Right Ventricular Dysfunction in Chronic Lung Disease

Todd M. Kolb, MD, PhD, Paul M. Hassoun, MD

KEYWORDS
• Right ventricle • Pulmonary hypertension • Cor pulmonale
• Chronic lung disease

Key Points
• The prevalence of pulmonary hypertension and right ventricular remodeling is variable in chronic lung disease but increases with disease progression.
• Chronic hypoxemia and disruption of pulmonary vascular beds contribute to increase pulmonary vascular resistance and promote right ventricular remodeling.
• Right ventricular contractility is generally preserved in chronic lung disease.
• Right ventricular dysfunction can be difficult to distinguish noninvasively from underlying progression of pulmonary disease.
• Correction of hypoxia with long term oxygen therapy and pulmonary disease-specific therapies are the mainstay of treatment.
• Pulmonary hypertension–specific therapies have not shown benefit in right ventricular dysfunction associated with chronic lung disease and may worsen hypoxia.
• Development of pulmonary hypertension and right ventricular dysfunction worsens survival in chronic lung disease.
• Right ventricular failure is rare except during acute exacerbations of chronic lung disease or when multiple comorbidities are present.

NATURE OF THE PROBLEM
Nearly 200 years ago, Laennec described the relationship between chronic pulmonary disease and right ventricular (RV) dysfunction: “All diseases which give rise to severe and long-continued dyspnea produced, almost necessarily, hypertrophia or dilatation of the heart, through the constant efforts the organ is called on to perform, to propel the blood into the lungs against the resistance opposed to it by the cause of the dyspnea.”¹ Our understanding of cardio-pulmonary pathophysiology has increased exponentially since that publication, although Laennec’s basic observation concisely described the essence of RV dysfunction in chronic lung disease. Structural changes of the lung parenchyma and functional abnormalities in gas exchange lead to pulmonary hypertension.

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* Corresponding author. Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, 1830 East Monument Street, 5th Floor, Baltimore, MD 21205.

E-mail address: phassou1@jhmi.edu

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(PH), with subsequent RV remodeling and hypertrophy. The term cor pulmonale was used to describe this relationship, although the importance of PH was not emphasized. More recently, several disorders associated with chronic lung disease or hypoxia have been grouped together in the classification of PH. In general, these disorders are characterized by mild PH, and RV dysfunction is characterized by hypertrophy with preserved cardiac function. However, RV failure can occur during disease exacerbations or when multiple comorbidities are present, and the development of PH increases mortality in many chronic pulmonary conditions.

The current review focuses on World Health Organization Group 3 disorders (Box 1), with primary attention to chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and sleep disordered breathing (SDB), because these account for the bulk of cases. COPD is estimated to account for approximately 80% of Group 3 disease. Other diseases, including sarcoidosis, pulmonary Langerhans cell histiocytosis, and scleroderma-associated lung disease, can produce both parenchymal lung disease and pulmonary hypertension, but given their complex effects on the pulmonary vasculature they are not grouped with other chronic lung diseases in the most recent PH classification.

Prevalence of PH in Chronic Lung Disease

The prevalence of PH in chronic lung disease has been difficult to quantify because of the limited population-based hemodynamic data available and variability in the definition used to identify PH in these patients. Chronic lung disease seems to be a common comorbidity in patients with PH and was present in 25.9% of all patients who died from pulmonary hypertension in the United States between 2000 and 2002. Prevalence estimates for PH in COPD range from 30% to 70%, 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 pulmonary artery (PA) pressure greater than 20 mm Hg. Because this value represents the upper limit of normal resting mean PA pressure most investigators have used this value to define PH in chronic lung disease, despite the higher mean PA pressure required to define pulmonary arterial hypertension. The prevalence of PH and RV dysfunction in other obstructive lung diseases, including asthma, cystic fibrosis, bronchiolitis obliterans, and bronchiectasis is less clear. Prevalence estimates for ILD-associated PH are even more variable (8%–84%), probably because of the heterogeneous nature of these disorders.

Pulmonary hypertension prevalence increases with the severity of ILD: from 8.1% in patients with idiopathic pulmonary fibrosis (IPF) at initial evaluation to 30% to 40% in patients with IPF at the time of transplant evaluation or referral to tertiary care. Obstructive sleep apnea (OSA) has been associated with PH prevalence estimates of 20% to 40%, although other comorbidities frequently confound the diagnosis. One study estimated that PH prevalence in isolated OSA with all other restrictive and obstructive lung disease excluded was 9%, whereas the prevalence of PH in patients with obesity hypoventilation syndrome (OHS) was nearly 58%.

**PATHOPHYSIOLOGY**

**Effects of Chronic Pulmonary Disease on Right Heart Structure and Function**

Hypertrophy of the RV with preserved systolic function is the predominant effect of chronic pulmonary disease. Chronic pulmonary disease results in fairly slow increases in PA pressure (about 3 mm Hg/year), allowing time for adequate compensation. The normally thin-walled, compliant RV is hypertrophied to mitigate intraluminal pressure increases and ultimately minimizes wall stress. Increased RV thickness is accompanied by hypertrophy of individual myocytes, remodeling of the myocardial extracellular matrix, alterations in glucose metabolism, and in some models, compensatory increases in capillary density.

Concentric RV hypertrophy can precede resting hypoxia in patients with stable COPD and was demonstrated at autopsy in 76% of patients with...
advanced COPD.21 RV hypertrophy was estimated to be present in 50% of patients with restrictive lung disease.22 One study showed that 71% of patients with OSA had RV hypertrophy at echocardiography.23 However, it remains unclear whether RV hypertrophy results from isolated OSA or other co-morbidities. Whereas RV wall thickness increased in subjects with SDB in the Framingham cohort,24 a later study of OSA patients without pulmonary disease or evidence of LV dysfunction, showed no increase in RV wall thickness.25

Despite these changes in RV structure, myocardial systolic function is generally preserved in PH associated with chronic lung disease. Although earlier studies demonstrated that slight reductions in RV ejection fraction occurred commonly in chronic lung disease,26 the dependence of ejection fraction on ventricular preload, afterload, and myocardial contractility made this observation difficult to interpret. Intrinsic myocardial contractility seems to be preserved in patients with COPD as demonstrated by the normal RV end-systolic pressure-volume relationship measured at rest and with exercise.27,28 RV diastolic function may be impaired in patients with chronic lung disease and PH, as demonstrated by the direct associations between PH and reduced early to late ventricular filling velocity ratio (E/A ratio) and prolonged myocardial relaxation time in patients with COPD.28 Impaired RV diastolic function can also be demonstrated in healthy individuals exposed to acute hypoxia.30

Effects of Chronic Pulmonary Disease on RV Afterload

Increased pulmonary vascular resistance (PVR) is the sine qua non of RV dysfunction in chronic pulmonary disease. Chronic hypoxemia and the disruption of pulmonary vascular beds through parenchymal loss and fibrosis are the key mechanisms through which chronic lung disease increases PVR.

Alveolar hypoxia induces rapid vasoconstriction of small precapillary pulmonary arteries to preserve the ventilation to perfusion (V/Q) ratio and minimize effects on arterial oxygen saturation. The mechanisms of hypoxic pulmonary vasoconstriction are reviewed elsewhere 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 or by increased sympathetic activity in OSA.14 However, supplemental oxygen administration does not fully reverse the increased PA pressure observed in patients with COPD and correlations between PA pressure and systemic oxygenation have not been robust.34 This probably reflects individual differences in the capacity for hypoxic pulmonary vasoconstriction and/or differences in pulmonary vascular remodeling in response to chronic hypoxia. Chronic hypoxia results in remodeling of the pulmonary vasculature, characterized by neo-muscularization of arterioles, medial hypertrophy of small muscular arteries, and intimal thickening and fibroelastosis.35

Systemic hypoxemia arises in chronic lung disease through diverse mechanisms. COPD is a chronic inflammatory disorder of small airways that leads to airflow limitation, impaired gas exchange, and parenchymal loss in the case of emphysema. Hypoxemia results from impaired V/Q matching and is compounded by the loss of alveolar surface area for diffusion in emphysema. Interstitial lung diseases represent a more heterogeneous group of disorders, characterized by inflammatory or fibrotic destruction of lung parenchyma, generally at the level of the alveolar interstitium. These changes may be associated with autoimmune disease, exposure to cigarette smoke and other respiratory irritants, granulomatous diseases, or may be idiopathic. Interstitial changes result in impaired diffusing capacity, which may be exacerbated by poor V/Q matching in some patients. In OSA, hypoxia results from hypoventilation during obstructive episodes and is by definition intermittent. However, in patients with OHS or an overlap syndrome of COPD and OSA, diurnal hypoxemia may be present. At altitude, pulmonary vascular remodeling induced by chronic alveolar hypoxia can be exacerbated by hypoventilation, resulting in chronic mountain sickness that is frequently associated with PH and right heart dysfunction.36

Another common factor in the increased PVR associated with chronic lung disease is the disruption of pulmonary capillary beds. In COPD, the loss of alveolated lung tissue that occurs in emphysema, may result in loss of pulmonary capillary beds. This finding is supported by the negative correlation observed between diffusing capacity for carbon monoxide (DLCO) and mean PA pressure in patients with severe COPD.37 Mechanical compression of extra-alveolar vessels by lung hyperinflation had been assumed to contribute to PVR but later evidence did not support this hypothesis.38 In ILD, interstitial fibrosis and inflammatory infiltrates may promote the loss of pulmonary vascular beds and compression of small vessels. Vessel ablation is common within fibroblastic foci and areas of ‘honeycombing’.39 Pulmonary vessel capacitance may also be reduced by nearby fibrosis or by compensatory proliferation of abnormal capillaries lacking normal
elastin layers. Thromboembolic lesions can further impede pulmonary vascular flow and they frequently complicate chronic lung diseases, such as COPD, sarcoidosis, and IPF.

**Effects of Chronic Pulmonary Disease on Cardiac Mechanics**

Chronic pulmonary disease may alter right and left ventricular function by changing intrathoracic pressure. Lung hyperinflation may increase right atrial pressure, leading to reduced venous return and subsequent reductions in RV preload. In patients with COPD, hyperinflation has been directly correlated with reduced atrial chamber size, global RV dysfunction, and reduced LV filling. In addition, highly negative pleural pressures may be necessary to facilitate ventilation in COPD or during episodes of airway obstruction in OSA. These highly negative pleural pressures reduce intrathoracic pressure and increase LV wall stress during ejection, potentially resulting in left atrial hypertension and increased RV afterload.

**CLINICAL EVALUATION**

**Physical Examination**

It can be difficult to distinguish chronic lung disease from associated PH and RV dysfunction. Increased exertional dyspnea may arise from new RV dysfunction or progression of the underlying parenchymal lung disease. Symptoms associated with advanced RV dysfunction (leg edema, ascites) may not be present, or may develop independently of RV dysfunction. In COPD, peripheral edema can develop as a consequence of chronic hypercapnia and renal vasoconstriction with activation of the renin-angiotensin-aldosterone system. Peripheral edema is not a common occurrence in ILD patients with equivalent levels of hypoxemia, and is rare in COPD patients without hypercapnea.

Physical signs may also be of limited value in the evaluation of chronic lung disease-associated PH and RV dysfunction. Classical signs of RV dysfunction, including a precordial heave, accentuated pulmonic component of S2, murmur of tricuspid regurgitation, or a right-sided gallop, may not be present in mild disease. Auscultatory findings may be limited by chest over-inflation (in COPD) and the abnormal pulmonary examination of most patients with parenchymal lung disease.

**Non-Invasive Evaluation**

Most noninvasive diagnostic modalities lack the sensitivity to identify new RV dysfunction in parenchymal lung disease. Electrocardiogram findings associated with RV dysfunction include a rightward P-wave axis, S1S2S3 pattern, S1Q3 pattern, RV hypertrophy, and right bundle branch block. ECG alone, however, is insensitive for the diagnosis of RV dysfunction. In one study of COPD patients with PH, abnormal ECG findings had a sensitivity of only 51%.

Plain chest radiography findings associated with PH and RV remodeling may include enlarged central pulmonary arteries and the loss of the retrosternal air space. In patients with COPD, these radiographic abnormalities had a sensitivity of 46% and specificity of 63% in detecting PH. However, on chest CT imaging, the enlargement of the main pulmonary artery to a diameter of 29 mm or greater was associated with high sensitivity (84%), specificity (75%), and positive predictive value (95%) in a heterogeneous group of patients with chronic lung disease. However, CT findings may be less reliable in patients with IPF.

Pulmonary function testing is necessary for the initial diagnosis of most chronic lung diseases that cause RV dysfunction and it provides objective evidence of disease progression or stability. Isolated reductions in Dl,CO have been associated with PH in IPF, sarcoidosis, and systemic sclerosis (SSc), as shown in Fig. 1. However, a reduced Dl,CO is not predictive of elevated PA pressure in patients with COPD. In patients with SSc, the distinction between pulmonary arterial hypertension and ILD-associated PH may be important in determining prognosis and response to therapeutics; and the ratio of forced vital capacity/Dl,CO can predict pulmonary arterial hypertension in SSc patients with mild fibrotic lung disease.

Assessment of exercise capacity may support a diagnosis of RV dysfunction in chronic lung disease. There is a modest negative correlation between the 6-minute walk distance (6MWD) and the estimated systolic PA pressure in patients with COPD. Significant reductions in 6MWD have been reported in IPF patients with moderate to severe PH. Cardiopulmonary exercise testing (CPET) may be more useful in the detection of increased PA pressure in patients with chronic lung disease. Chronic lung disease-associated increases in PVR impair the normal exercise-induced pulmonary vasodilatory response, resulting in elevated PA pressure, increased V/Q mismatch and dead space ventilation, and reduced ventilatory efficiency (VE/VCO2). Progressive increases in VE/VCO2 and reductions in end-tidal CO2 measurements with exercise, have been associated with secondary PH in COPD and ILD.

Elevated plasma levels of brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic
peptide (NT-proBNP) are promising serologic markers that may suggest RV dysfunction in chronic lung disease. Natriuretic peptides are released from cardiac myocytes in response to increased wall stress; their serum levels must be interpreted with caution because they vary in populations based on age, gender, body mass index, and the presence of renal dysfunction. However, elevated BNP levels were shown to predict PH in patients with chronic lung disease with a reasonably high sensitivity (85%) and specificity (88%).

Cardiac magnetic resonance imaging (cMRI) has been used increasingly to investigate the relationship between COPD and RV structure and function. cMRI has been used to show that concentric RV hypertrophy precedes RV dilatation in stable COPD patients without resting hypoxia, and that exercise-induced increases in stroke volume are preload-dependent and limited by increases in PA pressure in patients with COPD. Similarly, the MESA-Lung study used cMRI to demonstrate that LV end-diastolic volumes and stroke volume are inversely correlated to percent emphysema, as detected by CT scan. Whereas cMRI holds great promise in furthering the understanding of RV structure and function in chronic lung disease, expense and limited availability make the technique somewhat impractical for routine clinical use. However, research findings have shown that volumes measured by electrocardiographically-gated cardiac CT imaging were well correlated with those obtained from cMRI, and provide an additional tool for clinical use that may be more widely available.

RV Dysfunction in Chronic Lung Disease

![Figure 1](https://via.placeholder.com/150)

**Fig. 1.** Correlation of mean pulmonary arterial pressure (mPAP) with PaO₂ (left and percentage of predicted DLCO [% DLCO] right) in patients with idiopathic pulmonary fibrosis. (From 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(3):650–6; with permission.)

Transthoracic echocardiography is perhaps the best initial noninvasive study to assess RV function in chronic lung disease. The technique is noninvasive and allows for serial measurements over time. Two-dimensional estimates of RV chamber size, wall thickness, PA systolic pressure, and left heart function may be useful in the evaluation of PH in patients with chronic lung disease. However, image analysis is often limited by hyperinflation or parenchymal lung abnormalities. One study noted that a well-defined tricuspid regurgitant jet was present in only 20% of patients with chronic lung disease. The correlation between estimated systolic PA pressure and pulmonary pressures measured by RHC is poor in advanced lung disease and estimated PA pressures are insensitive for detection of PH in this patient population. In a study of patients with advanced COPD referred for lung volume reduction surgery, echocardiographic RV systolic pressure estimates detected PH with a sensitivity of only 60% and specificity of 74%. Tricuspid annular plane systolic excursion (TAPSE) seems to be an accurate measure of RV function in patients with PH, including those with PH secondary to chronic respiratory disease. This technique is not dependent on endocardial border recognition, which can be difficult in chronic lung disease patients. Newer techniques, including three-dimensional echocardiography, tissue Doppler ultrasonography, and ultrasound strain imaging may increase the potential for noninvasive assessment of the RV function in patients with chronic lung disease, and have been reviewed.
Invasive Hemodynamic Measurements

Right heart catheterization (RHC) remains the gold standard in the assessment of PH, regardless of etiology. However, the procedure is invasive, costly, and requires performance by a skilled practitioner for safety and accurate interpretation. Given the generally mild hemodynamic changes in PH associated with pulmonary disease and the lack of evidence that PH-specific therapies provide benefit in this particular group (see later), RHC is not routinely recommended in this patient population. However, patients with chronic lung disease with clinical or echocardiographic evidence of advanced RV dysfunction out of proportion to their lung disease, might benefit from RHC, because severe PH or RV failure is usually associated with additional comorbidities. Generally, the degree of PH is mild in chronic lung disease, with mean PA pressures ranging from 20 mm Hg to 35 mm Hg. In one large retrospective review of COPD patients undergoing RHC for lung transplant evaluation, 60% of the patients with a mean PA pressure greater than 40 mm Hg also had some other precipitant (chronic thromboembolic disease, OSA, left ventricular disease). RHC may also be indicated when patients are considered for lung transplantation, because the Lung Allocation Score emphasizes the presence of PH, particularly in ILD, thereby expediting organ allocation.

THERAPEUTIC OPTIONS

In general, therapies to ameliorate RV dysfunction in chronic lung disease (Table 1) are targeted at mitigating the increased PVR associated with these conditions. Long term oxygen therapy (LTOT) and therapeutics targeted at the underlying pulmonary disease constitute the basis for therapy. There is limited evidence that medications targeting the pulmonary vasculature directly have any benefit in chronic lung disease.

Long Term Oxygen Therapy

The survival benefit of LTOT in chronic obstructive lung disease has been recognized from the early

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Likely to Benefit</th>
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<tbody>
<tr>
<td>Long-term oxygen therapy</td>
<td>All patients with resting, ambulatory, or nocturnal hypoxemia</td>
</tr>
<tr>
<td>Diuretics</td>
<td>All patients with peripheral edema</td>
</tr>
<tr>
<td>Disease-specific therapy</td>
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<tr>
<td>Smoking cessation</td>
<td>All patients</td>
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<tr>
<td>Pulmonary rehabilitation</td>
<td>All patients with advanced obstructive or restrictive lung disease</td>
</tr>
<tr>
<td>Inhaled bronchodilators, anticholinergics,</td>
<td>Chronic obstructive pulmonary disease, asthma, other obstructive lung diseases</td>
</tr>
<tr>
<td>and corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids and other</td>
<td>Unknown, potential benefit in sarcoidosis, pulmonary Langerhans cell histiocytes</td>
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<tr>
<td>immunosuppressants</td>
<td></td>
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<tr>
<td>Weight loss</td>
<td>All patients with obesity</td>
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<tr>
<td>Uvulopalatopharyngoplasty</td>
<td>Patients with mild to moderate OSA</td>
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<tr>
<td>Nasal CPAP</td>
<td>All patients with sleep-disordered breathing</td>
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<tr>
<td>Pulmonary hypertension-specific therapy</td>
<td></td>
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<tr>
<td>Inhaled nitric oxide</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Phosphodiesterase-5 inhibitors</td>
<td>Unknown</td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>Unknown</td>
</tr>
<tr>
<td>Prostacyclin analogs</td>
<td>Unknown; may be of some benefit with inhaled formulation in COPD</td>
</tr>
<tr>
<td>Statins</td>
<td>Unknown</td>
</tr>
<tr>
<td>Surgical options</td>
<td></td>
</tr>
<tr>
<td>Lung volume reduction surgery</td>
<td>None</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>Selected patients with severe parenchymal lung disease complicated by PH</td>
</tr>
</tbody>
</table>
1980s. LTOT minimizes RV afterload in COPD, because patients using supplemental oxygen for at least 15 hours daily did not develop the increased PA pressure and PVR observed in patients with COPD who did not receive LTOT. Later, LTOT was shown to stabilize the mean PA pressure in patients with severe COPD during a 6-year course, despite progressive declines in PaO₂ and FEV₁. LTOT minimizes acute hypoxic pulmonary vasoconstriction and prevents further pulmonary vascular remodeling. Because pulmonary hemodynamic parameters stabilize but do not improve with LTOT, it is unlikely that pulmonary vascular remodeling is reversed.

In ILD, treatment of hypoxia with LTOT is widely accepted although it is not evidence-based. No studies have identified survival benefit for LTOT in patients with ILD. Supplemental oxygen therapy should be titrated carefully in ILD patients, because growing evidence supports a role for hyperoxia-mediated oxidative injury in the pathogenesis of some ILDs. There have been no studies evaluating the effects of LTOT on pulmonary hemodynamics or RV dysfunction in patients with ILD-associated PH.

### Pulmonary Disease-Specific Therapies

Therapies targeting the underlying pulmonary disease are routinely recommended for treatment of Group 3 disorders but these recommendations are not based on strong clinical evidence. Disease-specific therapies improve alveolar oxygenation, decrease V/Q mismatch, or limit the mechanical effects of hyperinflation on the pulmonary circulation.

Inhaled bronchodilators, anticholinergics, and corticosteroids remain the mainstay of therapy in obstructive lung diseases. These drugs, alone or in combination, have been shown to improve FEV₁ and reduce exacerbation frequency in COPD. Short-acting β-agonists and inhaled anticholinergics modestly reduced PA pressures during exercise in patients with COPD but there was no change in the PVR. Given the associated improvements in pulmonary artery occlusion pressure with these medications, PA pressure was probably reduced through improvements in lung mechanics. Oral theophylline has been associated with improved PA pressure, PVR, and cardiac index in patients with COPD but these effects are strongly dependent on blood levels, even within the therapeutic range. Theophylline is used infrequently in patients with COPD because of the narrow therapeutic window and because drug clearance be reduced in patients with diminished cardiac output.

Few effective disease-specific therapies are available for patients with ILD. These therapies are likely to have limited value in mitigating the associated PH, which usually develops in advanced disease when fibrotic remodeling is unlikely to respond to currently available therapies. There are limited data to suggest that corticosteroids may improve hemodynamics in diseases like sarcoidosis and pulmonary Langerhans cell histiocytosis. These hemodynamic improvements were not routinely associated with radiographic improvements and may be related to effects on the vasculitic components of these disorders. Idiopathic pulmonary fibrosis is poorly responsive to available therapies and current guidelines recommend against immunomodulatory pharmacotherapy for most patients with IPF.

In obstructive sleep apnea, weight loss is recommended for all obese patients and is effective in reducing the frequency of apneic episodes. In patients with OHS, surgically-induced weight loss has been associated with significant improvement in pulmonary hemodynamics. Patients with mild to moderate OSA can be treated surgically with uvulopalatopharyngoplasty (UVPP), which has been associated with modest increase in RV ejection fraction. In severe OSA, nasal continuous positive airway pressure (nCPAP) is the preferred treatment and directly improves hemodynamics. Patients with severe OSA treated with nCPAP for 4 months demonstrated reduced resting PA pressure and PVR; and exposure to acute hypoxia caused attenuated pulmonary vasoconstriction in nCPAP-treated patients when compared with pretreatment baselines. Although multiple potential benefits can explain these findings (including reduction in nocturnal hypoxic episodes and improvement in cardiac function), the reduction in acute hypoxic pulmonary vasoreactivity suggests that nCPAP probably improves endothelial cell function.

### Pulmonary Hypertension-Specific Therapies

Although therapies specifically designed to mitigate dysfunctional endothelial signaling and reduce pulmonary vascular tone have been used successfully to minimize the morbidity associated with pulmonary arterial hypertension, the data supporting use of these medications in PH and RV dysfunction associated with chronic lung disease are less compelling. The limited available data predominantly show acute improvements in cardio-pulmonary hemodynamics but fail to show longterm functional benefits. In several cases, these medications actually worsened...
hypoxemia by preventing hypoxic pulmonary vasoconstriction, and impaired RV function by reducing venous return. Currently, these therapies are not recommended for treatment of PH associated with chronic lung disease.92

Inhaled nitric oxide (NO) is a pulmonary vasodilator that has been successfully used in clinical trials to improve hemodynamics and exercise capacity in patients with COPD-associated pulmonary hypertension. COPD patients who inhaled NO in addition to supplemental oxygen, showed significant improvements in mean PA pressure, PVR, and cardiac output.93 Inhaled NO improved V/Q matching and stabilized PaO2 during exercise in patients with COPD-associated PH.94 However, the need for continuous inhalation makes this therapy too cumbersome to be practical.

Sildenafil enhances the effects of NO on pulmonary vascular smooth muscle cells and causes pulmonary vasodilatation by inhibiting the enzyme phosphodiesterase-5 (PDE5). PDE5 is the predominant phosphodiesterase isoform in lung tissue and is responsible for catabolism of the NO second messenger cyclic guanosine monophosphate (cGMP). By inhibiting PDE5, sildenafil promotes accumulation of cGMP after NO stimulation, leading to smooth muscle cell relaxation and growth inhibition. COPD patients with pulmonary hypertension showed an acute reduction in resting and exercise-induced mean PA pressure and increased cardiac output during exercise after the administration of sildenafil.95 Unfortunately, sildenafil was associated with a significant reduction in PaO2 because of adverse effects on V/Q matching. The long-term benefits of sildenafil in COPD patients with PH have not been demonstrated. The limited available data regarding the potential efficacy of PDE5 inhibitors in ILD are conflicting. Whereas an initial open label trial of sildenafil in IPF patients with PH showed improvements in 6MWD after 12 weeks of therapy,96 a later randomized clinical trial failed to replicate these findings.97 Patients with severe IPF treated with sildenafil reported less dyspnea and had improved PaO2 and Dl,CO when compared with patients treated with placebo, although the potential effects of sildenafil on pulmonary hemodynamics were not reported.97

Endothelin 1 is produced by endothelial cells and has direct vasoconstrictor and mitogenic effects on vascular smooth muscle cells. The vasoconstrictive effects of endothelin are mediated by 2 receptors (ERA and ERB) on pulmonary arterial smooth muscle cells. Conversely, ERB is also functional on endothelial cells and stimulation mediates NO production and prostacyclin release, resulting in endothelial-mediated vasodilatation. The endothelin receptor antagonists currently available, either target both receptors (bosentan), or selectively target ERA (sitaxsentan, ambrisentan). Bosentan has been evaluated in a randomized, controlled trial of PH patients with severe or very severe COPD.98 The results were disappointing, because patients treated with 12 weeks of bosentan therapy showed no improvement in 6MWD or pulmonary hemodynamics. Bosentan-treated subjects had reduced PaO2, widened alveolar-arterial oxygen gradient, and reported reduced quality of life when compared with subjects in the placebo arm.99 The selective ERA antagonist ambrisentan did not improve 6MWD in COPD or ILD patients with PH in the ARIES-3 trial,99 and a phase III study of ambrisentan in IPF patients with PH was stopped early because of lack of clinical efficacy.99

Prostacyclin, produced by the endothelial cells, is a potent vasodilator that inhibits platelet aggregation and effectively prevents the release of growth factors from endothelial cells, platelets, and macrophages. In the United States, prostacyclin analogs are available for delivery via intravenous (epoprostenol and treprostinil), subcutaneous (treprostinil), and inhaled (iloprost) routes. Acutely, intravenous prostacyclin analogs have been shown to improve mean PA pressure, PVR, and cardiac output in patients with COPD-associated pulmonary hypertension.100 Unfortunately, systemically administered prostacyclin analogs have been associated with worsened V/Q matching in patients with COPD, particularly those with acute respiratory failure,101 and ILD patients with PH.102 Intravenous prostacyclin analogs also carry a theoretical risk of precipitating pulmonary edema in some patients with ILD, because pulmonary veno-occlusive lesions have been described in several pulmonary disorders, including IPF, sarcoidosis, pulmonary Langerhans cell histiocytosis, and SSc-associated ILD.39

Prostacyclin analog 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 acute treatment with inhaled iloprost.103 Future studies that show sustained functional or hemodynamic effects with longer treatment courses would be encouraging.

**Statins**

Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) represent an intriguing class of medications that may improve RV dysfunction associated with chronic lung disease. A recent
randomized, placebo-controlled trial showed that COPD patients with PH, who were treated with pravastatin for 6 months demonstrated a significant increase in exercise capacity, improved estimated systolic PA pressure, and reduced dyspnea scores when compared with patients on placebo. In a cross-sectional study of patients with severe COPD undergoing right heart catheterization for lung transplant evaluation, statin use was associated with a modest reduction in mean PA pressure and pulmonary artery occlusion pressure, although there was no difference in PVR. The mechanism by which statins influence pulmonary hemodynamics remains unknown, although Lee and colleagues showed that the use of statins was associated with reduced endothelin-1 production in COPD patients with PH. The multicenter ASA-STAT trial that showed no improvement in 6MWD in patients with pulmonary arterial hypertension taking simvastatin for 6 months, suggested that the observed effects in COPD patients with PH may be associated with primary statin effects on the underlying lung disease or associated comorbidities.

**Surgical Options**

Surgical intervention is rarely warranted for the mild RV dysfunction associated with chronic lung disease. However, given the increased mortality associated with even mild PH in chronic lung disease (see later), associated PH is an indication for transplant listing based on the most recent guidelines. In patients with PH associated with chronic lung disease, the decision between single and double lung transplantation is highly individualized, although both single and double lung transplantation have been shown to effectively reduce mean PA pressure in patients with chronic lung disease and there seems to be no difference in longterm survival.

Lung volume reduction surgery (LVRS) was initially considered to be a potentially useful option to limit RV dysfunction in obstructive lung disease, because of the theoretical benefits of minimizing thoracic hyperinflation. Whereas LVRS was shown to improve respiratory mechanics and increase PaO₂, there was no improvement in hemodynamic indices in patients undergoing LVRS compared with those treated medically. Therefore, despite theoretical benefits, no data support the routine referral for LVRS in patients with PH associated with chronic lung disease.

**CLINICAL OUTCOMES**

Whereas RV remodeling and hypertrophy are fairly common in chronic lung disease, RV failure is not. Despite this, the development of PH is uniformly associated with increased mortality in patients with chronic lung disease. In COPD, modest increases in mean PA pressure (>20 mm Hg) have been correlated with reduced survival. Mean PA pressure was shown to be highly predictive of longterm survival in COPD patients on LTOT, with only 36% of patients with PA pressure greater than 25 mm Hg surviving for 5 years compared with 62% of COPD patients with PA pressure less than 25 mm Hg. Similarly, the development of pulmonary hypertension has been associated with reduced survival in ILD. In patients with advanced IPF complicated by PH there was 1-year mortality of 28%, whereas in patients with advanced IPF without PH there was 1-year mortality of 5.5%. Modest increases in PA pressure are predictive of reduced longterm survival in IPF patients, as shown in Fig. 2. IPF patients with mean PA pressure greater than 17 mm Hg had a 5-year survival of only 16.7%, compared with IPF patients with mean PA pressure less than 17 mm Hg, who had 5-year survival of 62.2%. In sarcoidosis, PH is an independent predictor of mortality and the hazard ratio for death in patients with PH was estimated to be 10.4 when compared with patients without PH. In patients with SSc-associated interstitial lung disease complicated by PH, there was a five-fold increased risk of death when compared with SSc patients with PAH, despite notoriously poor survival in this disorder. Data regarding mortality

**Fig. 2.** Prognostic impact of mean pulmonary arterial pressure (mPAP) on survival in patients with idiopathic pulmonary fibrosis (IPF). Thin line represents IPF patients with normal mPAP (n = 37); thick line represents IPF patients with elevated mPAP (n = 24). (Adapted from 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(3):650–6; with permission.)
caused by PH in patients with sleep-disordered breathing are more challenging to interpret, primarily because of the frequent comorbidities in this group. Whereas the 1-, 3-, and 5-year survival estimates in OSA patients with mean PA pressure greater than 25 mm Hg (93%, 75%, and 43%, respectively) were reduced when compared with survival estimates in patients with OSA with normal PA pressures (100%, 90%, and 76%), only 31% of subjects with elevated mean PA pressure had normal pulmonary artery occlusion pressure.114

COMPLICATIONS AND CONCERNS

The primary complication associated with RV dysfunction in chronic lung disease is progression to RV failure. This is a rare complication in most circumstances but some clinical scenarios require special consideration. In COPD, acute exacerbations are associated with increased V/Q mismatch and reduced PaO2.115 It was noted that during acute exacerbations, some patients with COPD developed markedly increased RV end-diastolic pressures, potentially consistent with RV failure.116 In this study, changes in RV end-diastolic pressure were associated with the development of peripheral edema, CO2 retention, decreased arterial oxygen saturation, and increased mean PA pressure. RV contractility was reduced in a small cohort of COPD patients evaluated by right heart catheterization following the development of peripheral edema.117 There is a subgroup of patients with COPD who appear to be at risk for development of more severe PH despite stable lung disease. This group accounted for 1.1% of all patients with COPD undergoing hemodynamic evaluation in one large retrospective analysis,73 and has a unique clinical phenotype characterized by mild to moderate airflow obstruction, severely reduced D1CO, and severe hypoxemia. The incidence of RV failure in this subgroup is unknown. Patients with multiple chronic lung diseases, including overlap syndromes between COPD and OSA or ILD, may also be at increased risk for more severe RV dysfunction.

SUMMARY

Although the exact prevalence of RV dysfunction is unknown, sufficient evidence suggests that it is a common complication of chronic pulmonary disease. The pathophysiology is characterized by mildly increased PA pressures, RV hypertrophy, and preserved RV contractility and cardiac output. However, RV dysfunction can occasionally progress to RV failure during disease exacerbations or when multiple cardio-pulmonary comorbidities are present. Patients with severe pulmonary hypertension that is out of proportion to the underlying lung disease should be screened for these comorbidities. The mechanism of RV dysfunction is associated primarily with hypoxic pulmonary vasoconstriction, pulmonary vascular remodeling, and disruption of pulmonary vascular beds caused by the underlying lung disease. Therefore, current recommendations support the use of LTOT and pulmonary disease-specific treatments, although evidence supporting improvements in RV function is limited. Therapies designed specifically to alter pulmonary vascular tone are currently not recommended for PH associated with chronic lung disease, because there are limited efficacy data and multiple reports of worsening hypoxemia. Some patients with severe pulmonary hypertension, associated only with chronic lung disease and out of proportion to the underlying pulmonary disease, should be considered for enrollment in clinical trials of these or other agents. For selected patients with severe parenchymal lung disease complicated by PH and RV dysfunction, lung transplantation should be an early consideration.

REFERENCES


