise capacity when compared with IPF patients without PH (Lettieri et al. 2006; Nathan et al. 2007).

Treatment options are limited for IPF patients with PH, and early referral to a transplant center should be considered. IPF is poorly responsive to currently available therapies, and current guidelines recommend against immunomodulatory medications in the majority of IPF patients (Raghu et al. 2011). These therapies are likely to have limited value in mitigating associated PH, which usually develops in advanced disease when fibrotic remodeling has already developed. Treatment with pulmonary vasodilators is not routinely recommended (Hoeper et al. 2009), primarily due to lack of definitive evidence demonstrating efficacy and potential for worsening V/Q matching and hypoxemia. Limited data on PDE5 (phosphodiesterase-5) inhibitors (which inhibit pulmonary cyclic guanosine monophosphate catabolism) in IPF are conflicting. While an initial open-label trial of sildenafil in IPF patients with PH showed improvements in 6MWD after 12 weeks of therapy (Collard et al. 2007), a recent randomized clinical trial failed to replicate these findings (Zisman et al. 2010). Patients with severe IPF treated with sildenafil reported less dyspnea and had improved PaO_2 and D_{LCO} when compared to placebo, though potential effects of sildenafil on pulmonary hemodynamics were not reported (Zisman et al. 2010). Data supporting beneficial effects of endothelin receptor antagonists (ERA) has been similarly disappointing. Despite early retrospective data suggesting an increase in 6MWD in a small cohort of IPF patients with PH (Minai et al. 2008), the findings were not sustained. Furthermore, a randomized, placebo controlled trial (BUILD) failed to show an increase in exercise capacity in IPF patients treated with bosentan (King Jr. et al. 2008), while two additional randomized controlled trials using the selective ERA ambrisentan (ARTEMIS, ARTEMIS-PH) were stopped early due to lack of efficacy (Ruggiero et al. 2012). Intravenous prostacyclins have been associated with worsened V/Q matching in patients with ILD (Ghofrani et al. 2002). There is also a theoretical risk of precipitating pulmonary edema in some ILD patients with intravenous prostacyclin analogues, as pulmonary veno-occlusive lesions have been described in several pulmonary disorders, including IPF, sarcoidosis, pulmonary Langerhans cell histiocytosis, and SSc-associated ILD (Shlobin and Nathan 2011). Small studies have demonstrated that inhaled forms of prostacyclin therapy may not be associated with significant systemic hypotension or increased shunting, while acutely improving pulmonary hemodynamics (Olschewski et al. 1999). However, longer-term data in randomized clinical trials demonstrating significant benefit are not currently available.

Connective Tissue Disease-Associated ILD

Interstitial lung disease is a common manifestation of many connective tissue diseases (CTD). Some have proposed the hypothesis that IIPs actually represent "formes frustes" of lung-specific autoimmune disease (Cottin 2006). Most commonly, clinically significant ILD has been associated with systemic sclerosis (SSc; reported prevalence ~40 % (Highland et al. 2007)), polymyositis/dermatomyositis (PM/DM; reported prevalence ~30 % (Schwarz 1998)), rheumatoid arthritis (RA; reported prevalence ~10 % (Turesson et al. 2003)), Sjogren's syndrome (SS; reported prevalence 8–38 % (Olson et al. 2012; Papathanasiou et al. 1986)), and systemic lupus erythematosus (SLE; 5-year incidence ~4 % (Bertoli et al. 2007)). Uniformly, subclinical radiographic disease has a higher prevalence in each of these CTDs.

While there is some variability to the radiographic pattern of disease, the ILD is most often consistent with nonspecific interstitial pneumonia (NSIP) (Fig. 4). This pattern is characterized predominantly by ground-glass opacities, though peripheral reticulations and traction bronchiectasis may be present (ATS/ERS 2002). The lung is usually diffusely involved, though abnormalities are more prominent peripherally and at the bases. Subpleural sparing is a highly specific feature for NSIP (Jawad et al. 2012). Unlike IPF, honeycombing is rare and when present is generally mild. Histologically, NSIP may demonstrate primarily cellular inflammation, primarily

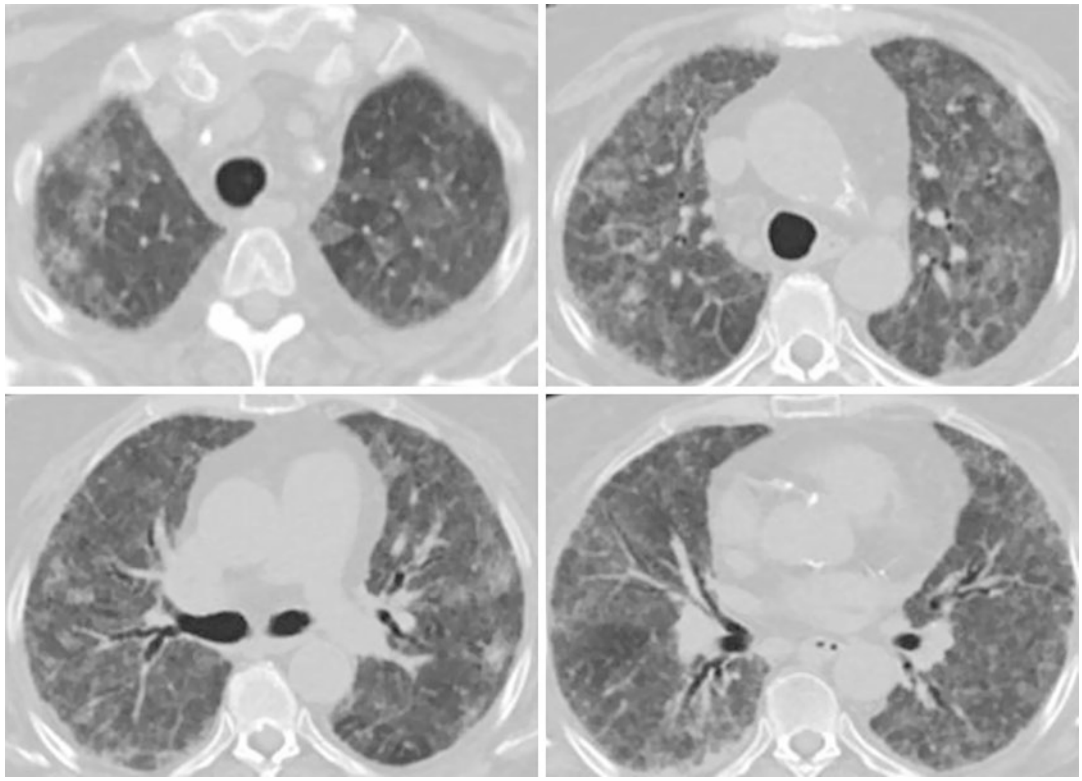

Fig. 4 Chest CT findings of nonspecific interstitial pneumonia. Serial sections throughout the chest demonstrate peripheral ground-glass opacities with diffuse parenchymal involvement (Images courtesy of Dr. Stanley Siegelman, Department of Radiology, Johns Hopkins University)

fibrosis, or a combination of the two. Cellular NSIP is generally characterized by chronic lymphocytic interstitial inflammation. In primarily fibrotic NSIP, fibrosis is temporally homogeneous, and fibroblastic foci are not present (in distinction to UIP, above) (ATS/ERS 2002). Distinction between IPF and fibrotic NSIP can only be made pathologically.

The prevalence of PH in CTD-associated ILD is not known, given the rare nature of both diseases. In general, there is a paucity of information regarding the prevalence of PH in NSIP (of any etiology). In terms of CTD-associated ILD-PH, most attention has been focused on patients with systemic sclerosis (SSc-ILD-PH). Chang et al. reported a prevalence of 18.1 % in one large cohort of SSc patients, with higher prevalence estimates among those with more severe restrictive ventilatory abnormalities (Chang et al. 2003). Risk factors associated with ILD-PH included older age and diffuse cutaneous involvement (Chang et al. 2003). When compared to SSc patients with PAH, the SSc-ILD-PH phenotype was associated with male sex, smoking, diffuse cutaneous disease, and a reduced prevalence of the anti-centromere antibody (Launay et al. 2011). The severity of PH associated with ILD in SSc patients appears to be than in other interstitial diseases and is similar to that observed in SSc patients with PAH. In one study, 68 % of SSc patients with ILD-PH had a mean PA pressure of $\geq$35 mmHg, and the average mPAP for the ILD-PH cohort (42 mmHg) was not different from a comparative cohort of SSc patients with PAH (45 mmHg) (Launay et al. 2011).

Despite similarities in hemodynamics, outcomes are uniformly worse for SSc-ILD-PH patients when compared to SSc-PAH patients. We have observed dramatic reduction in survival at 1 year (82 vs. 87 %), 2 years (46 vs. 79 %), and

3 years (39 vs. 64 %) after diagnosis in SSc-ILD-PH patients compared to SSc-PAH patients, despite better baseline hemodynamic indices (Mathai et al. 2009). These survival differences are likely related to a lack of response to current PH-specific therapies in SSc patients with ILD-PH. Unfortunately, these patients are routinely excluded from clinical trials of PH-specific therapy, so limited data exists. However, one retrospective analysis from 2 independent cohorts of SSc-ILD-PH patients treated with pulmonary vasodilator therapy showed no improvement in any clinical parameter, including functional class, exercise capacity, or hemodynamics (Le et al. 2011). Subgroup analyses showed no benefits in those with more severe disease (mean PA pressure $\geq$40 mmHg). More importantly, reductions in arterial oxygen saturation (likely associated with pulmonary vasodilator therapy) were associated with reduced survival in SSc-ILD-PH patients. Given the apparent lack of efficacy of currently available therapies and the dramatically reduced survival in SSc-ILD-PH patients, lung transplantation should be an early consideration in this group, barring other prohibitive comorbidities.

Granulomatous ILD

A spectrum of diffuse parenchymal lung disorders can be attributed to granulomatous inflammation. Hypersensitivity pneumonitis (HP), sarcoidosis, and pulmonary Langerhans cell histiocytosis (PLCH) have all been associated with the development of PH. Although these disorders differ significantly, excessive granuloma formation disrupts tissue architecture and impairs pulmonary function in each (Morgenthau and Padilla 2009). HP represents a complex spectrum of disease that manifests as an exuberant allergic (type III and type IV hypersensitivity) reaction to a wide variety of environmental antigens. In chronic HP, the prevalence of PH (diagnosed by echo with a PASP $>$ 50 mmHg) has been estimated at 19 % (Koschel et al. 2012). Sarcoidosis and PLCH are multisystem disorders with prominent pulmonary manifestations. PH associated with these diagnoses is classified as WHO Group V (PH with unclear multifactorial mechanisms) (Simonneau et al. 2009) and appears to be a fairly prevalent complication. PH prevalence in sarcoidosis has been estimated to be as high as 74 % in patients awaiting lung transplantation (Shorr et al. 2003) and as high as 92–100 % in patients with severe PLCH (Kiakouama et al. 2010; Lazor et al. 2009; Dauriat et al. 2006; Fartoukh et al. 2000). Most attention has been focused on sarcoidosis-associated PH in this group, with fewer studies regarding PLCH and HP.

The pathophysiology of sarcoidosis revolves around chronic inflammation mediated by T-lymphocytes and macrophages. Granulomas are noted predominantly in a lymphatic distribution, placing them in close proximity to pulmonary arteries and veins. Granulomatous inflammation of the pulmonary arteries is common and may involve the adventitia, media, or intima (Diaz-Guzman et al. 2008). In addition, assessment of the pulmonary microvasculature in sarcoidosis demonstrates reduced vessel density in regions of granulomatous fibrosis, intimal proliferation, and adventitial fibrosis (Farkas et al. 2011). Less commonly, plexiform lesions are observed. Increased endothelial cell proliferation is noted less frequently than in SSc-ILD-PH (Farkas et al. 2011). Multiple additional factors are likely to contribute to the pathology of PH in sarcoidosis, including hypoxic pulmonary vasoconstriction, granulomatous inflammation of larger pulmonary arteries, and sarcoidosis-related LV systolic and/or diastolic dysfunction. Importantly, pulmonary venous involvement is common (Diaz-Guzman et al. 2008), potentially contributing a PVOD-like phenotype.

The onset of PH in sarcoidosis is a poor prognostic factor. One study estimated the relative risk of death in sarcoidosis PH patients to be 10-fold higher than in those with sarcoidosis but no PH (Baughman et al. 2010). Moreover, hemodynamic indices associated with PH (increased RA pressure, mean PAP) have been shown to predict increased mortality among sarcoidosis patients awaiting lung transplant (Arcasoy et al. 2001; Shorr et al. 2003). Unfortunately, medical therapies have not demonstrated consistent improvements in PH associated with sarcoidosis. Immunosuppressive therapy with glucocorticoids

has shown improvement in pulmonary hemodynamics in some cohorts (Gluskowski et al. 1990; Baughman et al. 2006; Nunes et al. 2006), though these small trials have been unable to demonstrate reliable means for prediction of patients who might benefit from corticosteroids. Reports demonstrating the efficacy of pulmonary vasodilator therapy have been similarly inconsistent. One small retrospective review assessed response to PH-specific therapies in sarcoidosis patients with severe PH at two large referral centers (Barnett et al. 2009). After a median of 11 months of therapy, New York Heart Association (NYHA) functional classification had improved in 9 of 22 treated patients, while exercise capacity increased and mean PA pressure improved significantly among those receiving PH-specific therapies. Improvements in exercise capacity were more robust in patients with relatively preserved lung function (FVC $>$ 51 %). While these studies suggest potential benefit for pulmonary vasodilators in some patients with PH complicating sarcoidosis, it remains difficult to predict who might benefit. Given the impressive mortality risk associated with PH in patients with sarcoidosis, we generally recommend early lung transplant referral.

PLCH, though classically characterized as an ILD, actually has pathology more consistent with an inflammatory bronchiolitis in early stages (Suri et al. 2012). Loosely formed granulomas concentrate around small airways, and there is variability in the degree of interstitial involvement. The majority of cases include vasculopathy of medium and small pulmonary arteries and veins (Fartoukh et al. 2000), with intimal fibrosis and medial hypertrophy. These vascular lesions are frequently observed in lung regions unaffected by parenchymal changes, and PVOD may be present in up to one-third of patients. Vascular infiltration by Langerhans histiocytes appears to be rare (Fartoukh et al. 2000). PH has been associated with poor survival in PLCH (Fartoukh et al. 2000; Harari et al. 1997; Chaowalit et al. 2004), and definitive data regarding medical therapies does not exist. While the parenchymal disease will regress in some patients after smoking cessation, the effects of smoking cessation on PH have not been reported. The use of immunosuppressive medications in PLCH has not been universally effective (Suri et al. 2012). One small case series described significant improvements in pulmonary hemodynamics, exercise capacity, and WHO functional classification in patients treated with pulmonary vasodilator therapies without worsening hypoxemia or precipitating pulmonary edema (Le et al. 2012). Alternatively, lung transplantation for PLCH has been associated with good outcomes, despite a nearly 20 % disease recurrence and a high prevalence of severe PH prior to transplant (Dauriat et al. 2006). While careful pulmonary vasodilator trials at experienced centers may be considered in these patients, early consideration for lung transplantation is recommended.

Heritable ILD

Lymphangioleiomyomatosis (LAM) and neurofibromatosis I (NF) are heritable, multisystem disorders occasionally complicated by PH. Little is known about the significance of PH development in these disorders, though recent observational studies have begun to shed some light on PH in LAM.

LAM is a disorder affecting women of reproductive age and is characterized by proliferation of abnormal smooth muscle cells carrying a mutation in the tuberous sclerosis (TSC) genes. Lung involvement is characterized by diffuse cystic parenchymal disease, recurrent pneumothoraces, and pleural effusions (Fig. 5). Abnormal smooth muscle cells proliferate along the pulmonary lymphatics and have recently been demonstrated in the pulmonary arterial walls (Cottin et al. 2012). PH prevalence in this population is unknown, but appears to range from 7 % (as assessed by echo $>$35 mm) (Taveira-DaSilva et al. 2007) to 45 % in patients awaiting lung transplantation (assessed by right heart catheterization; (Reynaud-Gaubert et al. 2008). Reported severity is generally mild, with two studies demonstrating average mean PAP in the 32–33 mmHg range (Cottin et al. 2012; Reynaud-Gaubert et al. 2008). The etiology of elevated PA pressures is thought to be multifactorial, including chronic hypoxia, disruption of pulmonary vascular capacitance by cystic lesions,

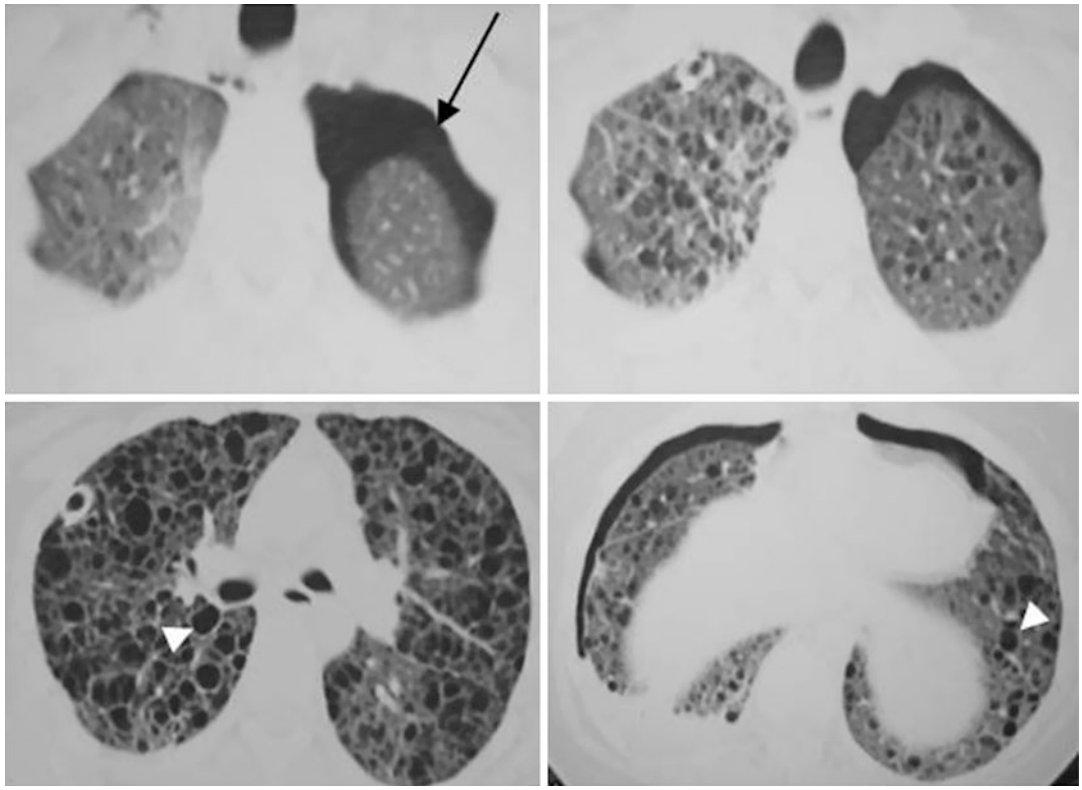

Fig. 5 Chest CT findings of lymphangioleiomyomatosis. Serial sections throughout the chest demonstrate diffuse parenchymal involvement. *Black arrow* denotes pneumothorax. *White arrowheads* denote multiple parenchymal cysts (Images courtesy of Dr. Stanley Siegelman, Department of Radiology, Johns Hopkins University)

and the aforementioned infiltration of abnormal smooth muscle cells in pulmonary arteries (Cottin et al. 2012). The clinical relevance of PH in LAM patients is uncertain. Lower D_{LCO}, more severe hypoxemia, and decreased exercise capacity have been described in patients with LAM and PH when compared to LAM patients without PH (Cottin et al. 2012), although it is unclear whether these differences are a cause or consequence of associated PH. Cottin et al. (2012) described a two-year survival of 94 % among 20 LAM patients with PH, and 78 % of them were transplant-free during this interval. Six patients in this observational study also received pulmonary vasodilator therapies (ERAs and PDE5 inhibitors), which were associated with significant reductions in mean PA pressure and PVR without worsening hypoxemia. However, these effects were not accompanied by significant improvements in cardiac function, exercise capacity, dyspnea. Overall, the significance of PH in LAM remains uncertain.

Obstructive Lung Disease

Obstructive lung disease is extremely common and includes a number of disorders that result in increased resistance to airflow. As noted above, the most important disorder in this classification in terms of PH is COPD, with less being known about the role of PH in asthma, cystic fibrosis, bronchiolitis obliterans, or bronchiectasis. Recently, the high prevalence of PH in combined obstructive and restrictive disease (chronic pulmonary fibrosis and emphysema, CPFE) has been recognized. Chronic hypoxemia appears to be the prominent precipitant of PH in these disorders, though additional mechanisms do play a role.

Chronic Obstructive Pulmonary Disease

COPD is a chronic inflammatory disorder of small airways that leads to airflow limitation, impaired gas exchange, and parenchymal loss (in emphysema). Hypoxemia results from impaired V/Q matching and is compounded by the loss of alveolar surface area for diffusion in emphysema. Prevalence estimates for PH in COPD range from 30 % to 70 % (Minai et al. 2010), with PH being more common in patients with advanced disease. In one trial of patients with severe emphysema evaluated for lung volume reduction surgery, 61.4 % of patients had a mean PA pressure greater than 20 mmHg (Scharf et al. 2002). As this value represents the upper limit of normal resting mean PA pressure (Badesch et al. 2009), many investigators have used this value to define PH in COPD, despite the higher mean PA pressure required to define PAH and PH in other chronic respiratory diseases (25 mmHg). Given the reduced survival noted in COPD patients with a mean PA pressure greater than 20 mmHg (Weitzenblum et al. 1981), this definition may in fact be appropriate. In general, PH associated with COPD is of mild severity, and PA pressures elevated out of proportion should prompt evaluation for other contributing diagnoses (obstructive sleep apnea, left ventricular dysfunction, and chronic thromboembolic disease). However, there is a subgroup of COPD patients that appears to be at risk for development of more severe PH despite stable lung disease. This group accounted for 1.1 % of all COPD patients undergoing hemodynamic evaluation in one large retrospective analysis (Chaouat et al. 2005) and has a unique clinical phenotype characterized by mild to moderate airways obstruction, severely reduced D_{LCO}, and severe hypoxemia. In addition, more severe PH can develop during COPD exacerbations, associated with increased V/Q mismatch, reduced PaO_2 (Barbera et al. 1997), and, in some cases, increased right ventricular filling pressures (Weitzenblum et al. 1994). Observed changes in right ventricular end-diastolic pressure were associated with development of peripheral edema, CO_2 retention, decreased arterial oxygen saturation, and increased mean PA pressure.

Development of PH in COPD is associated with increased mortality. While the survival benefit of long-term oxygen therapy (LTOT) in COPD has been recognized since the early 1980s (Medical Research Council Working Party 1981; Nocturnal Oxygen Therapy Trial Group 1980), mean PA pressure was shown to be highly predictive of long-term survival in COPD patients on LTOT (Oswald-Mammosser et al. 1995). Only 36 % of patients with a PA pressure greater than 25 mmHg survived for 5 years compared with 62 % of patients with PA pressure less than 25 mmHg.

As noted above, the primary pathological mechanism driving PH in COPD is chronic hypoxia related to impaired V/Q matching. Chronic hypoxia results in remodeling of the pulmonary vasculature and hypoxic pulmonary vasoconstriction. Loss of alveolated lung tissue, as occurs in emphysema, may result in loss of pulmonary capillary surface area, thereby increasing the PVR. This is supported by the negative correlation observed between diffusing capacity for carbon monoxide (D_{LCO}) and mean PA pressure in patients with severe COPD (Matsuoka et al. 2010). Impaired gas exchange may lead to chronic hypercapnia, and pulmonary vasoconstriction can be exacerbated by hypercapnia and acidemia in COPD (Enson et al. 1964). Mechanical compression of extra-alveolar vessels by lung hyperinflation had previously been assumed to contribute to increased PVR, though recent evidence does not support this hypothesis (Falk et al. 2007). However, lung hyperinflation and associated increasingly negative pleural pressures required for ventilation may increase both right and left heart filling pressures, as described above.

Treatment for most patients with PH secondary to COPD should focus on optimizing management of the underlying airways obstruction, with goals of improving V/Q matching, reducing work of breathing, and limiting chronic hypoxemia. Inhaled bronchodilators, anticholinergics, and corticosteroids remain the mainstay of therapy. These drugs, alone or in combination, have been shown to improve FEV_1 and reduce exacerbation frequency in COPD (Calverley et al. 2007; Tashkin et al. 2008). Short-acting β-agonists and

inhaled anticholinergics modestly reduce PA pressures during exercise in COPD patients, apparently by improving respiratory mechanics and lowering cardiac filling pressures (Saito et al. 1999). Oral theophylline has been associated with improved PA pressure, PVR, and cardiac index in COPD patients (Matthay 1987), though these effects are strongly dependent on blood levels, even within the therapeutic range (Mols et al. 1993). Theophylline is used infrequently in COPD patients due to the narrow therapeutic window, and drug clearance may be reduced in patients with diminished cardiac output. LTOT appears to be an effective treatment to combat PH development in COPD patients. In one study, COPD patients using supplemental oxygen for at least 15 h daily did not develop the increased PA pressure and PVR observed in COPD patients who did not receive LTOT (Medical Research Council Working Party 1981). More recently, LTOT was shown to stabilize the mean PA pressure in patients with severe COPD over a 6-year course, despite progressive declines in PaO_2 and FEV_1 (Zielinski et al. 1998). LTOT minimizes acute hypoxic pulmonary vasoconstriction and prevents further pulmonary vascular remodeling. As pulmonary hemodynamic parameters stabilize but do not improve with LTOT, it is unlikely that pulmonary vascular remodeling is reversed.

In general, pulmonary vasodilator therapies are not recommended for management of PH associated with COPD. Although some therapies can transiently improve hemodynamics, none has demonstrated long-term efficacy. More importantly, many PH-specific therapies have been associated with worsened V/Q matching and hypoxemia in COPD patients, potentially worsening long-term outcomes. Inhaled nitric oxide (NO) has been successfully used in clinical trials to improve hemodynamics and exercise capacity in patients with COPD-associated pulmonary hypertension. COPD patients who used inhaled NO, in addition to supplemental oxygen, showed significant improvements in mean PA pressure, PVR, and cardiac output (Vonbank et al. 2003). Importantly, inhaled NO improved V/Q matching and stabilized PaO_2 during exercise in patients with COPD-associated PH (Roger et al. 1997). However, the need for continuous inhalation makes this therapy too cumbersome to be considered practical. COPD patients with PH showed an acute reduction in resting and exercise-induced mean PA pressure and increased cardiac output during exercise following sildenafil administration (Blanco et al. 2010). However, sustained treatment with sildenafil (3 months) did not improve exercise capacity or quality of life in these patients (Blanco et al. 2013). Bosentan has been evaluated in a randomized, controlled trial of PH patients with severe or very severe COPD (Stolz et al. 2008). The results were disappointing, as patients treated with 12 weeks of bosentan therapy showed no improvement in 6MWD or pulmonary hemodynamics. Bosentan-treated subjects had a reduced PaO_2 and a widened alveolar-arterial oxygen gradient and reported a reduced quality of life when compared to subjects in the placebo arm (Stolz et al. 2008). The selective ERA ambrisentan did not improve 6MWD in COPD patients with PH in the ARIES-3 trial (Badesch et al. 2012). Acutely, intravenous prostacyclin analogues have been shown to improve mean PA pressure, PVR, and cardiac output in patients with COPD-associated pulmonary hypertension (Naeije et al. 1982). However, they have also been associated with worsened V/Q matching in COPD patients, particularly those with acute respiratory failure (Archer et al. 1996). Prostacyclin analogue administration through an inhaled route may mitigate the limiting issues with V/Q mismatch and hypoxemia. COPD patients with PH were recently shown to have improved V/Q matching, a reduced alveolar-arterial oxygen gradient, and longer 6MWD after an acute treatment with the inhaled prostacyclin iloprost (Dernaika et al. 2010). Future studies showing sustained functional or hemodynamic effects with longer treatment courses would be encouraging.

Finally, lung volume reduction surgery (LVRS) has been considered a potentially useful therapeutic option for PH in obstructive lung disease owing to theoretical benefits of minimizing thoracic hyperinflation. However, while LVRS was shown to improve respiratory mechanics and increase PaO_2, there was no improvement in hemodynamic indices in patients undergoing

LVRS compared to those treated medically (Criner et al. 2007). Therefore, despite theoretical benefits, no data support routine referral for LVRS in patients with PH associated with chronic lung disease.

Combined Pulmonary Fibrosis and Emphysema

Recently, a distinctive clinical entity characterized by concomitant obstructive and restrictive lung disease and highly associated with PH has been described. This syndrome, combined pulmonary fibrosis and emphysema (CPFE), is defined by characteristic radiographic findings (upper lobe predominant emphysema and lower lobe fibrosis; Fig. 6), pulmonary function testing (relatively preserved lung volumes and spirometry, with severely reduced D_{LCO}), and increased resting and exercise-induced hypoxemia (Cottin et al. 2005; Mejia et al. 2009). Importantly, PH appears to be highly prevalent in CPFE, estimated to complicate 50–90 % of cases (Cottin et al. 2005; Mejia et al. 2009). Retrospective analyses have suggested that PH is usually severe (mean PA pressure >40 mmHg; (Cottin et al. 2010) and that survival is markedly reduced (estimated at 60 % 1-year survival) (Cottin et al. 2010). These estimates would suggest that survival is worse than that for COPD patients with PH and at least as severe as IPF patients with PH. CPFE has generally been associated with male gender and smoking (Mejia et al. 2009), though more recently it has been associated with a variety of CTDs (Cottin et al. 2011). Of these, RA and SSc were most common, and PH was limited to those with SSc. In general, it appears that PH is less prevalent in CTD patients with CPFE than in idiopathic CPFE, suggesting that PH may be related to the underlying CTD (and not the lung parenchymal disease) in this population. There are extremely limited data on specific therapies for CPFE or for PH in patients with CPFE. One retrospective analysis showed that pulmonary vasodilator therapy did not improve survival in CPFE patients with PH (Cottin et al. 2010). However, as this diagnosis becomes increasingly recognized, the need for rigorous, prospective analyses of PH-specific therapies in CPFE will likely be necessary. At present, early referral for consideration of lung transplantation appears to be the most appropriate management option.

Summary and Conclusions

PH is a relatively common complication of a spectrum of chronic respiratory diseases. Although chronic hypoxia is an important contributor in most cases, a variety of additional mechanisms may contribute to increase pulmonary pressures. Early identification of PH in patients with chronic respiratory disease can be challenging, and the prognostic implications of PH development are uniformly poor. Treatment of the underlying respiratory disease should be the primary focus of, as PH-specific therapies have not

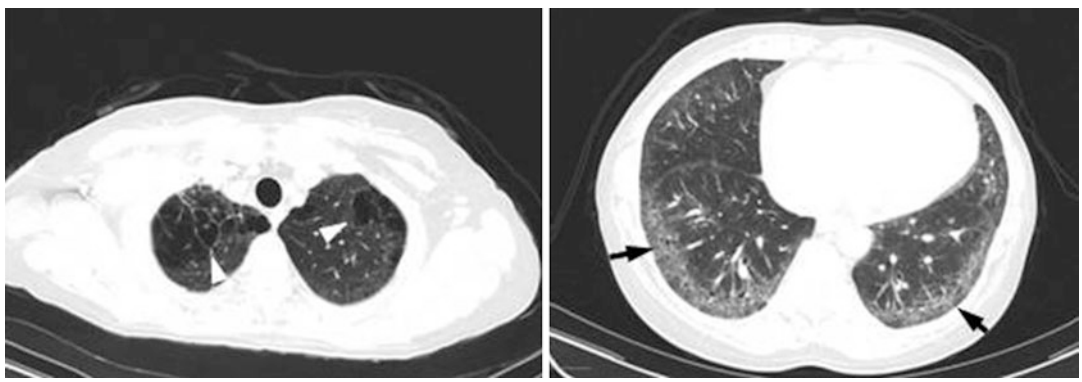

Fig. 6 Chest CT findings of combined pulmonary fibrosis and emphysema. At *left*, upper lobe emphysema is noted by white arrowheads. At *right*, peripheral reticular opacities are denoted in the lung bases by *black arrows*

consistently demonstrated benefit and in many cases have demonstrated the potential for harm. In some cases, however, patients with chronic respiratory disease and PH will have symptomatic improvement from pulmonary vasodilator therapies. Identifying those likely to benefit remains a challenge. Although treatment in clinical trials would provide the most information, limited options are currently available. In general, treatment with PH-specific therapies should be conducted in experienced centers where adverse effects can be closely monitored and early transplant referral can be made when appropriate.

Cross-References

► Hypoxic Pulmonary Hypertension

References

Arcasoy SM, Christie JD, Pochettino A, Rosengard BR, Blumenthal NP, Bavaria JE, Kotloff RM (2001) Characteristics and outcomes of patients with sarcoidosis listed for lung transplantation. Chest 120:873–880

Arcasoy SM, Christie JD, Ferrari VA, Sutton MS, Zisman DA, Blumenthal NP, Pochettino A, Kotloff RM (2003) Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 167:735–740

Archer S, Michelakis E (2002) The mechanism(s) of hypoxic pulmonary vasoconstriction: potassium channels, redox O(2) sensors, and controversies. News Physiol Sci 17:131–137

Archer SL, Mike D, Crow J, Long W, Weir EK (1996) A placebo-controlled trial of prostacyclin in acute respiratory failure in COPD. Chest 109:750–755

Arena R, Guazzi M, Myers J, Grinnen D, Forman DE, Lavie CJ (2011) Cardiopulmonary exercise testing in the assessment of pulmonary hypertension. Expert Rev Respir Med 5:281–293

ATS/ERS (2002) American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 165:277–304

Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A (2009) Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 54:S55–S66

Badesch DB, Feldman J, Keogh A, Mathier MA, Oudiz RJ, Shapiro S, Farber HW, McGoon M, Frost A, Allard M, Despain D, Dufton C, Rubin LJ (2012) ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. Cardiovasc Ther 30: 93–99

Barbera JA, Roca J, Ferrer A, Felez MA, Diaz O, Roger N, Rodriguez-Roisin R (1997) Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. Eur Respir J 10: 1285–1291

Barnett CF, Bonura EJ, Nathan SD, Ahmad S, Shlobin OA, Osei K, Zaiman AL, Hassoun PM, Moller DR, Barnett SD, Girgis RE (2009) Treatment of sarcoidosis-associated pulmonary hypertension. A two-center experience. Chest 135:1455–1461

Baughman RP, Engel PJ, Meyer CA, Barrett AB, Lower EE (2006) Pulmonary hypertension in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 23:108–116

Baughman RP, Engel PJ, Taylor L, Lower EE (2010) Survival in sarcoidosis-associated pulmonary hypertension: the importance of hemodynamic evaluation. Chest 138:1078–1085

Beghe B, Bazzan E, Baraldo S, Calabrese F, Rea F, Loy M, Maestrelli P, Zuin R, Fabbri LM, Saetta M (2006) Transforming growth factor-beta type II receptor in pulmonary arteries of patients with very severe COPD. Eur Respir J 28:556–562

Bertoli AM, Vila LM, Apte M, Fessler BJ, Bastian HM, Reveille JD, Alarcon GS (2007) Systemic lupus erythematosus in a multiethnic US Cohort LUMINA XLVIII: factors predictive of pulmonary damage. Lupus 16:410–417

Blanco I, Gimeno E, Munoz PA, Pizarro S, Gistau C, Rodriguez-Roisin R, Roca J, Barbera JA (2010) Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Am J Respir Crit Care Med 181:270–278

Blanco I, Santos S, Gea J, Guell R, Torres F, Gimeno-Santos E, Rodriguez DA, Vilaro J, Gomez B, Roca J, Barbera JA (2013) Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial. Eur Respir J 42:982–992

Buda AJ, Pinsky MR, Ingels NB Jr, Daughters GT, Stinson EB, Alderman EL (1979) Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 301:453–459

Budhiraja R, Tuder RM, Hassoun PM (2004) Endothelial dysfunction in pulmonary hypertension. Circulation 109:159–165

Burgess MI, Bright-Thomas R (2002) Usefulness of transcutaneous Doppler jugular venous echo to predict pulmonary hypertension in COPD patients. Eur Respir J 19:382–383

Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J (2007)

Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 356:775–789

Chang B, Wigley FM, White B, Wise RA (2003) Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. J Rheumatol 30: 2398–2405

Chaouat A, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducolone A, Ehrhart M, Kessler R, Weitzenblum E (2005) Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 172:189–194

Chaowalit N, Pellikka PA, Decker PA, Aubry MC, Krowka MJ, Ryu JH, Vassallo R (2004) Echocardiographic and clinical characteristics of pulmonary hypertension complicating pulmonary Langerhans cell histiocytosis. Mayo Clin Proc 79:1269–1275

Collard HR, Anstrom KJ, Schwarz MI, Zisman DA (2007) Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest 131:897–899

Colombat M, Mal H, Groussard O, Capron F, Thabut G, Jebrak G, Brugiere O, Dauriat G, Castier Y, Leseche G, Fournier M (2007) Pulmonary vascular lesions in end-stage idiopathic pulmonary fibrosis: histopathologic study on lung explant specimens and correlations with pulmonary hemodynamics. Hum Pathol 38:60–65

Cosgrove GP, Brown KK, Schiemann WP, Serls AE, Parr JE, Geraci MW, Schwarz MI, Cool CD, Worthen GS (2004) Pigment epithelium-derived factor in idiopathic pulmonary fibrosis: a role in aberrant angiogenesis. Am J Respir Crit Care Med 170:242–251

Cottin V (2006) Interstitial lung disease: are we missing formes frustes of connective tissue disease? Eur Respir J 28:893–896

Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, Israel-Biet D, Court-Fortune I, Valeyre D, Cordier JF (2005) Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 26:586–593

Cottin V, Le PJ, Prevot G, Mal H, Humbert M, Simonneau G, Cordier JF (2010) Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J 35:105–111

Cottin V, Nunes H, Mouthon L, Gamondes D, Lazor R, Hachulla E, Revel D, Valeyre D, Cordier JF (2011) Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. Arthritis Rheum 63:295–304

Cottin V, Harari S, Humbert M, Mal H, Dorfmuller P, Jais X, Reynaud-Gaubert M, Prevot G, Lazor R, Taille C, Lacronique J, Zeghmar S, Simonneau G, Cordier JF (2012) Pulmonary hypertension in lymphangioleiomyomatosis: characteristics in 20 patients. Eur Respir J 40:630–640

Criner GJ, Scharf SM, Falk JA, Gaughan JP, Sternberg AL, Patel NB, Fessler HE, Minai OA, Fishman AP (2007) Effect of lung volume reduction surgery on resting pulmonary hemodynamics in severe emphysema. Am J Respir Crit Care Med 176:253–260

Danoff SK, Terry PB, Horton MR (2007) A clinician's guide to the diagnosis and treatment of interstitial lung diseases. South Med J 100:579–587

Dauriat G, Mal H, Thabut G, Mornex JF, Bertocchi M, Tronc F, Leroy-Ladurie F, Dartevelle P, Reynaud-Gaubert M, Thomas P, Pison C, Blin D, Stern M, Bonnette P, Dromer C, Velly JF, Brugiere O, Leseche G, Fournier M (2006) Lung transplantation for pulmonary langerhans' cell histiocytosis: a multicenter analysis. Transplantation 81:746–750

Dernaika TA, Beavin M, Kinasewitz GT (2010) Iloprost improves gas exchange and exercise tolerance in patients with pulmonary hypertension and chronic obstructive pulmonary disease. Respiration 79: 377–382

Diaz-Guzman E, Farver, C, Parambil, J, Culver, DA (2008) Pulmonary hypertension caused by sarcoidosis. Clin Chest Med 29:549–63, x.

Ebina M, Shimizukawa M, Shibata N, Kimura Y, Suzuki T, Endo M, Sasano H, Kondo T, Nukiwa T (2004) Heterogeneous increase in CD34-positive alveolar capillaries in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 169:1203–1208

Enson Y, Giuntini C, Lewis ML, Morris TQ, Ferrer MI, Harvey RM (1964) The influence of hydrogen ion concentration and hypoxia on the pulmonary circulation. J Clin Invest 43:1146–1162

Falk JA, Martin UJ, Scharf S, Criner GJ (2007) Lung elastic recoil does not correlate with pulmonary hemodynamics in severe emphysema. Chest 132:1476–1484

Farkas L, Kolb M (2011) Pulmonary microcirculation in interstitial lung disease. Proc Am Thorac Soc 8: 516–521

Farkas L, Farkas D, Ask K, Moller A, Gauldie J, Margetts P, Inman M, Kolb M (2009) VEGF ameliorates pulmonary hypertension through inhibition of endothelial apoptosis in experimental lung fibrosis in rats. J Clin Invest 119:1298–1311

Farkas L, Gauldie J, Voelkel NF, Kolb M (2011) Pulmonary hypertension and idiopathic pulmonary fibrosis: a tale of angiogenesis, apoptosis, and growth factors. Am J Respir Cell Mol Biol 45:1–15

Fartoukh M, Humbert M, Capron F, Maitre S, Parent F, Le GC, Sitbon O, Herve P, Duroux P, Simonneau G (2000) Severe pulmonary hypertension in histiocytosis X. Am J Respir Crit Care Med 161:216–223

Fisher MR, Criner GJ, Fishman AP, Hassoun PM, Minai OA, Scharf SM, Fessler HE (2007) Estimating pulmonary artery pressures by echocardiography in patients with emphysema. Eur Respir J 30:914–921

Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, Chamera E, Corretti MC, Champion HC, Abraham TP, Girgis RE, Hassoun PM (2006) Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 174:1034–1041

Forfia PR, Vaidya A, Wiegers SE (2013) Pulmonary heart disease: The heart-lung interaction and its impact on patient phenotypes. Pulm Circ 3:5–19

Gartman EJ, Blundin M, Klinger JR, Yammine J, Roberts MB, Dennis MF (2012) Initial risk assessment for pulmonary hypertension in patients with COPD. Lung 190:83–89

Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, Gunther A, Walmrath D, Seeger W, Grimminger F (2002) Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet 360: 895–900

Girgis RE, Mathai, SC (2007) Pulmonary hypertension associated with chronic respiratory disease. Clin Chest Med 28:219–32

Glaser S, Noga O, Koch B, Opitz CF, Schmidt B, Temmesfeld B, Dorr M, Ewert R, Schaper C (2009) Impact of pulmonary hypertension on gas exchange and exercise capacity in patients with pulmonary fibrosis. Respir Med 103:317–324

Gluskowski J, Hawrylkiewicz I, Zych D, Zielinski J (1990) Effects of corticosteroid treatment on pulmonary haemodynamics in patients with sarcoidosis. Eur Respir J 3:403–407

Hamada K, Nagai S, Tanaka S, Handa T, Shigematsu M, Nagao T, Mishima M, Kitaichi M, Izumi T (2007) Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest 131: 650–656

Harari S, Brenot F, Barberis M, Simmoneau G (1997) Advanced pulmonary histiocytosis X is associated with severe pulmonary hypertension. Chest 111: 1142–1144

Hassoun PM, Mouthon L, Barbera JA, Eddahibi S, Flores SC, Grimminger F, Jones PL, Maitland ML, Michelakis ED, Morrell NW, Newman JH, Rabinovitch M, Schermuly R, Stenmark KR, Voelkel NF, Yuan JX, Humbert M (2009) Inflammation, growth factors, and pulmonary vascular remodeling. J Am Coll Cardiol 54: S10–S19

Highland KB, Garin MC, Brown KK (2007) The spectrum of scleroderma lung disease. Semin Respir Crit Care Med 28:418–429

Hoeper MM, Barbera JA, Channick RN, Hassoun PM, Lang IM, Manes A, Martinez FJ, Naeije R, Olschewski H, Pepke-Zaba J, Redfield MM, Robbins IM, Souza R, Torbicki A, McGoon M (2009) Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 54:S85–S96

Holverda S, Rietema H, Bogaard HJ, Westerhof N, Postmus PE, Boonstra A, Vonk-Noordegraaf A (2008) Acute effects of sildenafil on exercise pulmonary hemodynamics and capacity in patients with COPD. Pulm Pharmacol Ther 21:558–564

Hyduk A, Croft JB, Ayala C, Zheng K, Zheng ZJ, Mensah GA (2005) Pulmonary hypertension surveillance–United States, 1980–2002. MMWR Surveill Summ 54:1–28

Jawad H, Chung JH, Lynch DA, Newell JD Jr (2012) Radiological approach to interstitial lung disease: a guide for the nonradiologist. Clin Chest Med 33: 11–26

Kiakouama L, Cottin V, Etienne-Mastroianni B, Khouatra C, Humbert M, Cordier JF (2010) Severe pulmonary hypertension in histiocytosis X: long-term improvement with bosentan. Eur Respir J 36: 202–204

King TE Jr, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stahler G, Leconte I, Roux S, Raghu G (2008) BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 177:75–81

Koschel DS, Cardoso C, Wiedemann B, Hoffken G, Halank M (2012) Pulmonary hypertension in chronic hypersensitivity pneumonitis. Lung 190:295–302

Launay D, Humbert M, Berezne A, Cottin V, Allanore Y, Couderc LJ, Bletry O, Yaici A, Hatron PY, Mouthon L, Le PJ, Clerson P, Hachulla E (2011) Clinical characteristics and survival in systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease. Chest 140:1016–1024

Lazor R, Etienne-Mastroianni B, Khouatra C, Tazi A, Cottin V, Cordier JF (2009) Progressive diffuse pulmonary Langerhans cell histiocytosis improved by cladribine chemotherapy. Thorax 64:274–275

Le PJ, Girgis RE, Lechtzin N, Mathai SC, Launay D, Hummers LK, Zaiman A, Sitbon O, Simonneau G, Humbert M, Hassoun PM (2011) Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies. Arthritis Rheum 63:2456–2464

Le PJ, Lorillon G, Jais X, Tcherakian C, Feuillet S, Dorfmuller P, Simonneau G, Humbert M, Tazi A (2012) Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies. Chest 142:1150–1157

Lesur OJ, Mancini NM, Humbert JC, Chabot F, Polu JM (1994) Interleukin-6, interferon-gamma, and phospholipid levels in the alveolar lining fluid of human lungs. Profiles in coal worker's pneumoconiosis and idiopathic pulmonary fibrosis. Chest 106:407–413

Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF (2006) Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 129:746–752

Leuchte HH, Neurohr C, Baumgartner R, Holzapfel M, Giehrl W, Vogeser M, Behr J (2004) Brain natriuretic peptide and exercise capacity in lung fibrosis and pulmonary hypertension. Am J Respir Crit Care Med 170:360–365

Mathai SC, Hummers LK, Champion HC, Wigley FM, Zaiman A, Hassoun PM, Girgis RE (2009) Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. Arthritis Rheum 60:569–577

Matsuoka S, Washko GR, Yamashiro T, Estepar RS, Diaz A, Silverman EK, Hoffman E, Fessler HE, Criner GJ, Marchetti N, Scharf SM, Martinez FJ, Reilly JJ, Hatabu H (2010) Pulmonary hypertension and computed tomography measurement of small pulmonary vessels in severe emphysema. Am J Respir Crit Care Med 181:218–225

Matthay RA (1987) Favorable cardiovascular effects of theophylline in COPD. Chest 92:22S–26S

Medical Research Council Working Party (1981) Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet 1:681–686

Mejia M, Carrillo G, Rojas-Serrano J, Estrada A, Suarez T, Alonso D, Barrientos E, Gaxiola M, Navarro C, Selman M (2009) Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 136:10–15

Mertens LL, Friedberg MK (2010) Imaging the right ventricle–current state of the art. Nat Rev Cardiol 7:551–563

Minai OA, Sahoo D, Chapman JT, Mehta AC (2008) Vasoactive therapy can improve 6-min walk distance in patients with pulmonary hypertension and fibrotic interstitial lung disease. Respir Med 102:1015–1020

Minai OA, Chaouat A, Adnot S (2010) Pulmonary hypertension in COPD: epidemiology, significance, and management: pulmonary vascular disease: the global perspective. Chest 137:39S–51S

Mols P, Huynh CH, Dechamps P, Naeije N, Ham HR (1993) Dose dependency of aminophylline effects on hemodynamic and ventricular function in patients with chronic obstructive pulmonary disease. Chest 103:1725–1731

Morgenthau AS, Padilla ML (2009) Spectrum of fibrosing diffuse parenchymal lung disease. Mt Sinai J Med 76:2–23

Nadrous HF, Pellikka PA, Krowka MJ, Swanson KL, Chaowalit N, Decker PA, Ryu JH (2005) Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest 128:2393–2399

Naeije R, Melot C, Mols P, Hallemans R (1982) Reduction in pulmonary hypertension by prostaglandin E1 in decompensated chronic obstructive pulmonary disease. Am Rev Respir Dis 125:1–5

Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD (2007) Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. Chest 131:657–663

Nathan SD, Shlobin OA, Ahmad S, Koch J, Barnett SD, Ad N, Burton N, Leslie K (2008) Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Respiration 76:288–294

Nocturnal Oxygen Therapy Trial Group (1980) Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med 93:391–398

Nunes H, Humbert M, Capron F, Brauner M, Sitbon O, Battesti JP, Simonneau G, Valeyre D (2006) Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. Thorax 61:68–74

Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, Seeger W (1999) Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med 160:600–607

Olson AL, Brown KK, Fischer A (2012) Connective tissue disease-associated lung disease. Immunol Allergy Clin North Am 32:513–536

Oswald-Mammosser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Charpentier C, Kessler R (1995) Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest 107:1193–1198

Panos RJ, Mortenson RL, Niccoli SA, King TE Jr (1990) Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. Am J Med 88:396–404

Papathanasiou MP, Constantopoulos SH, Tsampoulas C, Drosos AA, Moutsopoulos HM (1986) Reappraisal of respiratory abnormalities in primary and secondary Sjogren's syndrome. A controlled study. Chest 90: 370–374

Peinado VI, Barbera JA, Abate P, Ramirez J, Roca J, Santos S, Rodriguez-Roisin R (1999) Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:1605–1611

Penaloza D, Arias-Stella J (2007) The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. Circulation 115:1132–1146

Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schunemann HJ (2011) An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 183:788–824

Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, Costabel U, Richeldi L, de Andrade J, Khalil N, Morrison LD, Lederer DJ, Shao L, Li X, Pedersen PS, Montgomery AB, Chien JW, O'Riordan TG (2013) Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med 158:641–649

Reynaud-Gaubert M, Mornex JF, Mal H, Treilhaud M, Dromer C, Quetant S, Leroy-Ladurie F, Guillemain R, Philit F, Dauriat G, Grenet D, Stern M (2008) Lung transplantation for lymphangioleiomyomatosis: the French experience. Transplantation 86:515–520

Rizkallah J, Man SF, Sin DD (2009) Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. Chest 135:786–793

Roger N, Barbera JA, Roca J, Rovira I, Gomez FP, Rodriguez-Roisin R (1997) Nitric oxide inhalation during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 156:800–806

Rosen Y, Moon S, Huang CT, Gourin A, Lyons HA (1977) Granulomatous pulmonary angiitis in sarcoidosis. Arch Pathol Lab Med 101:170–174

Rubens C, Ewert R, Halank M, Wensel R, Orzechowski HD, Schultheiss HP, Hoeffken G (2001) Big endothelin-1 and endothelin-1 plasma levels are correlated with the severity of primary pulmonary hypertension. Chest 120:1562–1569

Ruggiero RM, Bartolome S, Torres F (2012) Pulmonary hypertension in parenchymal lung disease. Heart Fail Clin 8:461–474

Saito S, Miyamoto K, Nishimura M, Aida A, Saito H, Tsujino I, Kawakami Y (1999) Effects of inhaled bronchodilators on pulmonary hemodynamics at rest and during exercise in patients with COPD. Chest 115: 376–382

Sajkov D, McEvoy RD (2009) Obstructive sleep apnea and pulmonary hypertension. Prog Cardiovasc Dis 51:363–370

Santos S, Peinado VI, Ramirez J, Morales-Blanhir J, Bastos R, Roca J, Rodriguez-Roisin R, Barbera JA (2003) Enhanced expression of vascular endothelial growth factor in pulmonary arteries of smokers and patients with moderate chronic obstructive pulmonary disease. Am J Respir Crit Care Med 167:1250–1256

Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE (2002) Hemodynamic characterization of patients with severe emphysema. Am J Respir Crit Care Med 166: 314–322

Schwarz MI (1998) The lung in polymyositis. Clin Chest Med 19:701–12, viii.

Shlobin OA, Nathan SD (2011) Pulmonary hypertension secondary to interstitial lung disease. Expert Rev Respir Med 5:179–189

Shorr AF, Davies DB, Nathan SD (2003) Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest 124:922–928

Shorr AF, Wainright JL, Cors CS, Lettieri CJ, Nathan SD (2007) Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. Eur Respir J 30:715–721

Simler NR, Brenchley PE, Horrocks AW, Greaves SM, Hasleton PS, Egan JJ (2004) Angiogenic cytokines in patients with idiopathic interstitial pneumonia. Thorax 59:581–585

Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R (2009) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 54: S43–S54

Steen VD, Graham G, Conte C, Owens G, Medsger TA Jr (1992) Isolated diffusing capacity reduction in systemic sclerosis. Arthritis Rheum 35:765–770

Stolz D, Rasch H, Linka A, Di VM, Meyer A, Brutsche M, Tamm M (2008) A randomised, controlled trial of bosentan in severe COPD. Eur Respir J 32:619–628

Suri HS, Yi ES, Nowakowski GS, Vassallo R (2012) Pulmonary langerhans cell histiocytosis. Orphanet J Rare Dis 7:16

Takemura T, Matsui Y, Oritsu M, Akiyama O, Hiraga Y, Omichi M, Hirasawa M, Saiki S, Tamura S, Mochizuki I (1991) Pulmonary vascular involvement in sarcoidosis: granulomatous angiitis and microangiopathy in transbronchial lung biopsies. Virchows Arch A Pathol Anat Histopathol 418:361–368

Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M (2008) A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 359:1543–1554

Taveira-DaSilva AM, Hathaway OM, Sachdev V, Shizukuda Y, Birdsall CW, Moss J (2007) Pulmonary artery pressure in lymphangioleiomyomatosis: an echocardiographic study. Chest 132:1573–1578

Tillie-Leblond I, Marquette CH, Perez T, Scherpereel A, Zanetti C, Tonnel AB, Remy-Jardin M (2006) Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. Ann Intern Med 144: 390–396

Tuder RM, Groves B, Badesch DB, Voelkel NF (1994) Exuberant endothelial cell growth and elements of inflammation are present in plexiform lesions of pulmonary hypertension. Am J Pathol 144:275–285

Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL (2003) Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis 62:722–727

Vignola AM, Chanez P, Chiappara G, Merendino A, Pace E, Rizzo A, la Rocca AM, Bellia V, Bonsignore G, Bousquet J (1997) Transforming growth factor-beta expression in mucosal biopsies in asthma and chronic bronchitis. Am J Respir Crit Care Med 156:591–599

Vonbank K, Ziesche R, Higenbottam TW, Stiebellehner L, Petkov V, Schenk P, Germann P, Block LH (2003) Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. Thorax 58:289–293

Vonbank K, Funk GC, Marzluf B, Burian B, Ziesche R, Stiebellehner L, Petkov V, Haber P (2008) Abnormal pulmonary arterial pressure limits exercise capacity in patients with COPD. Wien Klin Wochenschr 120: 749–755

Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, Magnussen H (2010) Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Chest 138:32–38

Weitzenblum E, Hirth C, Ducolone A, Mirhom R, Rasaholinjanahary J, Ehrhart M (1981) Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. Thorax 36:752–758

Weitzenblum E, Apprill M, Oswald M, Chaouat A, Imbs JL (1994) Pulmonary hemodynamics in patients with chronic obstructive pulmonary disease before and during an episode of peripheral edema. Chest 105: 1377–1382

Yamakami T, Taguchi O, Gabazza EC, Yoshida M, Kobayashi T, Kobayashi H, Yasui H, Ibata H, Adachi Y (1997) Arterial endothelin-1 level in pulmonary emphysema and interstitial lung disease. Relation with pulmonary hypertension during exercise. Eur Respir J 10:2055–2060

Zielinski J, Tobiasz M, Hawrylkiewicz I, Sliwinski P, Palasiewicz G (1998) Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. Chest 113:65–70

Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW (2010) A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 363:620–628

Further Reading

Forfia PR, Vaidya A, Wiegers SE (2013) Pulmonary heart disease: The heart-lung interaction and its impact on patient phenotypes. Pulm Circ 3:5–19.

Girgis RE, Mathai, SC (2007) Pulmonary hypertension associated with chronic respiratory disease. Clin Chest Med 28:219–32.

Nathan SD, Hassoun PM (2013) Pulmonary hypertension due to lung disease and/or hypoxia. Clin Chest Med 34:695–705.

Seeger W, Adir Y, Barberà JA, Champion H, Coghlan JG, MD, Cottin V, De Marco T, Galiè N, Ghio S, Gibbs S, Martinez FJ, Semigran MJ, Simonneau G, Wells AU, Vachiéry JL (2013) Pulmonary Hypertension in Chronic Lung Diseases. J Am Coll Cardiol 62:D109–16.