Since the discovery of hypoxic pulmonary vasoconstriction six decades ago, respiratory physiologists and clinicians have been fascinated by pulmonary hypertension in the setting of chronic lung disease (Table 1). The term “cor pulmonale” indicates an alteration in right ventricular structure and function due to parenchymal lung disease. The Third World Symposium on Pulmonary Arterial Hypertension grouped these conditions under the heading “Pulmonary Hypertension Associated with Lung Diseases and/or Hypoxemia.” While alveolar hypoxia likely plays an important role, it has become increasingly clear that these conditions do not simply represent chronic hypoxic pulmonary hypertension. Despite the widespread familiarity with cor pulmonale, its clinical importance remains poorly characterized and likely underestimated. This article will provide an overview of the most common respiratory diseases associated with pulmonary hypertension and recommendations for the diagnostic evaluation.

**Chronic Obstructive Pulmonary Disease**

The exact prevalence of pulmonary hypertension in chronic obstructive pulmonary disease (COPD) is unclear. In very advanced disease (GOLD stage IV: FEV₁ <30% predicted or <50% and associated with chronic hypoxemia and/or hypercapnia), the prevalence may be as high as 66%. On average, pulmonary hypertension is mild in severity (mPAP 25 to 35 mm Hg) with preserved right ventricular function (Table 2).

**Vascular Remodeling**

Although alveolar hypoxia with resultant pulmonary vasoconstriction is important, the lack of complete reversibility in response to oxygen or nitric oxide inhalation indicates that acute hypoxic vasoconstriction is not the sole determinant of pulmonary hypertension in these patients. Chronic hypoxia induces neomuscularization of previously nonmuscularized pulmonary arterioles and medial hypertrophy of small muscular pulmonary arteries. A prominent feature of the vascular remodeling of COPD–related pulmonary hypertension is intimal thickening by longitudinally oriented smooth muscle cells with abundant extracellular deposition of collagen and elastin (intimal fibroelastosis). These changes have also been described in mild, normoxemic COPD patients without pulmonary hypertension and in asymptomatic smokers. Small vessel thrombi and/or emboli may also occur. Medial hypertrophy, on the other hand, is prominent only in the setting of established pulmonary hypertension. These findings suggest that intimal changes are not sufficient to produce pulmonary hypertension at rest, but could contribute to luminal narrowing as medial hypertrophy develops with progressive disease.

**Mechanisms for Vascular Remodeling**

Pulmonary arterial rings of COPD patients have impaired endothelial-dependent vasodilatation and expression of endo-

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**Table 1. Respiratory Diseases Causing Pulmonary Hypertension.**

- Obstructive lung disease
  - Chronic obstructive pulmonary disease (COPD)
  - Cystic fibrosis/bronchiectasis
  - Obliterative bronchiolitis
- Interstitial lung disease
  - Connective tissue disease related
  - Idiopathic interstitial pneumonias
    - Idiopathic pulmonary fibrosis
    - Nonspecific interstitial pneumonia
    - Others
- Arterial hypoventilation
  - Obesity-hypoventilation syndrome
  - Thoracic cage disorders
    - Kyphoscoliosis
  - Neuromuscular disease
- Sleep-disordered breathing
  - Obstructive sleep apnea (OSA)
  - Central sleep apnea
  - Overlap syndrome (COPD in combination with OSA)
- Chronic exposure to high altitude
- Developmental abnormalities/neonatal lung disease
clinical nitric oxide synthase (eNOS) is reduced in advanced disease as well as in asymptomatic smokers. Exhaled nitric oxide has also been shown to be reduced in COPD patients with pulmonary hypertension. There may also be a link between certain polymorphisms in the eNOS or ACE genes and pulmonary hypertension in COPD. Excretion of prostacyclin metabolites is decreased in COPD patients with pulmonary hypertension. Pulmonary vascular expression of endothelin-1 is increased in established pulmonary hypertension, but not in early disease. Recent studies suggest an important role for serotonin (5-HT) and its transporter (5-HTT) in the vascular smooth muscle hyperplasia of pulmonary hypertension. The 5-HTT LL genotype, which is linked with greater 5-HTT expression, was associated with significantly higher pulmonary artery pressure in COPD patients compared with the other polymorphisms.

A correlation between small airway inflammation and vascular remodeling has also been demonstrated. Increased CD8 lymphocytes were detected in the adventitia of small muscular arteries of mild COPD patients and smokers and correlated with intimal thickening and endothelial dysfunction. These findings raise the possibility that smoking can have direct effects on the pulmonary vasculature.

Clinical Impact of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

Despite the relatively modest nature of pulmonary hypertension in COPD, its presence clearly has an adverse impact on survival. Oswald-Mammosser et al reported a 5-year survival of 36% among severe COPD patients whose mPAP exceeded 25 mm Hg compared with 62% in those without pulmonary hypertension. Pulmonary function and blood gas variables were not predictive of survival. Although several studies have demonstrated increased mortality in COPD patients with pulmonary hypertension, it remains unclear whether the pulmonary hypertension is a cause of death or simply a marker of underlying disease severity.

Interstitial Lung Diseases

Connective Tissue Diseases

Interstitial lung disease is the most common pulmonary manifestation of scleroderma, or systemic sclerosis. Patients with systemic sclerosis can develop pulmonary arterial hypertension as a “primary” vascular process or pulmonary hypertension secondary to more extensive pulmonary fibrosis. In either case, the presence of pulmonary hypertension is a poor prognostic sign in these patients. An abrupt worsening in symptoms, hypoxemia, and DL CO in a patient with pulmonary fibrosis should arouse suspicion for pulmonary hypertension. A recent review of 619 patients by the Johns Hopkins Scleroderma Center demonstrated that the prevalence of pulmonary hypertension increased with worsening restrictive ventilatory defect. Importantly, long-term survival of patients with combined pulmonary hypertension and interstitial lung disease was similar to that in patients with isolated pulmonary hypertension and significantly worse than that in isolated interstitial lung disease.

Idiopathic Pulmonary Fibrosis

Limited available data suggest that both the prevalence and the severity of pulmonary hypertension in idiopathic pulmonary fibrosis are greater compared with COPD. In a study of lung transplant candidates, 59% of 106 with idiopathic pulmonary fibrosis had a pulmonary artery systolic pressure ≥45 mm Hg compared with only 18% of 253 COPD patients. While exercise-induced elevation in pulmonary artery pressure is common in COPD, it appears to be a more consistent finding in idiopathic pulmonary fibrosis and is not associated with a rise in pulmonary artery wedge pressure. Moreover, a sizable proportion of unselected idiopathic pulmonary fibrosis patients have moderate to severe pulmonary hypertension. Leuchte et al reported that 6 of 28 consecutive patients had an mPAP >35 mm Hg.

Pulmonary hypertension is clearly a poor prognostic factor in idiopathic pulmonary fibrosis. Bishop and Cross demonstrated that mPAP was the single most important predictor of mortality. Patients with an mPAP ≥30 mm Hg had a 5-year mortality of 82% compared with 35% and 26% among those with an mPAP between 20 and 29 mm Hg and <20 mm Hg, respectively. In another large study, the presence of signs of pulmonary hypertension on a plain chest radiograph had equal power in predicting mortality as a total lung capacity <50% of predicted or a maximal exercise PaO 2 <35 mm Hg.

The mechanisms of pulmonary hypertension in idiopathic pulmonary fibrosis may differ from those in COPD, reflecting more profound structural vascular remodeling. Pathologically, the vasculopathy of idiopathic pulmonary fibrosis differs from COPD in that the intimal lesion can progress to acellular fibrosis with luminal obliteration (Figure 1). A weak correlation with PaO 2 suggests a relatively minor role for hypoxia. Alterations in vasoactive mediators similar to what is seen in

<table>
<thead>
<tr>
<th>Table 2. Pulmonary Hemodynamics in 178 Hypoxemic COPD Patients.*</th>
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<td><strong>Room Air</strong></td>
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<td><strong>Right atrial pressure (mm Hg)</strong></td>
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<td><strong>Mean pulmonary artery pressure (mm Hg)</strong></td>
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<td><strong>Pulmonary artery wedge pressure (mm Hg)</strong></td>
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<td><strong>Cardiac index (L/min-m²)</strong></td>
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<td><strong>Rest</strong></td>
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<td><strong>Exercise</strong></td>
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<tr>
<td><strong>Pulmonary vascular resistance (dyne<em>s</em>cm⁻⁵)</strong></td>
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<tr>
<td><strong>Rest</strong></td>
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<tr>
<td><strong>Exercise</strong></td>
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</tbody>
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*Adapted from Timms RM, Khaja FU, Williams GW. Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. Ann Intern Med. 1985;102(1):29-36. Mean values with standard deviations are in parentheses. All patients had room air PaO₂ ≤55 mm Hg or ≤59 in conjunction with signs of right heart failure or polycythemia. P <.01 for all comparisons between rest and exercise while breathing room air. 1P <.01 compared with room air.
idiopathic pulmonary arterial hypertension, such as increased expression and circulating levels of endothelin-1²⁰,²¹ have also been demonstrated.

Sarcoidosis, Langerhans Cell Histiocytosis, and Lymphangioleiomyomatosis

While these diseases are considered interstitial lung diseases, they have been grouped separately¹ because of the apparent greater frequency and severity of pulmonary hypertension observed in these groups. Active vascular granulomatous inflammation and/or healed lesions are a universal finding in sarcoidosis.²² The extent of vascular involvement may be related to the degree of parenchymal disease, corresponding to the clinical observation that overt pulmonary hypertension is uncommon with stage 0-II disease.

On the other hand, sarcoidosis with significant vascular involvement has also been noted. In a large review of lung transplant candidates, Shorr and coauthors reported mPAP of 34 mm Hg among 289 sarcoid patients, significantly higher than the average mPAP (25 mm Hg) in their idiopathic pulmonary fibrosis patients.²³ Patients who died awaiting lung transplantation had an average mPAP of 41 mm Hg compared with 32 mm Hg among survivors.

A prominent proliferative, inflammatory vasculopathy with occasional Langerhans cells involving both arteries and veins is well described in Langerhans cell histiocytosis. Farrouch et al reported on 21 consecutive patients referred for lung transplantation, all with very severe pulmonary hypertension (mPAP 59 mm Hg).²⁴ Two had clinical manifestations of venular obstruction. Although advanced parenchymal disease was present, there was no relationship between pulmonary function and mPAP. Moreover, vascular remodeling was observed in regions unaffected by parenchymal lesions and progressed on serial lung biopsies independent of the interstitial and bronchiolar processes.

Sleep-Disordered Breathing

The relationship between obstructive sleep apnea and pulmonary hypertension has recently been reviewed.²⁵ The prevalence has been estimated to be approximately 20% with mostly borderline to mild pulmonary hypertension (mPAP <25 to 30 mm Hg). Increasing body-mass index and more severe nocturnal desaturation are linked to pulmonary hypertension in obstructive sleep apnea, whereas the apnea-hypopnea index is not. Most studies have failed to exclude patients with associated COPD (overlap syndrome) and the obesity-hypoventilation syndrome, two commonly associated conditions that can independently cause pulmonary hypertension and augment the propensity for obstructive sleep apnea to contribute to pulmonary hypertension.

The Strasbourg group recently reviewed their experience with these subsets.²⁶ Among 181 patients with pure severe obstructive sleep apnea (apnea-hypopnea index: 73/h) without comorbid conditions, mPAP was 15 ± 5 mm Hg and only 9% had mPAP ≥20. In contrast, 27 obesity-hypoventilation syndrome patients, defined as having a body mass index >30 and PaCO₂ >45 mm Hg, had mPAP of 23 ± 10 mm Hg and 59% had mPAP ≥20. Overlap patients had intermediate values. It thus appears that abnormal daytime lung function and gas exchange are required to develop significant pulmonary hypertension in the setting of sleep disordered breathing.

Diagnostic Evaluation of Pulmonary Hypertension in Lung Disease

Traditionally, clinicians have not aggressively pursued the diagnosis of pulmonary hypertension in chronic respiratory diseases, probably because of the lack of effective therapy. With the increasing array of drugs for pulmonary arterial hypertension, there is the potential of treating some of these patients. Existing data on pulmonary hypertension therapies in this setting are discussed in an accompanying article. A proper diagnostic evaluation for pulmonary hypertension is important to: 1) identify other treatable causes for pulmonary hypertension (eg, left heart disease, chronic thromboembolic disease); 2) help delineate the basis for symptoms; 3) provide prognostic information that may guide decisions such as lung transplantation; and 4) guide the aggressiveness of certain interventions such as oxygen supplementation and nocturnal positive pressure ventilation.

Routine Clinical Assessments

While difficult to assess, dyspnea and fatigue seemingly out of proportion to the degree of respiratory impairment should raise the suspicion of superimposed pulmonary hypertension. Physical signs may often be obscured by hyperinflation or obesity. Enlargement of the central pulmonary arteries on chest radiography increases the likelihood that pulmonary hypertension is present, but is not sufficiently accurate to make a confident diagnosis. With right ventricular enlargement, the heart takes on a globular appearance and encroaches on the retrosternal airspace on the lateral view. If severe hyperinflation is present, this may be difficult to appreciate.
Using computed tomography, a main pulmonary artery diameter ≥29 mm was a good predictor for pulmonary hypertension in parenchymal lung disease, with sensitivity and specificity of 84% and 75%, respectively. The combination of main pulmonary artery enlargement and a segmental artery/bronchus ratio of >1 in 3 lobes increased the specificity to 100%. Electrocardiographic signs of cor pulmonale are also useful, but have low sensitivity.

Correlations between the degree of obstructive or restrictive ventilatory defect and pulmonary hypertension are only modest. The DL CO, which is mainly determined by the pulmonary capillary blood volume, is often severely reduced when pulmonary hypertension complicates lung disease. Among emphysema patients considered for lung volume reduction, DL CO was the only pulmonary function variable that correlated with pulmonary vascular resistance. The DL CO corrected for alveolar volume (DLVA) appears to be a more sensitive indicator of pulmonary vascular involvement in idiopathic pulmonary fibrosis.

Severe hypoxemia should also raise the suspicion of pulmonary hypertension. When daytime hypoxemia and moderate to severe hypercapnia (PaCO2 >50 mm Hg) are present, some degree of pulmonary hypertension is expected.

**Cardiopulmonary Exercise Testing**

When resting pulmonary hemodynamics are normal, moderate exercise during right heart catheterization or echocardiography may uncover exercise-induced pulmonary hypertension. However, normal values for exercise pulmonary artery pressure are not well defined and changes in left heart filling pressures are difficult to gauge. Moreover, the clinical significance of isolated exercise-induced pulmonary hypertension is not clear.

Oxygen desaturation with exercise frequently accompanies pulmonary hypertension associated with lung disease. Formal cardiopulmonary exercise testing, on the other hand, may be useful in distinguishing a ventilatory from a cardiovascular limitation to exercise.

**Brain Natriuretic Peptide**

The plasma brain natriuretic peptide level appears to be an emerging tool in detecting pulmonary hypertension in chronic lung disease. In one study of pulmonary fibrosis patients, plasma level was 242 ± 66 pg/mL among 11 patients with moderate to severe pulmonary hypertension (mPAP >35 mm Hg) compared to 24 ± 6 in the other 28 subjects. Using a cut-off value of 33 (normal <18), the sensitivity and specificity for moderate to severe pulmonary hypertension was 100% and 89%, respectively. Brain natriuretic peptide level was strongly correlated with pulmonary vascular resistance.

**Sleep Study**

A polysomnogram should be obtained in patients with any clinical suggestion of sleep disordered breathing. Screening for obstructive sleep apnea with portable devices may be feasible, but has not been studied in patients with comorbidities. While the importance of isolated nocturnal desaturation in the pathogenesis of pulmonary hypertension is controversial, it seems prudent to consider overnight oximetry in patients with established pulmonary hypertension and mild daytime hypoxemia (PaO2 of 60 to 70 mm Hg). Exercise-induced desaturation cannot be used to predict nocturnal desaturation.

**Right Heart Catheterization**

Given the still limited utility of noninvasive techniques, right heart catheterization is required to confirm a diagnosis and determine severity of pulmonary hypertension. Whether or not...
to perform right heart catheterization on a patient with lung-respiratory disease is really dictated by clinical judgment. If one feels that the pulmonary hypertension is potentially treatable with specific medications, performance of catheterization seems reasonable. Although acute vasodilator testing is recommended in patients with idiopathic pulmonary artery hypertension, there is no indication for such a study in patients with pulmonary hypertension and lung disease.

When Is Pulmonary Hypertension “Out of Proportion” to Degree of Lung Disease?

Given the availability of effective medications for pulmonary artery hypertension, this is a clinically important question. The pulmonary vascular response can vary widely among individuals exposed to similar insults. From a clinical practice perspective, the question being posed is: Is the pulmonary hypertension completely the result of the respiratory condition and, therefore, treatment should be focused on the latter or is there to some extent an independent pulmonary vascular process that can be targeted by specific pulmonary hypertension therapies? Although no hard answers exist, some general guidelines can be made based on the reported severity of pulmonary hypertension in the setting of various conditions. Pulmonary hypertension can be classified as follows: mild (mPAP 25 to 34 mm Hg); moderate (mPAP 35 to 44 mm Hg); or severe (mPAP ≥45 mm Hg or any degree of pulmonary hypertension accompanied by evidence of right ventricular failure).

Moderate to severe pulmonary hypertension is rare in pure obstructive sleep apnea. Pulmonary hypertension complicating COPD is not expected unless the FEV₁ is less than 50% of predicted and is typically mild to moderate. However, in the presence of profound hypercapnia, severe pulmonary hypertension is not uncommon. For these diseases, treating the underlying hypoxemia and sleep apnea should significantly improve the pulmonary hypertension. In interstitial lung disease, on the other hand, moderate to severe pulmonary hypertension usually occurs in the setting of advanced parenchymal disease: total lung capacity or forced vital capacity <50% of predicted or with extensive radiographic changes. For sarcoidosis, Langerhans cell histiocytosis, and lymphangioleiomyomatosis, where a prominent obstructive component may exist, an FEV₁ <50% predicted typically accompanies significant pulmonary hypertension. Advanced pulmonary hypertension in the presence of underlying lung disease of less severity raises the possibility of a primary vasculopathy.

Summary

Pulmonary hypertension is a common, yet often overlooked complication of chronic respiratory diseases. While often mild and overshadowed by the underlying condition, pulmonary hypertension and right ventricular dysfunction can dominate the clinical picture, particularly in certain interstitial lung diseases. A diagnosis of pulmonary hypertension has important prognostic implications and helps delineate the basis for symptoms. Importantly, newer therapies for pulmonary arterial hypertension may prove to be useful in this setting. Further research is needed to improve the diagnostic accuracy of noninvasive testing and understand the pathogenesis of pulmonary hypertension associated with lung disease.

References


Profile (continued from page 4)

practice. His landmark text, Respiratory Physiology: the Essentials, is used worldwide, including centers in Moscow and Beijing, and has been translated into 13 languages. The Zones of West—a three-zone model of blood flow in the lung—is part of a paradigm used throughout the world. It originated almost 50 years ago when Dr West and his colleagues encountered radioactive oxygen, which has a very short half life. “We were able to look at blood flow in the lung for the first time and we found a very uneven distribution from the top to the bottom of the lung. I spent several years figuring out the reason for that and that’s where the three-zone model comes from.”

Considering how his world has changed, Dr West reflects: “It is sad to see how junior faculty in the intensive care units sometimes founder when confronted with basic questions about pulmonary gas exchange or mechanics. This is because the fashion in research over the last 20 years has very much been in molecular biology. I’m not saying that is a bad thing because it is terribly exciting. But, as a result, the interests of young physicians in pulmonary medicine have moved away from pulmonary gas exchange and pulmonary mechanisms. In fact, regrettably, many of the young people are not as well informed in those areas as they should be. And those areas are terribly important in the ICU, where the immediate problems are not molecular but have to do with maintaining adequate gas exchange and ventilating the lung in an appropriate way.

“It’s a bit of an irony that we have a whole generation of young pulmonary physicians, but some of them tend to be rather weak in what I regard as the fundamentals of respiratory physiology.”