Pulmonary Diseases and the Heart

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Abstract — The complex nature of interactions between the pulmonary and cardiovascular systems is becoming increasingly appreciated. Pulmonary vascular abnormalities are frequently present in patients with respiratory disorders, including chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, sarcoidosis, neuromuscular or chest wall disorders, and disorders of ventilatory control including sleep apnea syndromes and obesity hypoventilation syndrome. Pulmonary hypertension, classified as group III in the World Health Organization classification scheme for pulmonary hypertension, may result in severe right ventricular dysfunction caused by lung disease, also known as cor pulmonale. The development of cor pulmonale is generally associated with poorer prognosis and increased death. Systemic manifestations of lung disease, particularly obstructive disorders, are also particularly relevant because they are associated with increased cardiac death and impaired health status. This article will discuss the most common pulmonary diseases and disorders of ventilatory control that cause pulmonary vascular abnormalities and cor pulmonale, with particular concentration on how treatment of these diseases may affect the heart. In addition, the complex nature of cardiac and lung disease will also be explored, particularly with respect to the relationship between chronic obstructive pulmonary disease, systemic inflammation, atherosclerosis, and cardiovascular death, which is currently a very active focus of research. (Circulation. 2007;116:2992-3005.)

Key Words: pulmonary heart disease • pulmonary disease, chronic obstructive • hypertension, pulmonary • inflammation

Systemic manifestations have become increasingly recognized in lung diseases, particularly obstructive disorders.1 Cardiovascular involvement is particularly relevant because it is associated with impaired health status and worsened mortality. In the present targeted review we will discuss evolving data regarding pulmonary vascular abnormalities in the most common respiratory disorders, including chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, sarcoidosis, neuromuscular or chest wall disorders, and disorders of ventilatory control. We will also explore the relationship between COPD and systemic inflammation, atherosclerosis, and cardiovascular death.

Pulmonary Vascular Disease in Respiratory Illness

The classification of pulmonary hypertension (PH) has recently been revised, and PH associated with hypoxemic pulmonary disorders falls into World Health Organization group III.2 Cor pulmonale was defined by the World Health Organization in 1963 as “hypertrophy of the right ventricle (RV) resulting from diseases affecting the function and/or structure of the lungs, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart, as in congenital heart disease.”3 Since then the definition has come to encompass both right ventricular hypertrophy, dilation, or both secondary to PH caused by pulmonary disorders.4 Between 10% and 30% of heart failure admissions in the US are the result of cor pulmonale with the most common cause in the United States being COPD, in 1 study accounting for 84% of cases.5,6 Other lung diseases known to cause cor pulmonale include interstitial lung diseases, restrictive ventilatory defects caused by thoracic cage deformities or neuromuscular diseases that cause respiratory muscle weakness, and disorders of ventilatory control including sleep-disordered breathing and obesity hypoventilation syndrome (OHS).

PH in hypoxemic lung diseases is likely the result of multiple factors including pulmonary vasoconstriction caused by alveolar hypoxia,7 acidemia,7 hypercarbia,8 the distortion of pulmonary vessels by parenchymal changes, and increased cardiac output and blood viscosity from polycythemia secondary to hypoxia. This has been best conceptualized in COPD (Figure 1). The hypoxic pulmonary vasoconstrictor response is an important adaptive mechanism in human physiology, shunting blood away from hypoxic regions toward better-ventilated areas of the lung, thus improving ventilation-perfusion matching within the lung. Pulmonary vascular remodeling in response to hypoxia is also mediated by a number of other factors including nitric oxide,9 endothelin,10 serotonin, and hypoxia inducible factor-1. The role...
of inflammatory mediators has become increasingly accepted. Acidosis increases pulmonary vascular resistance (PVR) and acts synergistically with hypoxia. With the development of structural changes such as intimal proliferation and smooth muscle cell hypertrophy, sustained PH ensues.

The RV is a thin-walled, compliant, low-pressure chamber that pumps the same stroke volume as the left ventricle (LV) with about 25% of the stroke work because of the normally low resistance of the pulmonary vasculature. The right coronary artery provides the blood supply to the RV free wall in both systole and diastole. When chronically pressure-overloaded, the RV hypertrophies and dilates, which results in both systolic and diastolic dysfunction. RV ischemia may also result because the right coronary artery is unable to provide adequate flow to the hypertrophied RV, caused in part by the reduced right coronary artery to right ventricular cavity pressure gradient in both systole and diastole. RV dysfunction is one of the most important prognostic factors in idiopathic PH. In addition, hyperinflation seen in patients with obstructive lung disease may also decrease venous return, further reducing right ventricular filling. In restrictive lung disease, the inability of the thoracic cage to distend has also been postulated to impair cardiac filling.

The degree of LV dysfunction secondary to RV dysfunction has been an issue of debate. The RV and LV share the interventricular septum and the pericardial sack, both of which may allow 1 ventricle to influence the other. The limited ability of the pericardium to stretch means that a large change in the volume of the RV may limit the volume of the LV because of a leftward shift of the interventricular septum. The markedly negative swings in pleural pressure that occur in patients with lung disease may also contribute to increases in pulmonary artery pressures (PAP) and increases in venous return to the right heart. Subsequent RV dilation may cause the LV to become stiffer, thus theoretically increasing LV end-diastolic pressure, decreasing pulmonary venous return, and reducing LV stroke volume. LV afterload may also increase with the fall in pleural pressure during inspiration, which may increase LV end-diastolic volume and thus decrease LV ejection fraction. In a retrospective review of 434 patients with end-stage pulmonary disease including COPD, interstitial lung disease, and PH (primary and Eisenmenger’s syndrome), the prevalence of RV dysfunction (RV ejection fraction <45%) was 66%, with prevalence being greater in those with PH as opposed to airway or parenchymal lung disease. However, LV dysfunction (LV ejection fraction <45%) was present in only 6.4% of patients, being more common in patients with PH (19.6%) as opposed to those with parenchymal or airway disease (3.6%). Thus clinically, ventricular interdependence likely plays a greater role when PH is severe.

**Clinical Presentation**

PH in hypoxemic lung diseases is relatively common but generally mild to moderate in severity. Dyspnea is the most common symptom, but may not be helpful because dyspnea is so prevalent in this patient population. A change in dyspnea or the development of additional symptoms such as chest pain, light-headedness, syncope, and lower extremity edema may prompt further evaluation. Physical examination findings common in idiopathic PH such as a RV heave, loud pulmonic component to the second heart sound, tricuspid regurgitant murmur, and right-sided S4 may also be masked by the presence of parenchymal lung disease. Severe PH may also lead to ascites and peripheral edema. Some patients with severe COPD may develop peripheral edema in the absence of RV failure, the cause of which is not well understood but appears to occur more frequently in patient with hypercapnia, suggesting that an elevated partial pressure of carbon dioxide may be responsible for sodium retention. Hypoxemia itself may also lead to renal vasoconstriction, thus reducing urinary sodium excretion and also leading to edema.

Several ECG findings reflective of cor pulmonale have been reported, including rightward P-wave axis deviation, an S1S3 pattern, an S1Q3 pattern, evidence of RV hypertrophy, and right bundle-branch block. Low-voltage QRS has also been reported, more frequently seen in cor pulmonale associated with COPD than other pulmonary diseases. Unfortunately, ECG findings are insensitive for detection of PH. In a small series of COPD patients, only 33% of patients with elevated PVR had ECG signs of cor pulmonale. In a separate study of COPD patients, the presence of ECG abnormalities associated with cor pulmonale in addition to an elevated alveolar-arterial oxygen gradient (>48 mm Hg) during oxygen therapy was associated with a 1.8 greater risk of death. Thus ECG abnormalities suggestive of RV hypertrophy can be helpful if present, but if the clinical picture is still suggestive of cor pulmonale, further testing should be pursued.
The chest x-ray may demonstrate enlargement of the proximal pulmonary arteries and reduction in retrosternal air space. Although echocardiography is an invaluable tool in the evaluation of most forms of PH, its utility is more limited in patients with parenchymal lung disease because suboptimal images are more frequently encountered. In a recent study of 374 lung transplant candidates, Doppler echocardiography and right heart catheterization were performed within a 72-hour period. The correlation between pulmonary arterial pressures made by echocardiography versus catheterization can be seen in Figure 2. In almost half of cases patients were misclassified as having PH by echocardiography. The sensitivity, specificity, and positive and negative predictive values of RV systolic pressure estimation by echocardiography for the diagnosis of PH is outlined in Table 1. Overall sensitivity was 85% and specificity was 55%. Given that sensitivity is better than specificity, a normal echocardiogram can help exclude significant cor pulmonale, but an elevated estimated RV systolic pressure must be interpreted with caution.

Right heart catheterization is required to make a definitive diagnosis of PH. The hemodynamic definition includes a mean PAP ≥25 mm Hg with a wedge pressure (or LV end-diastolic pressure) ≤15 mm Hg and a calculated PVR ≥3 Wood Units. Pressures should be carefully measured at end expiration. The role of pulmonary venous hypertension, that is, elevated left-heart filling pressures caused most commonly by LV systolic or diastolic dysfunction, cannot be overlooked, requiring an accurate measurement of left-heart filling pressures via pulmonary artery occlusion pressure measurement. Frequently, patients with chronic lung disease have diastolic LV dysfunction and may have PH in the setting of an elevated pulmonary artery occlusion pressure. In these patients, more aggressive blood pressure control and diuresis should be initiated. The role of vasodilator testing has not been extensively studied in this population. In sarcoid-associated PH, a small series has suggested frequent vasoreactivity, whereas another group has not confirmed this; the clinical significance of this finding remains unclear. Patients with significant PH should also be evaluated for chronic thromboembolic disease because this is a potentially treatable form of PH. A higher prevalence of pulmonary emboli in COPD patients with an acute exacerbation and in idiopathic pulmonary fibrosis (IPF) patients has been suggested.

Surrogate markers for the presence of PH in advanced lung disease have been evaluated. Natriuretic peptides are produced and released by cardiac myocytes; B-type natriuretic peptide (BNP) is produced and released by both the atria and ventricles. The propeptide circulates and is cleaved into a biologically active fragment and the N-terminal pro-B-type natriuretic peptide (NT-proBNP). The NT-proBNP has a longer plasma half-life and considerably higher concentra-

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Table 1. Sensitivity, Specificity, and Positive and Negative Predictive Values of Doppler Echocardiography Findings for Diagnosis of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Patient Group/Finding</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sPAP</td>
<td>85 (73 to 93)</td>
<td>55 (45 to 64)</td>
<td>52 (41 to 62)</td>
<td>87 (76 to 94)</td>
</tr>
<tr>
<td>RV findings†</td>
<td>82 (73 to 89)</td>
<td>57 (51 to 62)</td>
<td>39 (32 to 46)</td>
<td>90 (85 to 94)</td>
</tr>
<tr>
<td>OLD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sPAP</td>
<td>76 (50 to 93)</td>
<td>65 (54 to 75)</td>
<td>32 (18 to 48)</td>
<td>93 (83 to 98)</td>
</tr>
<tr>
<td>RV findings</td>
<td>84 (67 to 95)</td>
<td>56 (49 to 62)</td>
<td>22 (15 to 30)</td>
<td>96 (91 to 99)</td>
</tr>
<tr>
<td>ILD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sPAP</td>
<td>85 (68 to 95)</td>
<td>17 (5 to 39)</td>
<td>60 (44 to 74)</td>
<td>44 (14 to 79)</td>
</tr>
<tr>
<td>RV findings</td>
<td>76 (61 to 87)</td>
<td>53 (40 to 67)</td>
<td>57 (43 to 69)</td>
<td>74 (58 to 86)</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value; sPAP, systolic pulmonary artery pressure; RV, right ventricular; OLD, obstructive lung disease; and ILD, interstitial lung disease.

*Defined as the total group of patients for whom the Doppler echocardiography finding could be ascertained (n = 166 patients for whom sPAP could be estimated and n = 372 patients for whom RV could be visualized).

†RV findings are defined as the presence of RV dilation, hypertrophy, or systolic dysfunction.

tions. Importantly, intraindividual coefficients of variation vary greatly. Levels tend to rise with advancing age, female gender, and renal dysfunction, and they decrease with increasing body mass index. BNP (level >33.3 pg/mL) has been suggested to be significantly elevated in patients with pulmonary fibrosis and PH. Sensitivity for moderate to severe PH was 100% and specificity was 89%. BNP has also been investigated in patients with COPD. A study that examined 38 patients with COPD, 20 with cor pulmonale, demonstrated a significant correlation between BNP and PAPs. Patients with cor pulmonale had significantly higher BNP levels than those without (73.9 pg/mL versus 21 pg/mL). In a separate study of 176 patients with chronic lung disease, elevated BNP level identified PH with a sensitivity of 85% and specificity of 88%; an increased BNP also was an independent risk factor for death. A recent study examined the value of BNP and NT-proBNP in outpatients diagnosed with COPD by their primary care physicians (spirometrically independent risk factor for death). A recent study examined the value of BNP and NT-proBNP in outpatients diagnosed with COPD by their primary care physicians (spirometrically confirmed in 59%). BNP and NT-proBNP exhibited a high negative predictive value for systolic heart failure, slightly lower for diastolic heart failure; no patient had PH given the mild nature of the underlying pulmonary dysfunction. Given the high sensitivity of BNP for moderate to severe PH, we recommend including a BNP measurement in the evaluation of suspected PH. The combined utility of BNP in conjunction with echocardiography in patients with lung disease for the diagnosis of PH is an area where more prospective investigation is required.

Determination of the cause of increased dyspnea in patients with chronic lung disease is another arena where BNP measurement may be useful. Baseline BNP measurements may be elevated in COPD patients as compared with those without, but are not as high as those with heart failure. Substudy analysis of patients with asthma or COPD included in the Breathing Not Properly study revealed that a BNP cutoff of 100 pg/mL exhibited a 93.1% sensitivity, 77.3% specificity, 51.9% positive predictive value, and 97.7% negative predictive value for the diagnosis of heart failure, which was identified in 20.9% of patients. If added to clinical judgment, 95.4% of the congestive heart failure (CHF) subjects would have been diagnosed correctly. In the Brain Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) trial, patients with acute dyspnea were considered unlikely to have CHF with a BNP <100 pg/mL and very likely to have CHF with a BNP >500 pg/mL. Patients with BNP levels between 100 and 500 pg/mL were treated based on best clinical judgment. In a substudy that examined patients with chronic pulmonary disease (62% with COPD, 12% with asthma), the primary discharge diagnosis was CHF in 39% of patients and acute exacerbation of COPD in 33%. This approach resulted in significant reductions in length of stay and treatment costs. These data suggest that in patients with COPD, a low BNP (<100 pg/mL) can be very helpful in ruling out significant heart failure, and a very high BNP (>500 pg/mL) can be helpful in ruling in heart failure. Values between 100 and 500 pg/mL must be interpreted with caution and in context of the entire clinical picture.

**Chronic Obstructive Pulmonary Disease**

COPD has been defined as a “disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible and frequently progressive due to an abnormal inflammatory response of the lung to noxious particles or gases.” The percentage of COPD patients who develop cor pulmonale has not been clearly defined. Available studies vary widely with respect to the populations studied and the methodology used to define PH. Some of this variability is likely a result of diagnostic modality (echocardiography versus right heart catheterization) and diagnostic criteria. Table 2 lists a wide range of available studies, highlighting this variability in prevalence rates. In general the magnitude of PH is modest, with severe resting PH being uncommon. Studies that used exercise challenge document a higher overall prevalence of PH. Several groups have described “disproportionate” PH in small numbers of COPD patients. In general, these patients seem to be characterized by less severe airflow obstruction but more severe hypoxemia and decreased diffusing capacity.

Longitudinal data addressing PH in COPD are infrequent. One group examined 131 COPD patients who underwent 2 right heart catheterizations a mean of 6.8 years apart. At initial evaluation no patient had resting PH, although 76 patients exhibited exercise-induced PH. At the second evaluation 25% of patients exhibited resting PH (the majority in those patients with exercise-induced changes at initial evaluation); the magnitude of PH was mild. When PH is present in COPD, numerous groups have documented that its presence significantly increases the risk for hospitalization and is associated with worsened survival. At initial evaluation no patient had resting PH, although 76 patients exhibited exercise-induced PH. At the second evaluation 25% of patients exhibited resting PH (the majority in those patients with exercise-induced changes at initial evaluation); the magnitude of PH was mild. When PH is present in COPD, numerous groups have documented that its presence significantly increases the risk for hospitalization and is associated with worsened survival.

Theoretically, any therapy for COPD that slows the loss of lung function should positively impact cor pulmonale. Of all COPD therapies, smoking cessation has the most significant clinical impact in slowing progression of disease, although there are no longitudinal data linking hemodynamic changes with smoking cessation.

**Oxygen Therapy**

Oxygen is the only therapy for COPD that has been convincingly shown to improve PH and cor pulmonale and is 1 of the few noninvasive therapies for COPD that improves mortality. Two sentinel prospective, controlled studies of long-term O2 in COPD, the British Medical Research Council Long-Term Domiciliary Oxygen Treatment Trial and the Nocturnal Oxygen Therapy Trial (NOTT), reported hemodynamic studies in small subsets of patients. In the British Medical Research Council trial, PVR increased to a greater extent in those not treated with O2 as opposed to those treated ≥15 hours/d with 2 L/d of O2. The NOTT investigators reported that both resting and exercise PVR were more sharply reduced in those using continuous O2. The reported changes in pulmonary hemodynamics, however, were small. Although the decreased PVR and increased stroke volume index were associated with reduced death, NOTT failed to demonstrate that supplemental O2 was responsible for either the hemodynamic changes or the survival difference. In
addition, the NOTT hemodynamic data were limited to longitudinal measurement performed only once after treatment, a time point that may have been too soon to document substantial O₂-induced changes in hemodynamic variables. Finally, the NOTT was also unable to predict the long-term hemodynamic effects of O₂ on the basis of patients' acute responses to O₂. Three subsequent, small studies examined the long-term effects of supplemental oxygen on the pulmonary circulation in COPD. Long-term O₂ administration does appear to be associated with modest decreases in PAPs. However, the interruption of daily oxygen is followed by an increase in PVR. These studies, however, were small and lacked fully characterized subjects and documentation of compliance with O₂. They leave unclear the effect of intermittent versus continuous use of supplemental O₂ on hemodynamics in chronic mild-moderate hypoxemic COPD.

Vasodilators
There are limited data regarding the role of vasodilators to ameliorate PH in COPD patients. One group examined the effects of sildenafil (50 mg intravenously once followed by 50 mg twice daily orally for 3 months) in 6 patients with severe COPD (forced expiratory volume in 1 second (FEV₁) 16% to 48% predicted). The intravenous dose decreased mean PAP, whereas 3 months of dosing led to decreases in mean PAP in 5.0% of patients who completed the study (30.2 mm Hg to 24.6 mm Hg). In contrast, in a separate study 48 weeks of losartan led to little beneficial result in 40 COPD patients with PH. Similarly, a single administration of nifedipine resulted in modest improvement in mean PAP without much change in PVR in 33 COPD patients. Importantly, in a series of 6 patients with PH secondary to COPD, nifedipine reduced PVR but decreased arterial PaO₂ as a result of alteration in V/Q matching.

Interstitial Lung Disease
Diffuse parenchymal lung diseases (DPLDs) have also been associated with cor pulmonale. DPLDs are a heterogeneous group of disorders with similar clinical, radiographic, and physiological manifestations. These disorders result in

### Table 2. Prevalence, Incidence, and Characteristics of Pulmonary Hypertension in Selected COPD Cohorts

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort Characteristics</th>
<th>Diagnostic Modality</th>
<th>N</th>
<th>FEV₁</th>
<th>PaO₂</th>
<th>Proportion With PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Himelman et al³⁷</td>
<td>Nonhypoxemia cohort</td>
<td>Echocardiography</td>
<td>33</td>
<td>1.0 L</td>
<td>70.9 mm Hg</td>
<td>75% with cor pulmonale</td>
</tr>
<tr>
<td>Oswald-Mammosser et al³⁸</td>
<td>Emphysema cohort</td>
<td>Right heart catheterization</td>
<td>84</td>
<td>0.85 L</td>
<td>52</td>
<td>65 of 84 (77%) patients with mPAP &gt;20</td>
</tr>
<tr>
<td>Bach et al³⁹</td>
<td>LRVs evaluation</td>
<td>Echocardiography</td>
<td>206/207*</td>
<td>27.3% pred</td>
<td>67.0 mm Hg</td>
<td>40.1%† Resting mPAP &gt;35 mm Hg</td>
</tr>
<tr>
<td>Chaouat et al⁴⁰</td>
<td>Chronic respiratory failure</td>
<td>Right heart catheterization</td>
<td>998</td>
<td>50%</td>
<td>46 mm Hg</td>
<td>40%† Resting mPAP &gt;40 mm Hg</td>
</tr>
<tr>
<td>Christensen et al⁴¹</td>
<td>General cohort</td>
<td>Right heart catheterization</td>
<td>17</td>
<td>35% pred</td>
<td>10.4 kPa</td>
<td>mPAP with exercise &gt;30 mm Hg</td>
</tr>
<tr>
<td>Scharf et al⁴²</td>
<td>Emphysema cohort evaluated for LRVs</td>
<td>Right heart catheterization</td>
<td>120</td>
<td>27.0% pred</td>
<td>65.9 mm Hg</td>
<td>Resting mPAP &gt;20 mm Hg in 90.8%; resting mPAP &gt;35 mm Hg in 5.0%</td>
</tr>
<tr>
<td>Døi et al⁴³</td>
<td>Emphysema cohort</td>
<td>Right heart catheterization</td>
<td>53</td>
<td>39.8% pred</td>
<td>70.9 mm Hg</td>
<td>mPAP &gt;2.7 mPa in 43%</td>
</tr>
<tr>
<td>Kessler et al⁴⁴</td>
<td>Mild to moderate hypoxemia cohort</td>
<td>Right heart catheterization</td>
<td>131</td>
<td>44.6% pred</td>
<td>67.0 mm Hg</td>
<td>Resting mPAP &gt;20 mm Hg in 58%; mean of 6.8 years later, resting mPAP &gt;20 mm Hg in 25%</td>
</tr>
<tr>
<td>Thabut et al⁴⁵</td>
<td>LRVs or LT evaluation</td>
<td>Right heart catheterization</td>
<td>215</td>
<td>18.5% pred LT; 27.0% pred LRVS</td>
<td>55.4 mm Hg in LT; 66.2 mm Hg in LRVS</td>
<td>Resting mPAP &gt;25 mm Hg in 50.2%; resting mPAP 35 to 45 mm Hg in 9.8%; resting mPAP &gt;45 mm Hg in 3.7%</td>
</tr>
</tbody>
</table>

PaO₂ indicates partial pressure of oxygen in arterial blood: Oswald reference, 52 mm Hg and mPAP >20 mm Hg and mPAP >30 mm Hg; pred, predicted; mPAP, mean pulmonary artery pressure; LRVs, lung volume reduction surgery; and LT, lung transplantation.

* Adequate image for chamber assessment.
† Abnormal right heart.
changes in the alveolar walls, perialveolar tissue, and supporting structures. Occupational and environmental exposures can cause DPLD, although frequently the cause is unknown.

The prevalence of PH in patients with DPLDs varies greatly.62.66.67 Table 3 presents recent studies of IPF. The prevalence has varied from as low as 8% to as high as 84%. As in COPD, diagnostic modality and criteria contribute to the variability between studies, with prevalence tending to be higher where echocardiography was used. The recent work of Hamada and colleagues sheds the most valuable insight. This group performed a right heart catheterization on 61 IPF patients at initial evaluation.64 At the time of initial evaluation only 8.1% of patients exhibited PH; importantly the presence of elevated PAPs was associated with impaired survival. Studies of patients undergoing evaluation for lung transplantation have consistently demonstrated a higher prevalence (Table 3).63.65 An autopsy evaluation study of the RV in sarcoidosis; obstruction of vessel walls by granulomas or perivascular fibrosis has been described.76

Antiinflammatory Therapy
Antiinflammatory agents have been commonly used in treating DPLDs. Very little data that address the effect of

Table 3. Prevalence, Incidence, and Clinical Characteristics of Pulmonary Hypertension in Selected ILD Cohorts

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort Characteristics</th>
<th>Diagnostic Modality</th>
<th>N</th>
<th>FVC, % pred</th>
<th>DLCO, % pred</th>
<th>Proportion With PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadrous et al62</td>
<td>Random sample</td>
<td>Echocardiography</td>
<td>88</td>
<td>63.5 to 72.3*</td>
<td>38.8 to 53.9*</td>
<td>Resting estimated sPAP &gt;35 mm Hg in 84%; resting estimated sPAP &gt;50 mm Hg in 30.7%</td>
</tr>
<tr>
<td>Lettieri et al63</td>
<td>Evaluated for LT</td>
<td>Right heart catheterization</td>
<td>79</td>
<td>49.3†</td>
<td>31.1†</td>
<td>Resting mPAP &gt;25 mm Hg in 31.6%</td>
</tr>
<tr>
<td>Hamada et al64</td>
<td>Prospective random cohort</td>
<td>Right heart catheterization</td>
<td>70</td>
<td>76</td>
<td>45</td>
<td>Resting mPAP &gt;25 mm Hg in 8.1%</td>
</tr>
<tr>
<td>Nathan et al65</td>
<td>Mostly evaluated for LT</td>
<td>Right heart catheterization</td>
<td>118</td>
<td>54.6†</td>
<td>33.2†</td>
<td>Resting mPAP &gt;25 mm Hg in 40.7%</td>
</tr>
<tr>
<td>Sarcoidealosis</td>
<td>Sulica et al66</td>
<td>Random sample</td>
<td>106</td>
<td>54†</td>
<td>39†</td>
<td>Resting estimated sPAP ≥40 mm Hg in 50.9%</td>
</tr>
<tr>
<td>Shorr et al67</td>
<td>Listed for LT</td>
<td>Right heart catheterization</td>
<td>363</td>
<td>46.4†</td>
<td>NA</td>
<td>Resting mPAP &gt;25 mm Hg in 73.8%; resting mPAP ≥40 mm Hg in 36.1%</td>
</tr>
<tr>
<td>Handa et al68</td>
<td>Prospective study of random sample</td>
<td>Echocardiography</td>
<td>212</td>
<td>90†</td>
<td>81†</td>
<td>Resting estimated sPAP ≥40 mm Hg in 5.7%</td>
</tr>
</tbody>
</table>

pred indicates predicted; FVC, forced vital capacity.
*Lower values in those with lower estimated sPAP.
†In those with PH.
Antinflammatory therapy on pulmonary vascular disease in DPLDs are available. Theoretically, agents that slow progression of fibrotic lung disease should also slow progression of pulmonary vascular abnormalities. Several groups have examined the effect of corticosteroid treatment on PH in patients with sarcoidosis. In a retrospective case series of 10 patients with sarcoidosis and PH who were treated with either 0.5 to 1 mg/kg per d oral prednisone in addition to methotrexate or cyclophosphamide, 31.8% of the patients had PH in the absence of pulmonary fibrosis.26 Three of the 5 cases with PH and no pulmonary fibrosis experienced substantial and sustained improvement, which suggests that primary vasculopathy may play a significant role in PH in sarcoidosis that may be responsive to antinflammatory therapies, but more research is needed prior to recommending routine antinflammatory therapy to patients with sarcoidosis and PH in the absence of pulmonary fibrosis.

**Oxygen Therapy**

Several studies have shown that oxygen desaturation is associated with poorer prognosis in IPF.77–79 Scant data exist addressing the role of oxygen therapy in DPLD patients. A Cochrane review identified only 1 randomized controlled trial that failed to show a mortality difference between the oxygen-treated and control group.80

**Advanced Therapies**

Very limited data exist regarding novel vasodilators in DPLD patients. Such therapies can theoretically worsen ventilation-perfusion mismatch and thereby increase hypoxemia. One group documented that both sildenafil and intravenous epoprostenol decreased PVR in 16 patients with PH and pulmonary fibrosis; sildenafil improved oxygenation whereas epoprostenol decreased arterial oxygenation.81 An open-label study of sildenafil in 14 IPF patients suggested an increased 6-min walk distance (49 meters), although 3 of the subjects could not finish the 3-month trial.82 A retrospective study of 8 patients with sarcoidosis-associated PH noted hemodynamic improvement during an acute vasodilator trial in 6/7 patients; 5 of the 6 responding patients continued chronic therapy with an average clinical improvement of 1 to 2 New York Heart Association/World Health Organization classes.83 Such therapies should be considered investigational in DPLD patients.

**Neuromuscular and Chest Wall Diseases**

Restrictive lung disease may result from neuromuscular diseases such as muscular dystrophy, poliomyelitis, myasthenia gravis, or other factors affecting chest wall expansion such as severe obesity and kyphoscoliosis. This is a diverse category of diseases, and the exact prevalence of cor pulmonale in each is not known with certainty. Respiratory muscle weakness and abnormalities in lung and chest wall compliance lead to reductions in vital capacity and in extreme cases may result in hypoxemia, hypercapnia, and acidosis. For patients with advanced disease, mechanical ventilation may ultimately be initiated. Before the development of true respiratory failure, however, it is believed that the risk for cor pulmonale is increased by a high prevalence of sleep-disordered breathing, specifically nocturnal hypoventilation, in this patient population.84 Nocturnal hypoventilation may develop before daytime respiratory failure is apparent. Thus the clinician must be vigilant for patient complaints of daytime sleepiness, fatigue and lethargy, morning headaches or impaired concentration that may signal sleep disruption and nocturnal hypoventilation. Respiratory muscle weakness contributes to REM-associated nocturnal hypoventilation and oxygen desaturation, and the severity of diaphragmatic dysfunction has been shown to correlate with the extent of REM-associated nocturnal oxygen desaturation.85 Nocturnal oxygen desaturation is less frequent without concomitant daytime hypercapnia. In patients with neuromuscular disease and restrictive lung disease, PAP increases with alveolar hypoventilation during sleep, and a correlation between the severity of sleep-disordered breathing and cor pulmonale has been made in several studies.86–88

**Therapy**

Relief of hypoxemia has been demonstrated to improve hemodynamics. In a study of 8 patients with severe Duchenne muscular dystrophy, right heart catheterization documented severe PH in 5 patients. Correction of hypoxemia relieved the PH.89 Oxygen therapy alone, however, does not correct the hypoxemia that causes hypoxemia and may actually worsen preexisting hypoxemia. Frequently, therapy with nocturnal ventilation, either via tracheostomy and intermittent positive pressure ventilation or via noninvasive ventilation, may alleviate the symptoms of respiratory failure and correct hypercapnia, hypoxemia, and acidosis. Patients should be considered for nocturnal ventilation if daytime PaCO2 exceeds or equals 45 mm Hg or if nocturnal hypoventilation with sustained oxygen desaturation and symptoms of sleep disturbance are present.90 Noninvasive positive pressure ventilation has been documented in patients with neuromuscular and chest wall diseases to improve nocturnal alveolar hypoventilation, dyspnea, and symptoms associated with sleep-disordered breathing. In chest wall diseases, noninvasive positive pressure ventilation but not oxygen improves dyspnea and symptoms associated with sleep disturbance.91 Patients treated with noninvasive positive pressure ventilation demonstrate improved nocturnal and daytime oxygen saturations as compared with the group treated with oxygen alone. Several case reports have suggested that cor pulmonale can be at least partially reversed, and PH improved with the initiation of noninvasive positive pressure ventilation in patients with restrictive lung disease, although no prospective studies have specifically addressed this issue. Invasive ventilation with tracheostomy has also been demonstrated to RV failure in patients with restrictive lung disease.92

**Disorders of Ventilatory Control**

This category of disorders includes sleep-disordered breathing and obesity hypoventilation syndrome. Sleep-disordered breathing encompasses several disorders characterized by abnormalities of respiratory pattern or ventilation during sleep. Obstructive sleep apnea (OSA) is the most common of these disorders with an estimated prevalence of 9.1% of men and 4% of women.93 Diagnosis should be suspected in
patients that have excessive daytime somnolence, obesity, hypertension, neck circumference >16 inches in a woman or >17 inches in a man, history of habitual snoring, or observed reports of nocturnal choking or gasping. Polysomnography remains the gold-standard diagnostic test for OSA.

OHS is characterized by hypersomnolence, dyspnea, and resting hypoxemia, leading to PH in severe cases. Arterial blood gas testing is required to confirm daytime hypercapnia and typically demonstrates hypoxemia and a compensated respiratory acidosis. Laboratory testing may also reveal polycythemia caused by chronic hypoxemia. Whereas most patients with OSA do not have OHS, most patients with OHS have OSA. These patients frequently demonstrate both OSA and daytime hypventilation, likely secondary to a combination of increased work of breathing and a decreased respiratory drive.

Although OSA is frequently cited as a cause of secondary PH and chronic daytime hypoxemia clearly leads to PH and cor pulmonale, the data that link intermittent nocturnal hypoxemia and PH are less clear. OSA alone may cause mild PH, but coexisting daytime hypoxia is typically required for sustained severe PH and cor pulmonale. In 1 observational study of 50 patients with OSA, patients with cor pulmonale had more severe nocturnal and daytime hypoxemia; nocturnal hypoxemia in the absence of daytime hypoxemia was not associated with cor pulmonale, suggesting that prolonged hypoxemia was necessary to cause cor pulmonale. An observational study of 27 patients with OSA reported that 41% had mild PH but none had severe PH or cor pulmonale. A study of 90 patients with frequent respiratory disturbances during sleep noted that patients with more frequent respiratory disturbances had a small but statistically significant increase in RV wall thickness but no differences in right atrial size, ventricular size, or ventricular function. Therefore it is difficult to ascribe severe PH and cor pulmonale to OSA alone.

In addition to PH, OSA has also been associated with the development of hypertension, most clearly demonstrated in the Wisconsin Sleep Cohort study, which linked the presence of moderate OSA with a 3-fold increased risk of incident hypertension. Three randomized controlled trials have also shown that continuous positive airway pressure (CPAP) therapy for OSA resulted in small but significant reductions in systemic hypertension (1.3 to 5.3 mm Hg). OSA has been associated with increased risk for arrhythmias (including sinus bradycardia, atrioventricular block, atrial fibrillation, and ventricular ectopy) and stroke. It has been hypothesized that the hypoxemia, hypercapnia, sympathetic activation, and blood pressure alterations that accompany OSA may also result in myocardial ischemia. The Sleep Heart Health Study did report OSA as an independent risk factor for the development of coronary artery disease. ST segment depressions are also more frequent in those with severe OSA and CPAP therapy has been shown to reduce the duration of ST segment depressions in individuals with OSA. As with COPD, C-reactive protein (CRP) levels have also been demonstrated to be elevated in patients with OSA suggesting systemic inflammation may also be involved in the pathogenesis of atherosclerosis.

**Therapy**

For patients with OSA and OHS, loss of 10 kg has been shown to significantly reduce daytime Paco2 and facilitate treatment, although weight loss frequently is not curative. The mainstay of therapy for OSA is CPAP. Very few studies, however, have actually examined the effect of CPAP on PAP or cor pulmonale. The largest treatment effects have been noted in patients with elevated PAP prior to therapy. Theoretically, positive pressure ventilation may also have direct positive effects on cardiac function by decreasing preload, decreasing afterload, and improving LV performance. In a study of CPAP versus supplemental O2 in patients with chronic heart failure and central sleep apnea, patients who received CPAP for 12 weeks had significant improvements in LV ejection fraction.

 Surgical therapy for OSA includes uvulopalatopharyngoplasty, which may help select patients, and tracheostomy may be indicated in severe disease. A series of 19 patients undergoing uvulopalatopharyngoplasty for OSA demonstrated a statistically significant increase in RV ejection fraction (45% to 50%, P=0.007). Tracheostomy can be considered both in treatment refractory OSA and OHS.

**Atherosclerosis and COPD**

Beyond cor pulmonale and PH, other cardiac abnormalities may be present in patients with COPD. Impaired heart rate recovery after exercise has been reported in patients with abnormal spirometry, the cause of which is not clear but may be related to altered autonomic tone associated with pulmonary dysfunction. The prevalence of atrial fibrillation, atherosclerosis, and CHF is also high among patients with COPD. Although some of the association between COPD and atherosclerosis may be the result of common risk factors such as tobacco use, epidemiological evidence suggests that impaired lung function is a risk factor for increased cardiovascular death independent of tobacco use. Analysis of participants in the National Health and Nutrition Examination Survey revealed that patients in the lowest FEV1 quintile had the highest risk of cardiovascular death, with a relative risk of 3.36 after adjusting for Framingham risk factors such as smoking status, blood pressure, body mass index, and diabetes. Furthermore, in a meta-analysis of studies linking reduced FEV1 to increased cardiovascular death adjusted for smoking status, the relative risk was 1.77 (95% CI, 1.46 to 1.97).

COPD, like atherosclerosis, is a disease of systemic inflammation and as such may hasten the progression of atherosclerotic disease and contribute to the higher rate of cardiovascular-related morbidity and death in COPD. Recent evidence suggests that inflammation is noted in all stages of COPD; numerous systemic inflammatory markers, some of which are found in cardiovascular disease (IL-6, IL-1β, TNF-α, MMP-9, MCP-1, and high-sensitivity CRP), are elevated in COPD. Patients with more frequent or severe exacerbations exhibit particularly robust endogenous proinflammatory responses. A meta-analysis of 14 studies recently confirmed the association between reduced lung function in COPD and systemic inflammation (eg, CRP, fibrinogen, IL-6). A summary of studies examining CRP levels in COPD is presented in Table 4. It is notable that elevated CRP...
<table>
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<tr>
<th>Reference</th>
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<td>Dentener et al119</td>
<td>Stable COPD, median FEV₁, 34% predicted</td>
<td>55</td>
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<td>Dahl et al125</td>
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<td>Pinto-Plata et al128</td>
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levels correlate with the presence of COPD, the presence of exacerbations, severity of lung function, and risk for hospitalization and death. Importantly, these correlations have therapeutic implications. Sin et al noted that withdrawal of inhaled steroids in 27 of 41 COPD patients with moderate-to-severe disease led to a mean 71% increase in serum CRP levels. Subsequent therapy with inhaled or oral steroids resulted in 50% and 63% reductions in CRP (P = 0.039), respectively, whereas those receiving placebo had 8% reductions (NS). These data suggest that an inflammatory process within the COPD lung has systemic correlates and that antiinflammatory therapy can modulate this systemic inflammation. Another group suggested that COPD patients with PH exhibited higher serum CRP and TNF-α levels. Thus systemic inflammation may also play a role in the development of PH in COPD.

Multiple clinical trials confirm that ischemic heart disease is a leading but underrecognized cause of death in COPD. In fact, COPD patients are at 2 to 3 times greater risk for cardiovascular death, accounting for almost 50% of all COPD deaths. An inverse relationship exists between FEV1 and the presence of atherosclerosis, or cardiovascular death. FEV1 is an independent predictor of cardiovascular death. Patients with an FEV1 < 2.0 L have a 5-fold increase in cardiovascular death risk compared with patients with an FEV1 > 2.0 L (relative risk: 5.03, 95% CI, 3.07 to 8.22). The magnitude of death attributed to reduced FEV1 in COPD is comparable to the magnitude of cardiovascular death attributable to hypercholesterolemia. Furthermore, FEV1 decline is associated with increased cardiovascular death.

Additional support for a causal relationship between COPD and an increased risk for cardiovascular disease and death is provided by the Lung Health Study. More than 5887 patients with mild to moderate airways obstruction were followed, with 25% dying from a cardiovascular cause. Among patients hospitalized at least once over the 5-year period, cardiovascular causes accounted for 42% of the first hospitalizations and 48% of the second hospitalizations. The Tucson Epidemiologic Study of Airways Obstructive Disease reported cardiovascular as the primary cause of death in ~50% of obstructive lung disease cases.

Because 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce cardiovascular risk beyond their lipid-lowering effects and these non–lipid-reducing actions of statins appear to be antiinflammatory in nature, it has been hypothesized that statin therapy could have significant clinical impact in patients with COPD. A recent retrospective analysis of a large Canadian database suggests that statin therapy in COPD patients with a low known risk for cardiovascular disease can have a profound effect on reducing the likelihood of COPD hospitalization and cardiovascular morbidity and death (Figure 3). A second, retrospective cohort study similarly suggested improved survival in COPD patients treated with statins (hazard ratio, 0.57; 95% CI, 0.38 to 0.87).

**Conclusion**

The present review highlights the complex relationship between pulmonary and cardiac disease. The presence of cardiac disease in patients with chronic lung disease portends a poor prognosis. PH and cor pulmonale are perhaps the best described cardiac consequences of lung disease, and treatment should be directed at the underlying disorder. Patients who present with severe PH should be evaluated for another disease process that is responsible for high PAP before it is attributed to the underlying lung disease. Although the link between sleep-disturbed breathing and cor pulmonale is less clear, the degree of hypoxemia likely correlates with the development of PH. Sleep-disturbed breathing should certainly be sought out and treated in patients with PH and cor pulmonale and in those who have clear risk factors, including patients with neuromuscular disease, chest wall disease, and obesity. Although multiple therapies are currently available for the treatment of World Health Organization group I PH, none of these have been studied systematically for either efficacy or safety in the population with lung disease. Cardiovascular death in patients with COPD is high, and mounting evidence suggests that systemic inflammation, particularly in COPD, may also contribute to cardiovascular disease. Whether therapies such as statins should be initiated in COPD patients without known cardiovascular disease will need to be the area of future investigation. Clearly, this is an area of profound potential impact that requires active investigation.

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References


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