Pulmonary hypertension occurs commonly in cardiopulmonary disease. In 1998, a new clinical classification was proposed that divided pulmonary hypertension into 5 categories on the basis of the presumed underlying etiology of the pulmonary vascular disease1 (Table 1). Although it was never intended that this classification be used as a guideline to determine appropriate therapy, somewhat surprisingly, the regulatory authorities decided that all medications that were clinically tested and approved for patients with idiopathic pulmonary arterial hypertension (PAH) and patients with pulmonary hypertension associated with connective tissue disease be applied to all category 1 patients.2 The wisdom of this can be debated at a later date. However, it has left clinicians somewhat confused about the utilization of therapies to treat patients who fall outside of category 1 pulmonary hypertension, often referred to as secondary pulmonary hypertension.

There are 3 classes of approved therapies for PAH, all of which are considered to be pulmonary vasodilators: endothelin receptor blockers, phosphodiesterase-5 inhibitors, and prostacyclins.3 Their clinical efficacy has been based on a short-term improvement in exercise tolerance, as measured by a 6-minute walk test. In all of the clinical trials, an improvement in walk was apparent within the first 4 weeks of use, allowing a judgment about efficacy to be made quickly.4 Hemodynamically, their effects are modest, but they tend to raise cardiac output with little effect on pulmonary artery pressure. This has important implications when they are considered for unapproved use. We review the distinctive features of these causes of pulmonary hypertension and the data on the evidence that supports or refutes the use of these therapies in non–category 1 pulmonary hypertension.

**Category 2: Pulmonary Venous Hypertension**

Patients with pulmonary venous hypertension have elevated pulmonary venous pressure (as reflected in the pulmonary capillary wedge pressure), most frequently as a consequence of either mitral valve disease5 or left ventricular (LV) diastolic dysfunction.6 Although mitral stenosis was the most common cause of this entity decades ago, LV diastolic dysfunction or obstruction at the level of the mitral valve, (ie, pulmonary veno-occlusive disease), the characteristic of pulmonary venous hypertension include dyspnea with effort and eventually right ventricular (RV) failure with edema, similar to category 1 PAH. However, important and distinctive symptoms are orthopnea and paroxysmal nocturnal dyspnea, which are not features of PAH.13

Clinical tests will often reveal findings that suggest that the patient likely has pulmonary venous hypertension and not PAH (Table 2). The ECG may show LV hypertrophy rather than RV hypertrophy. The chest x-ray will often show pulmonary vascular congestion, pleural effusions, and, on occasion, pulmonary edema. High-resolution chest computed tomography can be helpful because it will often reveal
Table 1. Current Clinical Classification of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>PAH</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td>Familial</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension associated with:</td>
<td></td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td></td>
</tr>
<tr>
<td>Congenital systemic-to-pulmonary shunts</td>
<td></td>
</tr>
<tr>
<td>Portal hypertension</td>
<td></td>
</tr>
<tr>
<td>Drugs/toxins</td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td></td>
</tr>
<tr>
<td>Other (Gaucher’s, hereditary hemorrhagic telangiectasia, hemoglobinopathies, splenectomy)</td>
<td></td>
</tr>
<tr>
<td>Associated with significant venous or capillary involvement</td>
<td></td>
</tr>
<tr>
<td>Pulmonary veno-occlusive disease</td>
<td></td>
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<tr>
<td>Pulmonary capillary hemangiomatosis</td>
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<tr>
<td>Persistent pulmonary hypertension of the newborn</td>
<td></td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Pulmonary venous hypertension</td>
</tr>
<tr>
<td>Category 2:</td>
<td>Pulmonary venous hypertension associated with disorders of the respiratory system and/or hypoxemia</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Pulmonary hypertension associated with chronic thrombotic and/or embolic disease</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Pulmonary hypertension due to chronic thrombotic and/or embolic disease</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>Pulmonary hypertension due to miscellaneous disorders directly affecting the pulmonary vasculature, eg, sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)</td>
</tr>
</tbody>
</table>

ground-glass opacities and a mosaic perfusion pattern consistent with chronic pulmonary edema.

Essential in the evaluation of these patients is an echocardiogram, which readily allows the assessment of LV systolic function. It has been emphasized that the differentiation between systolic and diastolic dysfunction cannot be made on the basis of the history, physical examination, or chest x-ray. Pulmonary hypertension occurring in the setting of a reduced LV ejection fraction has been well described and appears to be one of the most powerful predictors of prognosis for patients with LV failure. The echocardiogram will also detect any significant underlying mitral or aortic valve disease. Doppler echocardiography is widely used to assess diastolic dysfunction in patients with both normal and reduced LV systolic function. However, because pulmonary hypertension itself produces diastolic filling abnormalities in the LV, Doppler echocardiography cannot be relied on to distinguish between category 1 and category 2 pulmonary hypertension.

Demonstration of an elevated pulmonary capillary wedge pressure at cardiac catheterization should secure the diagnosis of pulmonary venous hypertension. However, this determination is often imprecisely made because it is frequently difficult to get an accurate wedge pressure. Obtaining a blood sample for determination of oxygen saturation can be helpful in confirming that the catheter is in the wedged position. We have found that measurement of LV end-diastolic pressure (LVEDP) at the time of initial diagnosis is very helpful in confirming the wedge pressure measurement. In patients with severe RV failure, the effect of pericardial constraint and transmission of elevated RV filling pressure across the intraventricular septum may also be a factor. Some patients can have a markedly augmented “a” wave that can raise the LVEDP above the pulmonary capillary wedge pressure. An accurate assessment of LVEDP or pulmonary capillary wedge pressure can only be made at end expiration; using a digitally derived mean pulmonary capillary wedge pressure will generally yield erroneous information and often a misclassification of the patient as having normal filling pressures (Figure 2).

Two hemodynamic profiles have been described that are common in these patients. Some patients will have an elevation in pulmonary arterial pressure with only a minimal increase in the transpulmonary gradient (mean pulmonary arterial pressure–pulmonary capillary wedge pressure), as a reflection of the passive increase in pulmonary arterial pressure necessary to overcome the increased downstream resistance. Indeed, a preserved right ventricle must generate high systolic pressures to ensure adequate forward blood flow in these patients, and thus moderate degrees of pulmonary hypertension are not only characteristic but also favorable. However, a subset of these patients will have reactive pulmonary vasoconstriction, resulting in marked elevations in pulmonary arterial pressure beyond that which is necessary to maintain cardiac output. These patients are frequently distinguished by a marked elevation in pulmonary arterial diastolic pressure (Figure 3B). This has been studied extensively in patients with mitral stenosis and is less well characterized in patients with LV diastolic dysfunction. It is believed that these patients have a permissive genotype that, when exposed to high pulmonary venous resistance, develops reactive pulmonary hypertension with more severe arterial changes, including neointima formation, than the other subgroup.

A normal LVEDP at rest may, however, still be present in patients with LV diastolic dysfunction. When this occurs in the setting of reactive pulmonary hypertension, it is very difficult to know whether these patients have PAH or pulmonary venous hypertension. Using exercise, a vasodilator challenge, or an inotropic challenge at the time of diagnostic cardiac catheterization to increase the cardiac output may be helpful. If a significant increase in cardiac output is unaccompanied by an increase in pulmonary capillary wedge pressure, the patient more likely has PAH. On the other hand, if the increase in cardiac output is accompanied by an increase in pulmonary capillary wedge pressure, the patient likely has pulmonary venous hypertension. Interestingly, experimental studies indicate that an elevation in mean pulmonary arterial pressure may actually precede an elevation in pulmonary venous pressure. Thus, there may be no definitive way to identify pulmonary venous hypertension hemodynamically in some patients.

Treatment of these patients remains uncertain. Lessons learned from treating patients with mitral stenosis can be instructive. Patients with mitral stenosis who present with pulmonary edema will respond to the use of diuretics as a temporizing measure before the definitive therapy of mitral
valve repair or replacement. Several clinical studies have shown that removing the mitral valve gradient, either surgically or percutaneously, will result in an immediate fall in the pulmonary artery pressure.29–32 The magnitude of the fall, however, can be quite variable, with some patients achieving normal hemodynamics within 24 hours, and others taking many months to improve. The magnitude and rate of improvement may be related to the severity of the vascular disease dictated by both the duration of the pulmonary hypertension and genetic factors that either induce more severe vascular disease or impede regeneration and remodeling after removal of the mitral valve obstruction. It is likely that these same issues are relevant to pulmonary hypertension in patients with LV diastolic dysfunction.

A review of the management of LV systolic failure in patients with coexisting pulmonary hypertension is beyond the scope of this article. However, a few important points are worth mentioning. Regarding the approved treatments for category I pulmonary hypertension, bosentan has been demonstrated to be ineffective in patients with systolic heart failure,33 and epoprostenol was associated with increased mortality in patients with systolic heart failure.34 In contrast, patients with systolic heart failure and elevated pulmonary capillary wedge pressures tolerate the acute administration of sildenafil with a trend toward beneficial hemodynamic changes.35 Sildenafil has also been shown to be associated with improvement in measures of exercise performance when added to existing therapy in patients with systolic heart failure and pulmonary hypertension.36

Chronic pulmonary vasodilator therapy has not been successful in patients with mitral stenosis and is unlikely to be beneficial in patients whose pulmonary hypertension is a result of LV diastolic dysfunction. Because the major hemodynamic effect of these therapies is to raise cardiac output, it will predictably cause a worsening of pulmonary edema if the pulmonary venous obstruction is not being relieved. There are multiple reports of rapid deterioration and death when pulmonary vasodilators are used in the presence of pulmonary venous hypertension.37–39

There are no randomized clinical trials of pulmonary vasodilator therapy for patients with pulmonary venous hypertension associated with normal LV systolic function, and no treatment has yet been shown to favorably affect patients with pulmonary hypertension associated with LV diastolic heart failure. Our approach to treating these patients has been to use medical measures to lower LV filling pressures (such as nitrates, diuretics, and aggressive treatment of systemic hypertension). When successful, we have found that the pulmonary arterial pressure will also fall, and the cardiac output will increase. Given the expense of the approved treatment with pulmonary vasodilators and the potential for clinical deterioration, we believe that these treatments should only be considered in the setting of a supervised clinical trial.

Category 3: Patients With Pulmonary Hypertension Associated With Lung Disease

Pulmonary hypertension occurs in patients with lung disease. However, because it would be inappropriate to characterize all cardiac disease associated with pulmonary hypertension as similar, it would be equally inappropriate to characterize all lung diseases associated with pulmonary hypertension as
similar. The most commonly encountered lung disease, chronic obstructive pulmonary disease (COPD), has quite different clinical manifestations than interstitial lung disease (ILD). In both COPD and ILD, there are changes in the distal pulmonary arterial vessels related to hypoxia similar to those observed in experimental animals and in high-altitude dwellers, as well as changes due to the loss of lung parenchyma. Hypoxia induces muscularization of distal vessels and medial hypertrophy of more proximal arteries as well as a loss of vessels, which is compounded by a loss of lung parenchyma in the setting of lung disease. Neither neointima formation nor the development of plexiform lesions is observed. However, in patients with mild COPD in association with smoking, severe fibroproliferative neointimal formation can be observed (Figure 4).

Clinically, patients with COPD will present with dyspnea and signs of right heart failure, usually in the setting of marked hypoxemia. Pulmonary function tests and chest computed tomographic imaging are helpful in making a diagnosis in these patients. At cardiac catheterization, the level of the pulmonary hypertension typically is relatively mild. Indeed, the mean pulmonary arterial pressure seen in these patients is usually lower than the mean pulmonary arterial pressure obtained in patients with PAH who respond favorably to pulmonary vasodilator therapy. The fact that these patients are clinically failing may indicate that it is not the severity of the pulmonary hypertension but the degree of hypoxemia that is determining their clinical symptomatology. When RV failure occurs at this level of pulmonary hypertension, it is probable that the RV in these patients is adversely affected by the hypoxemia and behaves more like an ischemic RV than a pressure-loaded RV. Pulmonary hypertension in COPD patients can also be affected by additional factors, including acidemia, hypercarbia, compression of pulmonary vessels by high lung volume, loss of small vessels in the vascular bed of regions of emphysema and lung destruction, and increased cardiac output and blood viscosity from polycythemia secondary to hypoxia.

Although relatively mild, the level of the PAH is predictive of prognosis in patients with COPD. Nonetheless, there has never been a clinical trial showing a sustained beneficial effect of any pulmonary vasodilator in these patients. Worsening ventilation-perfusion mismatch from vasodilators has been demonstrated with short-term use and is justification for why these medications are not used. The only effective treatment for patients with COPD and pulmonary hypertension has been supplemental oxygen, with several studies showing an improvement in morbidity and mortality.

Clinicians also need to monitor the level of hemoglobin in these patients. Patients with hypoxemia should have reactive polycythemia as a basic biological mechanism to compensate for their cardiopulmonary disease. A hemoglobin level in the low-normal range, although well tolerated in patients with polycythemia as a basic biological mechanism to compensate for their cardiopulmonary disease, may not be tolerated in patients with hypoxemia and pulmonary hypertension.

There is a subset of patients with COPD who develop severe PAH (mean pulmonary arterial pressure >45 mm Hg). Their clinical characteristics have been described. These patients have a distinctive pattern of cardiopulmonary abnormalities with mild to moderate airway obstruction, severe hypoxemia, hypocapnia, and a very low diffusing capacity for carbon monoxide. These observations suggest that a different biological mechanism results in changes in the pulmonary vascular bed in susceptible patients and that severe pulmonary hypertension occurs in the presence of lung disease rather than as a result of the lung disease. For example, a genetic predisposition to pulmonary hypertension in COPD patients as a result of a 5-HTT polymorphism has been described, which may predispose to more severe pulmonary hypertension in hypoxemic patients. These patients have a hemodynamic profile more typical of PAH with a dramatic increase in pulmonary arterial pressure,
normal pulmonary capillary wedge pressures, and markedly elevated pulmonary vascular resistance. There are no data regarding whether pulmonary vasodilators have any clinical benefit in this subset of patients.

ILD can also be associated with pulmonary hypertension. The majority of these patients will have an underlying connective tissue disease. Patients without diagnostic findings of a connective tissue disease are considered to have idiopathic pulmonary fibrosis. Patients with connective tissue disease (eg, scleroderma) represent an additional diagnostic challenge. Approximately 20% of those who have pulmonary fibrosis will have pulmonary hypertension, and ~20% of those without pulmonary fibrosis will also have pulmonary hypertension. This makes it often uncertain if the pulmonary hypertension is due to the lung disease, pulmonary vascular disease, or both. Most series show that a marked reduction in diffusing capacity for carbon monoxide is a consistent feature of the patients with connective tissue diseases who have pulmonary hypertension, but it does not correlate with the degree of pulmonary fibrosis.

The hemodynamic profile of patients with ILD (without scleroderma) and pulmonary hypertension is quite distinct from that of patients with idiopathic PAH. It is rare for the mean pulmonary arterial pressure ever to be >40 mm Hg in these patients, whereas it is rare for the mean pulmonary arterial pressure ever to be <40 mm Hg in patients with idiopathic PAH. Consequently, the combination of an abnormality consistent with ILD on the chest computed tomographic scan and mild pulmonary hypertension should point to the diagnosis of pulmonary hypertension associated with ILD and not idiopathic PAH.

Most therapies for ILD have been directed toward halting progression or inducing regression of the interstitial disease process with immunosuppressive and anti-inflammatory agents. Overall, the results of these trials have been disappointing, which makes the treatment of any associated pulmonary hypertension an attractive therapeutic target. However, although pulmonary vasodilator therapy has been available for decades, there are no randomized clinical trials showing benefit of these agents in ILD. One rationale for their use has been to reduce the effects of chronic hypoxic vasoconstriction. In hypoxic rabbits, it has been demonstrated that sildenafil can prevent the development of RV hypertrophy, and iloprost was able to prevent the development of PAH. One clinical study compared the acute effects of inhaled nitric oxide, intravenous epoprostenol, and oral sildenafil in 16 patients with pulmonary fibrosis in which improved gas exchange was noted with the oral sildenafil but not the intravenous prostacyclin. Recent results of a randomized clinical trial with bosentan showed no effect on the primary end point, the 6-minute walk test. Given their potential to cause worsening gas exchange, we strongly caution against their anecdotal use in any patient until more definitive data support their chronic use. To date, lung transplantation is the only intervention proven to improve survival.

**Category 4: Chronic Thromboembolic Pulmonary Hypertension**

Chronic thromboembolic pulmonary hypertension (CTEPH) is a very distinctive disorder that has been well characterized. Although the physiological trigger (procoagulant state, inadequate thrombolytic system, antecedent deep vein throm-
bosis) can be quite variable, these patients characteristically present similar to those with idiopathic PAH. They have a slowly progressive onset of dyspnea with effort and ultimately develop signs and symptoms of right heart failure. Hypoxemia is very common. A perfusion lung scan is always abnormal, although the perfusion scan will often underestimate the severity of the underlying thromboembolic disease. Spiral computed tomographic scanning is the favored imaging modality to determine the presence, severity, and proximal extent of thromboembolic disease and is essential in

Figure 3. Simultaneous pulmonary arterial and LV pressures. A, Patient with LV diastolic dysfunction. In this patient, the LVEDP is elevated, and the pulmonary arterial diastolic pressure equals the LVEDP. The increase in pulmonary arterial pressure (PAP) is directly related to the elevated LV filling pressure. B, In contrast, the simultaneous pulmonary arterial and LV pressures are shown in another patient with LV diastolic dysfunction. In this patient, there is a substantial gradient between the pulmonary arterial diastolic pressure, which is 35 mm Hg, and the LVEDP, which is 20 mm Hg. In this situation, it is believed that changes in the pulmonary arteriolar bed occur from reactive pulmonary vasoconstriction, which contributes further to the severity of the pulmonary hypertension.
determining whether the patients would be surgical candidates for pulmonary thromboendarterectomy.

The pathology of CTEPH has features that usually can distinguish it from idiopathic PAH (Figure 5). The lesions are frequently more variable, i.e., there are arterial pathways that appear relatively unaffected by vascular disease and others that typically show recanalized vascular thromboses. However, the involvement of distal microvessels, particularly when the thromboses have occurred in subsegmental arteries, often indicates a worse prognosis. In these cases, the pathology may more closely resemble that of IPAH with associated plexiform lesions.70,71

Hemodynamically, these patients are indistinguishable from patients with category 1 PAH. However, because there is no way for the clinician to know whether the vessel that is utilized to obtain the wedge pressure tracing has distal thrombus, we recommend direct measurement of LVEDP at the time of diagnosis if there is any doubt. Interestingly, some patients will have a reactive component to their pulmonary hypertension believed to be a response to the increase pulmonary resistance created by the thromboembolic disease. It has been suggested that pulmonary vasoconstriction is occurring in the vasculature that is uninvolved with pulmonary thromboemboli. One clinical dilemma involves the patient with a documented solitary pulmonary embolism who develops pulmonary hypertension. Whether this represents coincidence, a cause-and-effect phenomenon, or a subset of genetically susceptible individuals may be impossible to resolve.

The definitive therapy of these patients is pulmonary thromboendarterectomy.72 In specialized centers, these patients can have a dramatic improvement in their symptoms, hemodynamics, and survival, and this is the treatment of choice. However, some patients will have extensive disease that is either inoperable or only partially amenable to surgical removal. The use of pulmonary vasodilators has been tested in open-label acute and short-term studies with some success.73-74 One study tested sildenafil over 6 months in 12 patients who were deemed inoperable and found a modest reduction in pulmonary arterial pressure that was associated with a 54-m increase in the 6-minute walk.75 Another trial used bosentan in 16 patients who were inoperable and showed a 92-m improvement in the 6-minute walk without hemodynamic monitoring.76 Because there have never been any prospective randomized trials of vasodilators in CTEPH, it remains unknown whether these changes will translate into a clinically meaningful and sustained improvement in the patients. Nonetheless, in patients with inoperable CTEPH, a clinical trial of pulmonary vasodilator therapy may be warranted, with the goal of improving the patient’s symptomatology and quality of life.

Category 5: Miscellaneous Causes

This category includes uncommon causes of pulmonary hypertension such as sarcoidosis, schistosomiasis, histiocytosis X, and lymphangiomatosis. The pathology between these entities is quite diverse, and their clinical presentations are highly variable. There have never been controlled trials of pulmonary vasodilator therapy, and thus there is no way to know their potential efficacy. Open-label trials have demonstrated favorable effects of intravenous epoprostenol in patients with sarcoidosis and severe pulmonary hypertension.77,78 However, given the lack of established benefit of these drugs for other secondary forms of pulmonary hypertension, we urge caution before attempting to use them in these patients.

Because the diagnosis of pulmonary hypertension is being made more frequently in patients with coexisting cardiac and lung diseases, the following guidelines may be helpful:

Figure 4. Histological stains of serial sections of a pulmonary muscular artery from a patient with COPD. a, Orcein stain; b, Masson’s trichrome stain; c, Alcian blue stain. Observe the abundant amount of elastin (a) and collagen (b) within the intimal layer, with a scarce proportion of proteoglycans (c). Internal scale bar = 100 μm. Observe the abundant amount of elastin (a) and collagen (b) within the intimal layer, with a scarce proportion of proteoglycans (c). Internal scale bar = 100 μm. Reprinted from Santos et al.80
In distinction from category 1 pulmonary hypertension, in which the treatment is focused on lowering the pulmonary arterial pressure, in non–category 1 pulmonary hypertension, the treatment should focus on treating the underlying disease.

The use of conventional therapies (diuretics, oxygen) should be tried initially to correct related clinical problems. Exercise testing may be helpful to uncover exercise-induced hypoxemia, which may benefit from treatment.

The acute testing of short-acting pulmonary vasodilators with hemodynamic guidance is recommended to evaluate the potential for beneficial or adverse effects before pulmonary vasodilators are considered as chronic therapy:

- inhaled nitric oxide (20 to 40 ppm).
- intravenous adenosine (50 to 200 μg/kg per minute).
- intravenous epoprostenol (2 to 6 ng/kg per minute).

Patients who respond favorably to pulmonary vasodilators should manifest unequivocal improvements within 4 to 6 weeks:

- symptoms related to the pulmonary hypertension should improve by 1 functional class.
- echocardiography should show a reduction in RV enlargement.
- exercise testing should demonstrate substantial increases (>20%) that correlate with the patient’s symptoms.
- catheterization should document an important reduction in pulmonary arterial pressure and pulmonary vascular resistance (>20%).
- Patients who fail to improve or who demonstrate worsening clinical findings (tachycardia, hypoxemia, hypotension, or worsening edema) should have the pulmonary vasodilator therapy promptly discontinued.

In conclusion, pulmonary hypertension is a common clinical feature of cardiac and pulmonary diseases. Making a secure diagnosis can be clinically challenging, and at times it can be impossible to distinguish patients with coexisting PAH. In all series, the development of pulmonary hypertension portends a worse prognosis. However, the use of pulmonary vasodilators as a chronic therapy remains largely unproven.

Disclosures

None.

References


Key words: heart failure • hypertension • pulmonary • pulmonary heart disease
Diagnosis and Treatment of Secondary (Non–Category 1) Pulmonary Hypertension
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