Evaluation and Management of the Patient with Pulmonary Arterial Hypertension

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Increased pressure in the pulmonary circulation, or *pulmonary hypertension*, is a common disorder that may complicate various cardiopulmonary conditions, including severe obstructive airways disease and left ventricular dysfunction. An increase in pulmonary arterial pressure that is not due to coexistent cardiopulmonary disease, known as *pulmonary arterial hypertension*, may occur in the absence of a demonstrable cause (idiopathic or familial); as a complication of systemic conditions, such as connective tissue disease, HIV infection, or chronic liver disease; or as a result of the use of fenfluramine anorexigens, amphetamines, or cocaine. The development of disease-specific therapies for pulmonary arterial hypertension over the past decade underscores the importance of diagnosing pulmonary hypertension early in the course of the condition and implementing a treatment strategy that is based on the condition's cause and severity. In this review, the authors present approaches to the diagnosis and management of pulmonary arterial hypertension, using a hypothetical case to highlight the key management points.

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Until recently, management of pulmonary arterial hypertension (PAH) was generally ineffective in alleviating symptoms or improving survival. However, the past decade has witnessed remarkable advances in our understanding of the pathogenesis of PAH, advances that have led to the development of disease-specific treatments. Despite these achievements, PAH remains a challenging condition to diagnose and manage. This article reviews recent developments in the diagnosis and management of PAH in the context of a typical case, illustrating the importance of collaboration between the internist and the specialist in patient care.

A 33-year-old woman presented to her primary care physician with a 6-month history of gradually progressive exertional dyspnea. She had lightheadedness and near-syncope while climbing steps. She was mildly obese but had otherwise previously been in good health. Her vital signs were normal, her lungs were clear, and cardiac examination showed a slightly prominent second heart sound and a systolic murmur over the left-heart border. An initial diagnosis of exercise-induced asthma was made, and use of an inhaled bronchodilator was prescribed.

The patient's symptoms did not diminish. A chest radiograph showed mild cardiomegaly and a slightly prominent main pulmonary artery. Pulmonary function tests showed only a mild reduction in the diffusing capacity for carbon monoxide, and an electrocardiogram showed right-axis deviation and possible right ventricular hypertrophy. On the basis of these results, echocardiography was done, and the echocardiogram showed right ventricular hypertrophy, right atrial enlargement, flattening of the interventricular septum, and moderate tricuspid regurgitation with an estimated pulmonary artery systolic pressure of 60 mm Hg. Serologic test results did not suggest connective tissue disease. A ventilation–perfusion lung scan was normal. Overnight oximetry showed mild nocturnal oxygen desaturation, and a formal sleep study excluded sleep apnea syndrome. The patient was referred to a regional center

What Is Pulmonary Hypertension, and When Is It Considered To Be Present?

Pulmonary hypertension is an elevation in pulmonary vascular pressure that can be caused by an isolated increase in pulmonary arterial pressure or by increases in both pulmonary arterial and pulmonary venous pressures. The term *pulmonary arterial hypertension* refers to conditions that share common isolated elevations in pulmonary arterial pressure (**Table 1**), hemodynamically defined as a resting mean pulmonary arterial pressure greater than 25 mm Hg with a normal pulmonary capillary or left atrial pressure (<15 mm Hg) (1, 2). Pulmonary arterial hypertension that occurs without a demonstrable cause, formerly known as *primary pulmonary hypertension,* may occur sporadically (idiopathic PAH) or as an inherited condition (familial PAH). Mutations in the bone morphogenetic protein receptor II gene occur in approximately 50% of families with a history of familial PAH and in nearly 25% of patients believed to have sporadic idiopathic PAH (3, 4). Genetic testing and counseling have been recommended for relatives of patients with familial PAH (4). Pulmonary arterial hypertension occurs in association with connective tissue diseases, particularly scleroderma (5–9); HIV infection (10–12); sickle-cell disease (13); and chronic liver disease (14, 15). Pulmonary hypertension is suggested when an echocardiogram-derived estimate of pulmonary arterial systolic pressure exceeds 40 mm Hg at rest.

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When Should PAH Be Suspected?

Although PAH may be asymptomatic, exertional dyspnea is the most frequently encountered symptom (16). Accordingly, PAH should be suspected in patients with unexplained dyspnea. Angina or syncope is less common and portends a poor prognosis. Peripheral edema or ascites indicates right ventricular failure. The symptoms of PAH are nonspecific and are similar to those in more common diseases, such as obstructive lung disease and left-sided heart disease.

A family history of pulmonary hypertension may lead to early recognition of clinical disease in other persons (17). A history of use of fenfluramine appetite suppressants (18, 19) and current or previous use of amphetamines or cocaine should be explored, because these factors have been implicated in the development of PAH in some users. A history of acute pulmonary embolism requires a careful search for chronic thromboembolic pulmonary hypertension, although this condition may occur in the absence of symptomatic venous thromboembolic disease (20).

When PAH Is Suspected, How Do You Confirm the Diagnosis and Establish a Cause?

The diagnostic strategy systematically uses testing to determine whether the patient's symptoms are due to PAH and, if so, the underlying cause (**Figure**). Screening with less invasive, less complex, and lower-risk tests is followed by specific and direct confirmatory tests.

The electrocardiogram may provide evidence of hemodynamically significant pulmonary hypertension, such as right ventricular hypertrophy, right-axis deviation, or right atrial enlargement. Radiographic signs of pulmonary hypertension include enlarged main and hilar pulmonary arterial shadows (>17 mm) with attenuation of peripheral pulmonary vascular markings (pruning). Right ventricular enlargement is evidenced by anterior displacement of the right ventricle into the retrosternal space on the lateral view. The chest radiograph is also useful in showing comorbid or causal conditions, such as pulmonary venous congestion, chronic obstructive pulmonary disease, or interstitial lung disease.

Doppler echocardiography is often the first test with results that suggest a diagnosis of pulmonary hypertension (21). Echocardiography also provides information about the cause and consequences of pulmonary hypertension. Studies in patients with PAH (22–25) have reported good correlations between Doppler-derived estimates of pulmonary arterial systolic pressure and direct measurements obtained by right-heart catheterization. Echocardiography also provides direct evidence about left ventricular systolic and diastolic function, as well as valvular function and morphologic characteristics that can give clues to causes of pulmonary hypertension due to elevated pulmonary venous pressures. Left atrial enlargement, even in the absence

Table 1. **Nomenclature and Classification of Pulmonary Hypertension***

Pulmonary arterial hypertension
- Sporadic
- Familial
- Related to:
  - Collagen vascular disease
  - Congenital systemic-to-pulmonary shunts (large, small, repaired, or nonrepaired)
  - Portal hypertension
  - HIV infection
  - Drugs and toxins
  - Other (glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
- Associated with significant venous or capillary involvement
  - Pulmonary veno-occlusive disease
  - Pulmonary capillary hemangiomatosis

Pulmonary venous hypertension
- Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease

Pulmonary hypertension associated with hypoxemia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Long-term exposure to high altitude

Pulmonary hypertension due to chronic thrombotic or embolic disease
- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Pulmonary embolism (tumor, parasites, foreign material)

Miscellaneous
- Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

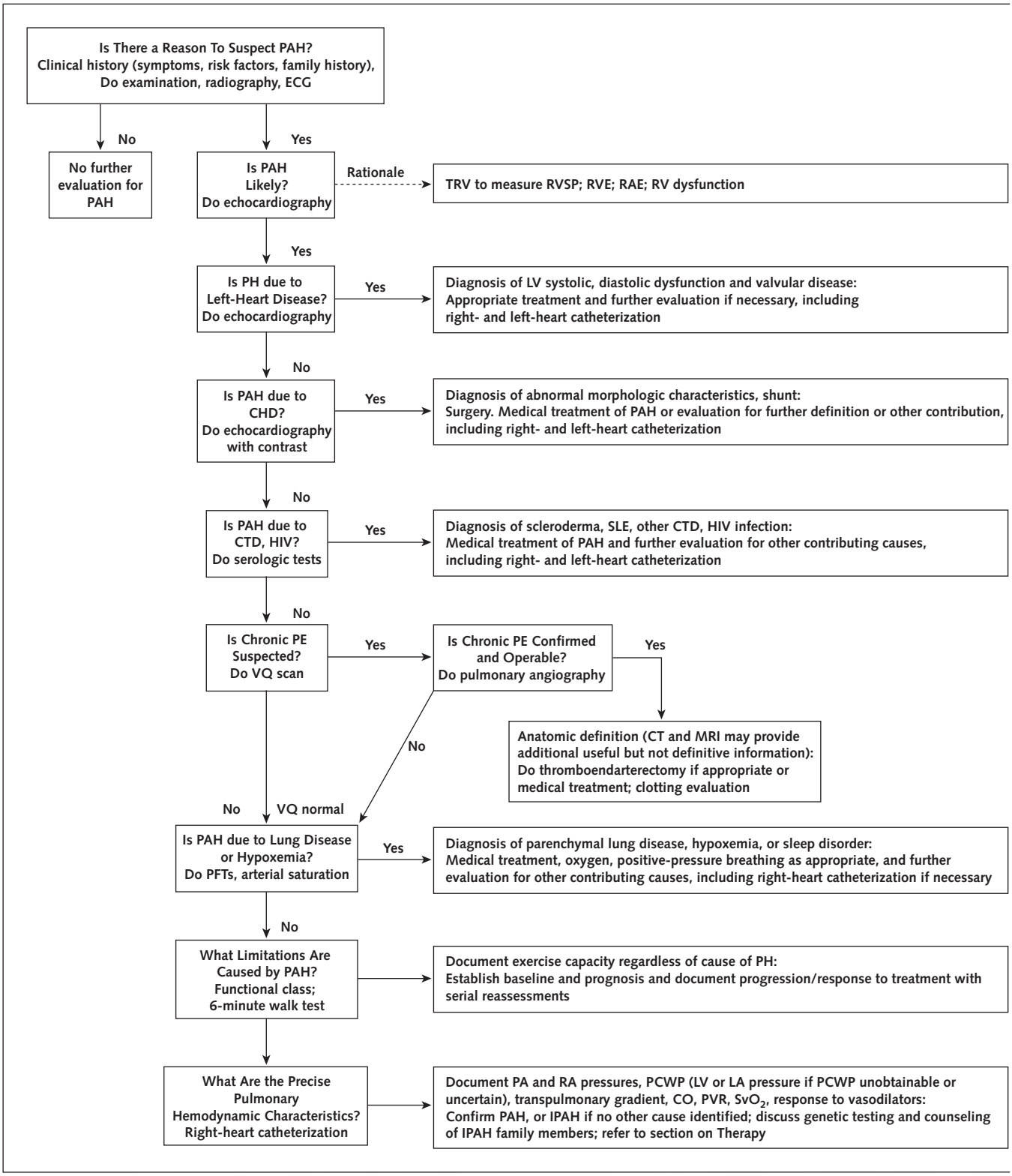
* Adapted with permission from reference 1. This classification schema was based on one proposed at the 3rd World Conference on Pulmonary Hypertension, Venice, Italy, 2003.

possibility of elevated left-sided filling pressures that may contribute to pulmonary hypertension.

The evaluation of PAH includes assessment for an underlying autoimmune–collagen vascular disorder, including physical examination and serologic testing for antinuclear antibodies. However, as many as 40% of patients with idiopathic PAH have serologic abnormalities (16), usually an antinuclear antibody in a low titer and nonspecific pattern. Additional serologic studies may be appropriate if initial testing suggests an underlying autoimmune disorder.

Pulmonary function testing is necessary in the initial evaluation of patients with suspected pulmonary hypertension, primarily to exclude or characterize the contribution of underlying airways or parenchymal lung disease. In general, the degree of pulmonary hypertension in patients with chronic obstructive lung disease is less severe than that in patients with PAH, and the presence and severity of pulmonary hypertension correlate with the degree of airflow obstruction and hypoxemia. Approximately 20% of patients with idiopathic PAH have a mild restrictive defect

Figure. **Guideline for approaching the differential diagnosis of pulmonary hypertension *(PH).***



CHD = congenital heart disease; CO = cardiac output; CT = contrast-enhanced computed tomography of the chest; CTD = connective tissue disease; ECG = electrocardiogram; Echo = Doppler transthoracic echocardiogram; IPAH = idiopathic pulmonary arterial hypertension; LA = left atrial; LV = left ventricular; MRI = magnetic resonance imaging; PA = pulmonary arterial; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PE = pulmonary embolism; PFTs = pulmonary function tests; PVR = pulmonary vascular resistance; RA = right atrial; RAE = right atrial enlargement; RV = right ventricular; RVE = right ventricular enlargement; RVSP = right ventricular systolic pressure; SLE = systemic lupus erythematosus;

a mild to moderate restrictive defect is thought to be due to parenchymal scarring from previous infarctions (26). In both conditions, the diffusing capacity for carbon monoxide is often mildly to moderately reduced (16, 26). Mild to moderate arterial hypoxemia is due to ventilation–perfusion mismatch and reduced mixed venous oxygen saturation resulting from low cardiac output. Severe hypoxemia is due to right-to-left intracardiac or intrapulmonary shunting. Twenty percent of patients with systemic sclerosis have an isolated reduction in diffusing capacity (27); a diffusing capacity less than 45% to 55% of predicted or one that is decreasing may signal the development of pulmonary hypertension (28).

Overnight oximetry may show frequent desaturations and may be the first clue to sleep apnea sufficient to contribute to pulmonary hypertension. Nocturnal hypoxemia occurs in more than 75% of patients with idiopathic PAH without sleep apnea (29). Because hypoxemia is a potent pulmonary vasoconstrictor, all patients with unexplained pulmonary hypertension require assessment of oxygen saturation during both sleep and exercise (30).

Chronic thromboembolic pulmonary hypertension is potentially curable and should be sought in all patients with pulmonary hypertension. Ventilation–perfusion lung scanning is the preferred test to evaluate for this condition (4). Chronic thromboembolic pulmonary hypertension manifests as at least 1 segmental-sized or larger perfusion defect, which is typically mismatched and larger than ventilation abnormalities (20, 31, 32). Patchy, nonsegmental defects are less specific but may be associated with chronic thromboembolic pulmonary hypertension. Perfusion scans tend to underestimate the extent of large-vessel obstruction in this condition (32). Although a normal perfusion scan essentially excludes surgically accessible chronic thromboembolic disease, scans suggestive of thromboembolic disease may also be seen in patients with pulmonary arterial sarcoma, large-vessel pulmonary arteritis, extrinsic vascular compression, or pulmonary veno-occlusive disease (33). Pulmonary angiography is the definitive test for diagnosing chronic thromboembolic pulmonary hypertension and determining operability, and it should be done in experienced centers when chronic thromboembolic pulmonary hypertension remains possible.

Computed tomographic scanning may suggest a cause of PAH, such as severe airway or parenchymal lung diseases. A spectrum of abnormalities on computed tomographic scans has been described in chronic thromboembolic pulmonary hypertension, including right ventricular enlargement, dilated central pulmonary arteries, chronic thromboembolic material within the central pulmonary arteries, increased bronchial artery collateral flow, variability in the size and distribution of pulmonary arteries, parenchymal abnormalities consistent with previous infarctions, and mosaic attenuation of the pulmonary parenchyma inantly in the lower lobes is also suggestive of pulmonary veno-occlusive disease (35).

Cardiac catheterization is ultimately required to confirm the presence of pulmonary hypertension, definitively establish its cause, assess severity, and guide therapy. Open or thoracoscopic lung biopsy entails substantial risk for hemorrhage, hypoxemia, and death in patients with PAH. Because it has a low likelihood of altering the clinical diagnosis, routine biopsy is discouraged. Under certain circumstances, histopathologic diagnosis may be needed when vasculitis, granulomatous or interstitial lung disease, pulmonary veno-occlusive disease, or bronchiolitis are suggested clinically (36).

Initial evaluation at the referral center included a 6-min walk test of 305 m. Right-heart catheterization showed a pulmonary arterial pressure of 65/30 mm Hg (mean, 42 mm Hg), right atrial pressure of 12 mm Hg, pulmonary capillary wedge pressure of 6 mm Hg, and cardiac output of 3.2 L/min. Little change was seen in hemodynamic measurements with the inhalation of nitric oxide. The patient was thought to have idiopathic PAH, falling into New York Heart Association (NYHA) functional class III on the basis of her symptoms. Treatment options were discussed with the patient and her family. Medical therapy, diet, exercise, travel, altitude exposure, and pregnancy were all discussed.

There are few data on which to base recommendations about physical activity or cardiopulmonary rehabilitation in patients with PAH. Potentially hazardous exposure activities are listed in **Table 2**. We encourage cautious, graduated physical activity. Heavy physical activity can precipitate exertional syncope. Hot baths or showers are discouraged because the resultant peripheral vasodilatation can produce systemic hypotension and syncope. Excessive sodium intake can contribute to fluid retention.

We discourage exposure to high altitudes (more than approximately 1800 m above sea level), as this may produce hypoxic pulmonary vasoconstriction and further compromise oxygen transport. Supplemental oxygen should be used to maintain oxygen saturations greater than 91%. Air travel can be problematic for patients with PAH, as commercial aircraft are typically pressurized to the equivalent of approximately 2400 m above sea level. While on commercial aircraft, patients who have borderline oxygen saturations at sea level may require 3 to 4 L/min of supplemental oxygen, and those already using supplemental oxygen at sea level should increase their oxygen flow rate. Because of the potentially devastating effects of respiratory infections, immunization against influenza and pneumococcal pneumonia is recommended.

The hemodynamic changes occurring during pregnancy impose substantial stress in women with PAH, leading to a 30% to 50% mortality rate (37, 38). Although successful use of long-term intravenous epoprostenol and

Table 2. **Potentially Hazardous Activities for Patients with Pulmonary Arterial Hypertension**

Activity	Potential Adverse Effects	Recommendations
Exposure to high altitude	Hypoxemia, pulmonary vasoconstriction, worsening pulmonary hypertension, right-heart failure	Avoid altitudes > 1800 m above sea level; use supplemental oxygen as needed to keep oxygen saturation ≥ 91% at all times
Air travel	Hypoxemia, pulmonary vasoconstriction, worsening pulmonary hypertension	Use supplemental oxygen as needed to keep oxygen saturation ≥ 91% at all times
Heavy exertion	Near-syncope, syncope	Engage in low-level activity or cautious, graduated exercise, such as walking
Bending over and rising quickly	Near-syncope, syncope	Rise slowly from bending, sitting, or lying positions
Use of decongestant medications	Vasoconstriction, worsening pulmonary hypertension	Avoid using decongestants; consider nonsedating antihistamines or local treatments, such as nasal steroids
Use of appetite suppressants or diet pills	Worsening pulmonary hypertension	Have dietary and nutritional consultation; engage in cautious low-level exercise
High sodium intake	Fluid retention, right-heart failure	Follow 2-g sodium diet
Cigarette smoking	Worsening of intrinsic lung disease; nicotine is a vasoconstrictor and may contribute to worsening pulmonary hypertension	Stop smoking (preferably without use of nicotine replacement therapy)

pathic PAH has been reported (39–42), most experts recommend early termination of the pregnancy (43).

Estrogen-containing contraceptives may increase risk for venous thromboembolism and are not recommended for women of childbearing potential with PAH. Also, the endothelin-receptor antagonist bosentan may decrease the efficacy of hormonal contraception, and dual mechanical barrier contraceptive techniques are recommended in women of childbearing age using this medication.

Physicians should discuss with their patients the use of any concomitant medications or herbal preparations. The use of vasoconstricting sinus or cold medications (such as pseudoephedrine) or the use of serotonergic medications for migraine headaches may be problematic. Concomitant use of glyburide or cyclosporine with bosentan is contraindicated, and use of azole-type antifungal agents is discouraged because of potential drug interactions that may increase risk for hepatotoxicity. Patients using warfarin should be cautioned about the many drug interactions possible with this medication. Bosentan may slightly decrease international normalized ratios in patients using warfarin.

Invasive procedures and surgery can be associated with increased operative and perioperative risks. Patients with severe PAH are especially prone to vasovagal events leading to syncope, cardiopulmonary arrest, and death. Cardiac output is particularly dependent on heart rate in this setting, and the bradycardia and systemic vasodilatation accompanying a vasovagal event can result in hypotension. Heart rate should be monitored during invasive procedures, and an anticholinergic agent should be readily available. Oversedation can lead to ventilatory insufficiency and precipitate clinical deterioration. Caution should be used with laparoscopic procedures in which carbon dioxide is used for abdominal insufflation, as absorption can produce hypercarbia, which is a pulmonary vasoconstrictor. Anesthesia and intubation can be particularly problematic because of a lack of evidence supporting efficacy, an increased risk for gastrointestinal bleeding in patients with scleroderma, and an increased risk for hemoptysis in patients with congenital heart disease. The relative risks and benefits of anticoagulant therapy should be considered on a case-by-case basis. Patients with documented right-to-left intracardiac shunting due to an atrial septal defect or patent foramen ovale and a history of transient ischemic attack or embolic stroke should receive anticoagulation. Patients treated with long-term intravenous epoprostenol generally receive anticoagulation in the absence of contraindications, partly because of the additional risk for catheter-associated thrombosis.

Diuretics are indicated for right ventricular volume overload. However, rapid and excessive diuresis may precipitate systemic hypotension and renal insufficiency. Spi-

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