Pulmonary Hypertension, Secondary

Article Last Updated: Jun 23, 2006

INTRODUCTION

Secondary pulmonary artery hypertension (SPAH) is defined as a pulmonary artery systolic pressure higher than 30 mm Hg or a pulmonary artery mean pressure higher than 20 mm Hg secondary to either a pulmonary or a cardiac disorder. If no etiology can be identified, the pulmonary arterial hypertension (PAH) is termed primary pulmonary hypertension. An increased volume of pulmonary blood flow, escalating resistance in the pulmonary vascular bed, or an elevation in pulmonary venous pressure can induce the rise in pulmonary arterial pressure.

Cardiac disorders, pulmonary disorders, or both in combination are the most common causes of secondary pulmonary hypertension. Cardiac diseases produce pulmonary hypertension via volume or pressure overload, although subsequent intimal proliferation of pulmonary resistance vessels adds an obstructive element. Perivascular parenchymal changes along with pulmonary vasoconstriction are the mechanism of pulmonary hypertension in respiratory diseases.

Therapy for secondary pulmonary hypertension is targeted at the underlying cause and its effects on the cardiovascular system. Novel therapeutic agents such as prostacyclin and others undergoing clinical trials have led to the possibility of specific therapies for these once untreatable disorders.

Pathophysiology
Three predominant pathophysiologic mechanisms may be involved in the pathogenesis of SPAH, (1) hypoxic vasoconstriction, (2) decreased area of the pulmonary vascular bed, and (3) volume/pressure overload.

**Hypoxic vasoconstriction**

Chronic hypoxemia causes pulmonary vasoconstriction by a variety of actions on pulmonary artery endothelium and smooth muscle cells, including down-regulation of endothelial nitric oxide synthetase and reduced production of the voltage-gated potassium channel alpha subunit. Chronic hypoxemia leading to pulmonary hypertension can occur in patients with chronic obstructive pulmonary disease (COPD), high-altitude disorders, and hypoventilation disorders (eg, obstructive sleep apnea).

COPD is the most common cause of SPAH. These patients have worse 5-year survival rates, more severe ventilation perfusion mismatch, and nocturnal or exercise-induced hypoxemia. Other disorders, such as obstructive sleep apnea, neuromuscular disorders, and disorders of the chest wall, may lead to hypoxic pulmonary vasoconstriction and eventually SPAH.

**Obliteration of pulmonary vasculature**

A variety of causes may decrease the cross-sectional area of the pulmonary vascular bed, primarily due to disease of the lung parenchyma. The pulmonary arterial pressure rises only when the loss of the pulmonary vessels exceeds 60% of the total pulmonary vasculature. Patients with collagen vascular diseases have a high incidence of SPAH, particularly patients with systemic sclerosis or CREST (calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, scleroderma, and telangiectasia) syndrome. A mild-to-moderate elevation in mean pulmonary artery pressure occurs secondary to acute pulmonary embolism. The peak systolic pressures usually do not rise above 50 mm Hg, and they generally normalize following appropriate therapy. Chronic pulmonary emboli can result in progressive PAH. HIV infection and several drugs and toxins are also known to cause PAH.

**Volume and pressure overload**

Disorders of the left heart may cause SPAH, resulting from volume and pressure overload. Pulmonary blood volume overload is caused by left-to-right intracardiac shunts, such as in patients with atrial or ventricular septal defects. Left atrial hypertension causes a passive rise in pulmonary arterial systolic pressure in order to maintain a driving force across the vasculature. Over time, persistent pulmonary hypertension accompanied by vasculopathy occurs. This may occur secondary to left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, and cardiomyopathy.

Pulmonary venous obstruction is a rare cause of pulmonary hypertension. This may occur secondary to mediastinal fibrosis, anomalous pulmonary venous drainage, or pulmonary venoocclusive disease.

**Frequency**

**United States**

The frequency of secondary pulmonary hypertension is not known. Secondary pulmonary hypertension is observed as a complication of pulmonary or cardiac disorders, although not all patients with the underlying disorder develop this complication.

**Mortality/Morbidity**

Patients who develop SPAH have a poorer prognosis and higher mortality rates compared to those without SPAH, although no published reports document this in the literature.

**History**

The clinical manifestations of SPAH are frequently masked by the underlying etiology. Obtaining a careful history may help exclude some of the numerous causes of secondary pulmonary hypertension. Important clues to a specific secondary cause include past history of heart murmur, deep venous thrombosis or pulmonary embolism, Raynaud phenomenon, arthritis or arthralgias, rash, heavy alcohol consumption, hepatitis, heavy snoring, daytime hypersomnolence, morning headaches, morbid obesity, and a family history of hypertension.

- Patients with SPAH often have nonspecific symptoms that reflect the underlying etiology.
- Other symptoms
  - Dyspnea upon exertion
  - Fatigue
  - Lethargy
  - Syncope with exertion
  - Chest pain
● Less common symptoms
  ● Cough
  ● Hemoptysis
  ● Hoarseness (due to compression of the recurrent laryngeal nerve by the distended pulmonary artery)

● Typical exertional angina has been reported in as many as 8.5% of patients with SPAH secondary to mitral stenosis. This most likely occurs because of the pulmonary artery distension and/or right ventricular ischemia.

Physical

Physical examination findings may include the following:

● The intensity of the pulmonic component of the second heart sound (P₂) may be increased, and a systolic ejection murmur may be heard over left sternal border. The P₂ may demonstrate fixed or paradoxic splitting. A right ventricular heave may be palpated.

● A prominent a wave may be observed in the jugular venous pulse, and a right-sided fourth heart sound (S₄) with a left parasternal heave may be heard.

● Right ventricular failure leads to systemic venous hypertension and cor pulmonale. Signs are the high-pitched systolic murmur of tricuspid regurgitation, hepatomegaly, a pulsatile liver, ascites, and peripheral edema. In this scenario, a right ventricular third heart sound is also heard.

● Signs of underlying cardiac, pulmonary, liver, or collagen vascular disease are often present.

Causes

Causes of secondary pulmonary hypertension can be divided based on primary pathophysiologic mechanisms, as follows:

● Hypoxic vasoconstriction
  ● Chronic obstructive pulmonary disease
  ● Sleep apnea, alveolar hypoventilation
  ● Neuromuscular diseases causing hypoventilation (e.g., poliomyelitis, myasthenia gravis, kyphoscoliosis)
  ● Interstitial lung disease
  ● High-altitude residence

● Obliteration of pulmonary vasculature
  ● Collagen-vascular diseases
  ● Acute pulmonary embolism
  ● Chronic proximal pulmonary emboli
  ● HIV infection
  ● Toxins (rapeseed oil, crack cocaine)
  ● Portal hypertension
  ● Drugs (e.g., fenfluramine, amphetamines, aminorex, chemotherapeutic drugs, tryptophan)
  ● Schistosomiasis
  ● Sickle cell disease
  ● Pulmonary capillary hemangiomatosis

● Volume and pressure overload
  ● Atrial and ventricular septal defects
  ● Left atrial hypertension secondary to mitral valve dysfunction or left ventricular dysfunction or systolic or diastolic dysfunction
  ● Pulmonary venous obstruction from lymphadenopathy, mediastinal fibrosis, or pulmonary venoocclusive disease (a rare idiopathic disorder that leads to SPAH)
Lab Studies

- Arterial blood gas determinations should be performed to assess for hypoxemia.
  - A collagen vascular disease screen should be performed. This includes measuring the erythrocyte sedimentation rate, rheumatoid factor levels, and antinuclear antibody levels.
  - Synthetic liver function test results (ie, albumin levels, prothrombin time, bilirubin levels) may indicate liver disease associated with portal hypertension.
  - HIV testing and hepatology serology tests should be performed on patients at risk.
  - A complete blood cell count, biochemistry panel, prothrombin time, and activated partial thromboplastin time should be performed at baseline.

Imaging Studies

- Chest radiograph
  - The classic finding on a chest radiograph from a patient with PAH is enlargement of central pulmonary arteries, attenuation of peripheral vessels, and oligemic lung fields.
  - Findings of right ventricular and right atrial dilatation are possible.

- Two-dimensional echocardiography
  - Signs of chronic right ventricular pressure overload are present, which include increased thickness of the right ventricle with paradoxical bulging of the septum into the left ventricle during systole.
  - In later stages, right ventricular dilatation occurs, leading to right ventricular hypokinesis.
  - Right atrial dilatation and tricuspid regurgitation are also present.

- Doppler echocardiography
  - Doppler echocardiography is the most reliable noninvasive method to estimate pulmonary arterial pressure.
  - Tricuspid regurgitation is usually present in patients with PAH, which aids measurement of pulmonary artery pressure when using the modified Bernoulli equation. The efficacy of Doppler echocardiography depends on the ability to adequately locate the tricuspid regurgitant jet. Furthermore, acoustic windows may be limited in patients who have other diseases (eg, COPD) or in those who are obese.
  - Tricuspid regurgitation is generally detected in more than 90% of patients with severe SPAH, and a correlation of greater than 95% is observed when the pressure is measured using catheterization. Doppler echocardiography is a useful noninvasive test for long-term follow-up.

Other Tests

- Electrocardiogram
  - Signs of right ventricular hypertrophy or strain may be observed.
  - These include right axis deviation, an R-to-S wave ratio greater than 1 in lead V₁, increased P-wave amplitude, and an incomplete or complete right bundle-branch block pattern.

- Ventilation perfusion lung scan
  - Ventilation perfusion scan should be performed to exclude chronic thromboembolic pulmonary hypertension. A high- or low-probability scan result is most useful, whereas intermediate-probability results should lead to performing pulmonary angiography.
  - Diffuse mottled perfusion can be observed in patients with primary pulmonary hypertension, as opposed to segmental or subsegmental mismatched defects observed in patients with SPAH.

- Pulmonary function tests
  - Pulmonary function tests (ie, spirometry and diffusing capacity for carbon monoxide) should be performed in patients with SPAH to exclude an underlying pulmonary disorder. Diffusing capacity is universally reduced in patients with pulmonary hypertension.
  - These tests may show an obstructive pattern suggestive of COPD or a restrictive pattern suggestive of an interstitial lung disease. Furthermore, the severity of the lung disorder may be established by pulmonary function test findings because they provide both the qualitative and quantitative data.

Procedures

- Right heart catheterization
  - Right heart catheterization is the criterion standard test for the diagnosis, quantification, and characterization of PAH. Left heart dysfunction and intracardiac shunts can be excluded, and the cardiac output can be measured.
  - The indications for this procedure are (1) difficulty with the accurate measurement of PAH with Doppler echocardiography and (2) the need for a precise measurement of pulmonary vascular resistance to conduct a vasodilator trial to assess the acute response to vasodilators.
  - Acute vasoreactivity is determined by administering a short-acting vasodilator such as prostacyclin, inhaled nitric oxide, or adenosine. An acute response often predicts a beneficial effect from oral agents, such as calcium channel blockers.

Histologic Findings

The histopathologic lesions in patients with secondary pulmonary hypertension are similar to those observed in patients with primary pulmonary hypertension. These pathological changes are the result of long-standing hypertension rather than a consequence of different causes.
The plexiform lesion is observed in patients with all types of PAH. These lesions consist of medial hypertrophy, eccentric or concentric laminar intimal proliferation and fibrosis, fibrinoid degeneration, and thrombotic lesions. Fresh or organized and recanalized thrombi may also be present. Diverse types of intimal and muscular lesions of the small muscular arteries may cause the clinical syndrome of pulmonary hypertension, and a plexiform lesion reflecting the abrupt onset of pulmonary hypertension is likely, rather than the lesion being a distinctive cause.

Medical Care

The treatment of SPAH is primarily directed at treatment of the underlying disease. Effective therapy should be instituted in the early stages, before irreversible changes in pulmonary vasculature occur. Once the cause of SPAH has been established, the management consists of specific interventional therapy, specific medical therapy, or general supportive therapy.

Specific interventional and medical therapies are instituted for conditions such as atrial septal defects, mitral stenosis, sleep apnea, and chronic pulmonary thromboembolic disease. General supportive therapy is provided to patients who have right ventricular failure or to those patients in whom the cause cannot be addressed directly. General supportive therapy is as follows.

- **Oxygen supplementation**
  - Oxygen has a proven benefit in reducing patient mortality in selected patients with PAH. Two large trials have demonstrated a definite mortality benefit for patients with COPD, the most common cause of PAH. Survival rates are highest in patients who have less severe SPAH, patients in whom the pulmonary arterial pressure decreases, or patients in whom exercise capacity improves with oxygen therapy.
  - Although long-term study results are not available, oxygen administration may also benefit other groups of patients with SPAH. Therefore, patients who have PaO₂ of less than 55 mm Hg at rest from any cause, those who have desaturation during exercise, and those who perform better on oxygen therapy should be prescribed long-term oxygen therapy.
  - Medicare indications for continuous long-term oxygen therapy include the following:
    - Arterial PaO₂ less than or equal to 55 mm Hg or an arterial oxygen saturation (SaO₂) less than or equal to 88%
    - PaO₂ 55-59 mm Hg or SaO₂ of 89%, in the presence of evidence of cor pulmonale, right heart failure, or erythrocytosis (hematocrit >55%)
  - Additional Medicare indications for oxygen supplementation during sleep or exercise, but not for continuous therapy while the patient is awake and at rest, include the following:
    - PaO₂ of 55 mm Hg or less, SaO₂ of 88% or less, a decrease in the PaO₂ of 10 mm Hg, or a decrease in SaO₂ of more than 5% during sleep
    - Reduction in PaO₂ to 55 mm Hg or less or in SaO₂ to 88% or less during exercise

- **Vasodilators:** Although vasodilator therapy can decrease pulmonary vascular resistance, very few studies show long-term clinical improvement in patients with SPAH. Vasodilators increase cardiac output, and reduced peripheral vascular resistance results in only modest changes in pulmonary artery pressure. Furthermore, vasodilators have short-term deleterious effects in a significant number of patients with SPAH. These adverse effects include deterioration of right ventricular function, severe hypotension, worsening of ventilation due to ventilation-perfusion mismatch, and hypoxemia.

- **Calcium channel blockers:** Since pulmonary artery vasoconstriction may contribute to the pathogenesis of pulmonary arterial hypertension, patients who may benefit from long-term therapy with calcium channel blockers can be identified by performing an acute vasodilator challenge. After baseline measurements have been performed during right heart catheterization, the patient's response to short-acting agents, such as intravenous prostacyclin, adenosine, or inhaled nitric oxide, are tested. A reduction of both pulmonary artery pressure and pulmonary vascular resistance by at least 20% are usual indications for the initiation of oral therapy with calcium channel blockers. Long-term therapy with a calcium channel blocker is not recommended unless these criteria are met.

- **Prostacyclin therapy**
  - **Intravenous prostacyclin**
    - Prostacyclin induces relaxation of vascular smooth muscle and inhibits its growth and platelet aggregation.
    - A prospective, randomized, open trial was conducted in 81 patients with PPH. After 12 weeks, epoprostenol therapy led to functional improvement, as shown by an improved 6-minute walk test, and a decrease of 8% in mean pulmonary artery pressure. However, no long-term randomized trial of epoprostenol in patients with pulmonary arterial hypertension has been conducted. Intravenous epoprostenol improved exercise tolerance, hemodynamics, and long-term survival in a cohort of 178 patients with PPH as compared with historical controls. Another trial, in which a cohort of 162 patients was studied after 1 year of receiving epoprostenol therapy, confirmed that the patients' clinical function improved significantly, even though improvements in hemodynamic measures were modest. Improvements with epoprostenol have also been reported in patients who had PPH associated with congenital left-to-right cardiac shunts, portopulmonary hypertension, and infection with the human immunodeficiency virus (HIV).
  - Epoprostenol is administered only by continuous intravenous infusion with the use of a portable infusion pump connected to a permanent catheter. Common side effects of epoprostenol include jaw pain, headache, diarrhea, flushing, leg pain, and nausea, although they are generally mild and dose-related. Other complications include catheter-related sepsis, pump failure, or dislocation of the central venous catheter. Sudden drug interruption may be life threatening.

  - **Subcutaneous treprostinil:** Treprostinil is a stable prostacyclin analogue administered as a continuous subcutaneous infusion. A recent study showed that patients with PPH had an increase in 6-minute walk distance, dyspnea, signs and symptoms of pulmonary hypertension, and hemodynamic measurements. Local pain at the infusion site is a potential issue with this therapy.

http://www.emedicine.com/med/topic2946.htm
Oral beraprost: Beraprost sodium is absorbed rapidly after oral administration and reaches a peak concentration after 30 minutes and has an elimination half-life of 35-40 minutes. A 12-week randomized, double-blind, placebo-controlled trial involving patients with PAH caused by various conditions (including idiopathic pulmonary arterial hypertension, connective-tissue diseases, congenital left-to-right shunts, portal hypertension, HIV infection) led to a mean increase of 25 m on the 6-minute walk test. Beraprost is an approved therapy for pulmonary arterial hypertension in Japan.

Inhaled iloprost: Iloprost is a chemically stable prostacyclin analogue that can be delivered by inhaler by producing aerosol particles that deposit in the alveoli. The disadvantage of iloprost is short duration of action; therefore, it must be inhaled as many as 6 times a day. One 12-week trial involving 207 patients showed an increase in patient's scores on a 6-minute walk test and improvement in New York Heart Association (NYHA) functional class as well as improved hemodynamics. Side effects included cough, hypotension, and syncope. The long-term efficacy of inhaled iloprost remains to be established. Iloprost has been approved for treating PPH in Europe and the United States.

Endothelin-receptor antagonists

Bosentan

- Endothelin-1 exerts a direct vasoconstrictor effect and leads to the proliferation of vascular smooth-muscle cells and is a proinflammatory mediator. The effects of endothelin-1 are mediated through the ETA and ETB endothelin receptors. ETA receptors mediate sustained vasoconstriction and proliferation of vascular smooth-muscle cells. ETB receptors result in clearance of endothelin and induce the production of nitric oxide and prostacyclin by endothelial cells. Bosentan is an orally active dual (ETA and ETB) endothelin-receptor antagonist.

- The efficacy of oral bosentan in patients with PAH that was either primary or associated with scleroderma was demonstrated whereby walking distance increased significantly. Bosentan also improved the cardiac index, right ventricular systolic function, and improved function of the left ventricle. Less clinical worsening defined as death, lung transplantation, and hospitalization for pulmonary hypertension were present.

- Bosentan is metabolized by the liver and may induce an increase in hepatic aminotransferase levels; this effect is dose-dependent. The drug is contraindicated during pregnancy because of its teratogenic potential. Monthly monitoring of liver function tests is mandatory. However, no reports of permanent liver dysfunction or failure with bosentan have been described.

Sitaxsentan: Selective blockers of the endothelin receptor ETA, such as sitaxsentan, are being evaluated for the treatment of PAH. While blocking the vasoconstrictor effects of ETA receptors, the vasodilator and clearance effects of ETB receptors can be maintained simultaneously. Continuous monitoring of liver function is recommended.

Sildenafil

Sildenafil increases the activity of endogenous nitric oxide and enhances cGMP-mediated pulmonary vasodilatation through inhibition of the breakdown of cGMP by phosphodiesterase type 5. They have acute and prolonged vasodilator effects in PAH. One short-term study of intravenous sildenafil during right heart catheterization reduced pulmonary vascular resistance in a dose-dependent manner.

Sildenafil is a drug that has shown promise in pulmonary hypertension. A recent randomized placebo-controlled study evaluated the efficacy of oral sildenafil in idiopathic PAH and PAH caused by Eisenmenger syndrome. The primary end point of efficacy was the improvement in distance covered in a 6-minute walk test, which improved from 262 to 358.9 after treatment with sildenafil. Pulmonary artery pressure decreased from 98 mm Hg to 78 mm Hg and NYHA class improved. No significant fall in blood pressure existed with placebo and sildenafil, and no serious side effects of the drug were observed in the study. Although all the patients in this study had PPH, the drug could be effective in SPAH as well.

Combination therapy: To maximize the clinical benefit, the combined use of drugs with different mechanisms of action is a promising option for the treatment of PAH. Long-term combination therapy has recently been evaluated in patients with severe disease. Combined therapy with sildenafil or bosentan has produced favorable outcomes in some patients already receiving oral, inhaled, or intravenous prostacyclin analogues. Additional studies are needed to guide optimal use of combined therapy in patients with PAH.

Other Therapies

- Anticoagulants are used regularly in patients with primary PAH because they help reduce symptoms and may provide a survival benefit. The role of anticoagulation has not been established in patients with SPAH. Nonetheless, anticoagulation with warfarin is indicated in patients with chronic pulmonary embol, pulmonary venocclusive disease, and atrial fibrillation induced by left or right heart failure. Furthermore, long-term anticoagulation therapy should be considered in patients who are at high risk for developing venous thromboembolism (eg, those with cor pulmonale and patients with immobility secondary to severe dyspnea).

- Fluid removal with diuretics reduces hepatic congestion and pulmonary edema. However, diuresis should be instituted with caution to avoid hypokalemia, metabolic alkalosis, and a decrease in cardiac output. Phlebotomy should be considered if the patient's hematocrit value is greater than 60%.

- Digoxin has been shown to be beneficial for patients with supraventricular tachycardia or associated left ventricular dysfunction multifocal atrial tachycardia, but verapamil has been proven to be better than digoxin for controlling the heart rate.

Surgical Care

Patients with an atrial septal defect, mitral stenosis, or chronic pulmonary thromboembolic disease should be considered for surgical management. PAH resolves following successful surgical procedures, unless it is too far advanced.

Although lung transplantation is reserved for patients with severe pulmonary hypertension, a subset of patients with SPAH has undergone successful transplantation at several centers. These patients had SPAH due to collagen vascular disease, drug-induced PAH, or pulmonary venous obstruction. Stability of the underlying causative disorder and the patient's ability to tolerate an extensive surgical procedure are prerequisites. Heart-lung transplantation has been performed in patients with SPAH due to congenital cardiac disease or severe left ventricular dysfunction.

Chronic pulmonary hypertension from thromboembolism is much more prevalent than is generally appreciated. Pulmonary endarterectomy offers a cure for the condition, and wider recognition of the efficacy of the operation and the entity are therefore important. Pulmonary endarterectomy is a technically demanding procedure, now performed with success at only selected centers. However, excellent results can be obtained with proper patient selection, meticulous surgical technique, and careful postoperative management. An endarterectomy (not an embolectomy) of all affected parts of the lung is performed, and cardiopulmonary bypass, systemic cooling, and circulatory arrest are essential to clear all affected areas of the pulmonary vasculature. Pulmonary endarterectomy has proven to be permanently curative, although an inferior vena caval filter should be placed in all patients to prevent recurrence, and the patients must have life-long anticoagulation.

The largest of the case series for thromboendarterectomy operation for thromboembolic pulmonary hypertension was recently published. The outcomes of 743 patients who underwent this operation between 1999 and 2004 were reviewed. The patients were divided into 2 groups: group 1 had preoperative pulmonary artery systolic
pressures of greater than 100 mm Hg and group 2 had preoperative pulmonary artery systolic pressures of less than 100 mm Hg. The overall perioperative survival was slightly lower in group 1 patients (89.2% vs 96.5% for group 2). The reduction in pulmonary vascular resistance was quite similar as well. Therefore, even the patients with extreme pulmonary hypertension might benefit from this operation.

Although treatment of secondary pulmonary hypertension consists primarily of that necessary for the underlying disease, several medications and oxygen are used in different clinical settings. Currently, definite proof of effectiveness is lacking for several of these treatments.

**Drug Category: Anticoagulants**

Long-term anticoagulation with warfarin should be considered in selected patients with SPAH. These include patients with chronic pulmonary emboli, pulmonary venoocclusive disease, and atrial fibrillation induced by left or right heart failure who are at high risk for developing venous thromboembolism (eg, those with cor pulmonale or immobility secondary to severe dyspnea).

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Warfarin (Coumadin)</th>
</tr>
</thead>
</table>
| **Description**| Interferes with hepatic synthesis of vitamin K–dependent coagulation factors. Used for prophylaxis and treatment of venous thrombosis, pulmonary embolism, and thromboembolic disorders. Babydose to maintain an INR in the range of 2-3. Tailor dose to maintain desired INR. Recurrence of DVT and PE increases dramatically when INR drops to <2 and decreases when INR is kept at 2-3. Serious bleeding risk (including hemorrhagic stroke) is approximately constant when INR is 2.5-4.5 but rises dramatically when INR is >5. Procoagulant vitamin K–dependent proteins are responsible for a transient hypercoagulable state when warfarin is first started and when it is stopped. This phenomenon occasionally causes warfarin-induced necrosis of large areas of skin or of distal appendages. Heparin is always used to protect against this hypercoagulability when warfarin is started; however, when warfarin is stopped, the problem resurfaces, causing an abrupt temporary rise in the rate of recurrent venous thromboembolism. At least 186 different foods and drugs have been reported to interact with warfarin. Clinically significant interactions have been verified for a total of 26 common drugs and foods, including 6 antibiotics and 5 cardiac drugs. Every effort should be made to keep the patient adequately anticoagulated at all times because procoagulant factors recover first when warfarin therapy is inadequate. Patients who have difficulty maintaining adequate anticoagulation while...
Taking warfarin may be asked to limit their intake of foods that contain vitamin K. Foods that have moderate-to-high amounts of vitamin K include Brussels sprouts, kale, green tea, asparagus, avocado, broccoli, cabbage, cauliflower, collard greens, liver, soybean oil, soybeans, certain beans, mustard greens, peas (black-eyed peas, split peas, chick peas), turnip greens, parsley, green onions, spinach, and lettuce.

### Drug Category: Calcium channel blockers

Efficacy has been evaluated primarily in patients with primary pulmonary hypertension. Efficacy of these agents is unclear in patients with SPAH. In selected patients (ie, patients with scleroderma), these agents may be tried only after a vasodilator response is demonstrated. Act by inhibiting calcium ions from entering slow channels or select voltage-sensitive areas of vascular smooth muscle.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Nifedipine (Adalat, Procardia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Vasodilator that dilates both systematic and pulmonary vascular beds. Higher than usual doses are required for optimal vasodilation of pulmonary arteries.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>10-20 mg IR cap PO tid initially; gradually increase as BP allows (not &lt;90-100 mg Hg systolic)</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>0.6-0.9 mg/kg/d PO divided tid/qid</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; severe CHF, sick sinus syndrome, second- or third-degree AV block, and hypotension (&lt;90 mm Hg systolic)</td>
</tr>
<tr>
<td>Interactions</td>
<td>Caution with coadministration of any agent that can lower BP, including beta-blockers and opioids; H2 blockers (cimetidine) may increase toxicity; decreases levels of phenobarbital, quinidine, and rifampin; increases levels of theophylline and vincristine</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>May cause lower extremity edema; allergic hepatitis has occurred but is rare; caution in patients with angina, CHF, or patients on concomitant therapy with beta-blockers or digoxin; monitor for hypotension; adverse effects include flushing, lightheadedness, nausea, and weakness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Diltiazem (Cardizem, Dilacor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>During depolarization, inhibits calcium ions from entering slow channels and voltage-sensitive areas of vascular smooth muscle and myocardium. Produces vasodilation but causes less reflex tachycardia compared to nifedipine. May be useful if patients develop excessive hypotension with nifedipine.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>30 mg PO tid/qid initially; increase gradually to 360 mg/d as BP allows</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; severe CHF, sick sinus syndrome, second- or third-degree AV block, and hypotension (&lt;90 mm Hg systolic)</td>
</tr>
</tbody>
</table>
### Drug Name: Amlodipine (Norvasc)

**Description:** Longer duration of action and requires less frequent dosing compared to nifedipine and diltiazem. Experience in pulmonary hypertension not as extensive as with other agents. Fewer effects on conduction and infrequent AV block.

**Adult Dose:** 2.5-5 mg PO qd; not to exceed 10 mg/d

**Pediatric Dose:** Not established

**Contraindications:** Documented hypersensitivity

**Interactions:** Increases cyclosporine levels; hypotensive effects increase with benazepril; increased myocardial depression with concomitant use of beta-blockers

**Pregnancy:** C - Safety for use during pregnancy has not been established.

**Precautions:** Caution in patients with impaired renal or hepatic function, CHF, sick sinus syndrome, and those on concomitant therapy with beta-blockers and digoxin; adverse effects include peripheral edema, headache, dizziness, rash, nausea, and shortness of breath

---

### Drug Name: Epoprostenol (Flolan)

**Description:** Long-term infusion improves outcome in patients with primary pulmonary hypertension and selected patients with secondary pulmonary hypertension. Short-term vasodilator response appears unrelated because favorable impact on disease progression occurred with long-term therapy. Dose is determined during dose/effect study performed in cath lab or ICU. Selected dose produces maximum vasodilation with minimum systemic hypotension.

**Adult Dose:** 4 mg/kg/min IV initially; adjust dose by 1-2 mg/kg/min for persistent or worsening symptoms

**Pediatric Dose:** Not established

**Contraindications:** Documented hypersensitivity; hyaline membrane disease, presence of dominant left-to-right shunt, respiratory distress syndrome

**Interactions:** Coadministration with anticoagulants may increase bleeding risk because of shared effects on platelet aggregation; hypotension may be exacerbated by other vasodilators and diuretics

**Pregnancy:** B - Usually safe but benefits must outweigh the risks.

**Precautions:** Whenever possible, coadminister with anticoagulants to reduce risk of thromboembolism; sudden discontinuation or reduction in therapy may result in rebound pulmonary hypertension; during a vasodilator study, some patients developed pulmonary edema (venoocclusive disease); adverse effects include flushing, tachycardia, shock, fever, chills, headache, diarrhea, nausea, jaw pain, myalgia, paresthesia, hypoxia, and flulike symptoms

---

### Drug Name: Treprostinil (Remodulin)

---

**Drug Category:** Peripheral vasodilators

Strong vasodilator of all vascular beds and potent endogenous inhibitor of platelet aggregation. Platelet effects result from activation of intracellular adenylate cyclase and increase in cyclic adenosine monophosphate concentrations within platelets. May decrease thrombogenesis and platelet clumping in the lungs by inhibiting platelet aggregation.
### Description
Used to treat PAH. Elicits direct vasodilation of pulmonary and systemic arterial vessels and inhibits platelet aggregation. Vasodilation reduces right and left ventricular afterload and increases cardiac output and stroke volume.

### Adult Dose
1.25 ng/kg/min SC via continuous infusion initially; may increase by 1.25 ng/kg/min each wk for 4 wk, then may increase by 2.5 ng/kg/min each wk; not to exceed 40 ng/kg/min
Note: If initial dose not tolerated, decrease to 0.625 ng/kg/min, then slowly titrate upward; must taper slowly if discontinued

### Pediatric Dose
Not established

### Contraindications
Documented hypersensitivity

### Interactions
Additive hypotensive effect with antihypertensive agents or diuretics; may increase risk of bleeding with other antiplatelet drugs (eg, aspirin) or anticoagulants (eg, warfarin, heparin)

### Pregnancy
B - Usually safe but benefits must outweigh the risks.

### Precautions
May cause pain or irritation at infusion site; common adverse effects include diarrhea, jaw pain, edema, vasodilatation, and nausea; do not discontinue abruptly

**Drug Name**: Iloprost (Ventavis)

### Description
Synthetic analogue of prostacyclin PG12 that dilates systemic and pulmonary arterial vascular beds. Indicated for pulmonary arterial hypertension (WHO class I) in patients with NYHA class III or IV symptoms to improve exercise tolerance and symptoms and to delay deterioration.

### Adult Dose
Initial: 2.5 mcg via nebulizer
Maintenance: If first dose tolerated, increase to 5 mcg/dose via nebulizer 6-9 times/d; do not administer more frequently than q2h
Note: Administration studied only with Prodose AAD system nebulizer

### Pediatric Dose
Not established

### Contraindications
Documented hypersensitivity

### Interactions
May increase hypotensive effect of vasodilators and antihypertensives; may increase bleeding risk when coadministered with anticoagulants

### Pregnancy
C - Safety for use during pregnancy has not been established.

### Precautions
Monitor vital signs during initial treatment to decrease syncope risk; avoid eye and skin contact and oral ingestion; inhibits platelet function, but clinical relevance is unclear

**Drug Category**: Diuretics

For patients who develop right-sided heart failure and those who have systemic congestion manifested by hepatomegaly, ascites, and marked lower extremity edema. Severe right heart failure may also compromise function of left ventricle and may lead to pulmonary congestion. Therefore, judicious use of diuretics helps reduce systemic congestion and edema. However, excessive hypovolemia may lower cardiac output further and interfere with tissue oxygenation.

### Drug Name
Furosemide (Lasix)

### Description
 Increases excretion of water by interfering with chloride-binding cotransport system, which, in turn, inhibits sodium and chloride reabsorption in ascending loop of Henle and distal renal tubule. Dose must be individualized to patient. Depending on response, administer at increments of 20-40 mg, no sooner than 6-8 h after the previous dose, until desired diuresis occurs. When treating infants, titrate with increments of 1 mg/kg/dose until a satisfactory effect is achieved.

### Adult Dose
20-80 mg/d PO/IV/IM; titrate up to 600 mg/d for severe edematous states

### Pediatric Dose
PO: 1-2 mg/kg/dose; not to exceed 6 mg/kg/dose; do not administer >q6h IV/IM: 1 mg/kg slowly under close supervision; not to exceed 6 mg/kg

### Contraindications
Documented hypersensitivity; hepatic coma, anuria, and state of severe electrolyte depletion

### Interactions
Metformin decreases concentrations; interferes with hypoglycemic effect of antidiabetic agents and antagonizes muscle-relaxing effect of tubocurarine; auditory toxicity appears to be increased with coadministration of aminoglycosides; hearing loss of varying degrees may occur; anticoagulant activity of warfarin may be enhanced when taken
concurrently; increased plasma lithium levels and toxicity are possible when taken concurrently

Pregnancy
C - Safety for use during pregnancy has not been established.

Precautions
Perform frequent serum electrolyte, carbon dioxide, glucose, creatinine, uric acid, calcium, and BUN determinations during first few months of therapy and periodically thereafter

Drug Category: Endothelin receptor antagonists

Competitively bind to endothelin-1 (ET-1) receptors ET<sub>A</sub> and ET<sub>B</sub>, causing reduction in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and mean right atrial pressure (RAP).

Drug Name
Bosentan (Tracleer)

Description
Endothelin receptor antagonist indicated for the treatment of PAH in patients with WHO class III or IV symptoms to improve exercise ability and decrease rate of clinical decline. Inhibits vessel constriction and elevation of BP by competitively binding to ET-1 receptors ET<sub>A</sub> and ET<sub>B</sub> in endothelium and vascular smooth muscle. This leads to significant increase in cardiac index associated with significant reduction in PAP, PVR, and mean RAP. Due to teratogenic potential, can only be prescribed through the Tracleer Access Program (phone: 1-866-228-3546).

Adult Dose
<40 kg: 62.5 mg PO bid; not to exceed 125 mg/d
>40 kg: 62.5 mg PO bid for 4 wk initially, then increase to 125 mg PO bid

Pediatric Dose
Not established; 62.5 mg PO bid recommended if <40 kg or >12 y; not to exceed 125 mg/d

Contraindications
Documented hypersensitivity; coadministration with cyclosporine A or glyburide

Interactions
Toxicity may increase when administered concomitantly with inhibitors of isoenzymes CYP450 2C9 and CYP450 3A4 (eg, ketoconazole, erythromycin, fluoxetine, sertraline, amiodarone, cyclosporine A); induces isoenzymes CYP450 2C9 and CYP450 3A4, causing decrease in plasma concentrations of drugs metabolized by these enzymes (eg, glyburide and other hypoglycemics, cyclosporine A, hormonal contraceptives, simvastatin, and possibly other statins); hepatotoxicity increases with concomitant administration of glyburide

Pregnancy
X - Contraindicated in pregnancy

Precautions
Causes at least 3-fold elevation of liver aminotransferase levels (ie, ALT, AST) in approximately 11% of patients; may elevate bilirubin levels (serum aminotransferase levels must be measured prior to initiation of treatment and then monthly); caution in patients with mildly impaired liver function (avoid in patients with moderate or severe liver impairment); not recommended while breastfeeding; monitor hemoglobin levels after 1 and 3 mo of treatment and every 3 mo thereafter; exclude pregnancy before initiating treatment and prevent thereafter by use of reliable contraception; headache and nasopharyngitis may occur

Drug Name
Ambrisentan (Letairis)

Description
Endothelin receptor antagonist indicated for pulmonary arterial hypertension in patients with WHO class II or III symptoms. Improves exercise ability and decreases progression of clinical symptoms. Inhibits vessel constriction and elevation of blood pressure by competitively binding to endothelin-1 receptors ET<sub>A</sub> and ET<sub>B</sub> in endothelium and vascular smooth muscle. This leads to significant increase in cardiac index associated with significant reduction in pulmonary artery pressure, pulmonary vascular resistance, and mean right atrial pressure. Because of the risks of hepatic injury and teratogenic potential, only available through the Letairis Education and Access Program (LEAP). Prescribers and pharmacies must register with LEAP in order to prescribe and dispense. For more information, see http://www.letairis.com or call (866) 664-LEAP (5327).

Adult Dose
5 mg PO qd initially; may increase to 10 mg PO qd if 5 mg/d tolerated; do not chew, crush, or split tab

Pediatric Dose
Not established
### Contraindications

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Sildenafil (Revatio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Promotes selective smooth muscle relaxation in lung vasculature possibly by inhibiting PDE5. This results in subsequent reduction of BP in pulmonary arteries and increase in cardiac output.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>20 mg PO tid</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; concurrent or intermittent use of organic nitrates in any form</td>
</tr>
<tr>
<td>Interactions</td>
<td>Potentiates vasodilatory effect of NO, resulting in potentially fatal drop in BP; coadministration with ketoconazole, erythromycin, or cimetidine increases plasma sildenafil concentrations; coadministration with rifampin decreases plasma levels of sildenafil</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Adverse effects include headaches (16%), flushing (10%), upset stomach (7%), nasal congestion (4%), and a blue haze at the periphery of vision (3%); adverse effects occur more often in men taking the 100-mg dose; serious adverse effects occur in patients with severe heart disease and those who are taking nitrates; rates of MI were 1.7 and 1.4 per 100 man-years for sildenafil and placebo groups</td>
</tr>
</tbody>
</table>

### Drug Category: Cardiac glycosides

For prevention and treatment of supraventricular arrhythmias associated with SPAH and for patients who have concomitant left-sided heart failure. Digoxin not useful in treatment of right-sided ventricular failure.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Digoxin (Lanoxin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Cardiac glycoside with direct inotropic effects and indirect effects on the cardiovascular system. Acts directly on cardiac muscle, increasing myocardial systolic contractions. Indirect actions result in increased carotid sinus nerve activity and enhanced sympathetic withdrawal for any given increase in mean arterial pressure.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>0.125-0.375 mg PO qd</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>5-10 years: 20-35 mcg/kg PO TDD  &gt;10 years: 10-15 mcg/kg PO TDD  Maintenance dose: 25-35% of PO loading dose</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; beriberi heart disease, idiopathic hypertrophic subaortic stenosis, constrictive pericarditis, and cardiot sinus syndrome</td>
</tr>
<tr>
<td>Precautions</td>
<td>Medications that may increase levels include alprazolam, benzodiazepines, bepridil, captopril, cyclosporine, propafenone,</td>
</tr>
</tbody>
</table>
Complications

- Patients with SPAH usually develop cor pulmonale, which further worsens the hypoxemia and perpetuates pulmonary hypertension.

Prognosis

- Increasing pulmonary arterial pressure is associated with a progressive decline in survival for patients with COPD or other interstitial lung diseases. The prognosis of patients with severe SPAH is variable and depends on the severity of hemodynamic derangement and the underlying primary disorder.

- Patients with severe pulmonary hypertension or right heart failure survive approximately 1 year. Patients with moderate elevations in pulmonary artery pressure (mean pressure <55 mm Hg) and preserved right heart function have a median survival of 3 years from diagnosis.

Patient Education

- For excellent patient education resources, visit eMedicine's Lung and Airway Center. Also, see eMedicine's patient education article Chronic Obstructive Pulmonary Disease (COPD).

Medical/Legal Pitfalls

- Reversible causes of SPAH must be excluded.

- Ongoing clinical trials may prove the benefit of vasodilator therapy in patients with various forms of pulmonary hypertension.

- Preliminary data with inhaled iloprost, a prostacyclin analog, appears promising, although frequent inhalations were required.

- Balloon atrial septostomy has been tried with success in patients without the evidence of right ventricular failure. The benefit (improved exercise function) occurs at the cost of a fall in SaO₂. The technique has been applied via a femoral catheter, with a Brockenbrough septal needle and Mansfield balloons to dilate the septostomy.

Special Concerns

- An approach to evaluate a patient with secondary pulmonary hypertension
  - Findings from the history, physical examination, chest radiographs, and electrocardiogram may suggest the presence of PAH and right ventricular dysfunction.
  - Two-dimensional transthoracic echocardiography with Doppler analysis is used to confirm the diagnosis of PAH and to exclude possible cardiac disease.
In patients without cardiac disease, pulmonary function tests should be performed, including blood gas determinations and assessment for possible nocturnal desaturation. Any abnormality should be evaluated further with a CT scan and possibly a lung biopsy.

- Patients with normal pulmonary function test results should have a perfusion lung scan, and, if defects are present, pulmonary angiography or spiral CT scan should be performed.
- Right heart catheterization is recommended if noninvasive testing does not provide definitive results, if assessment of the reversibility of PAH with a vasodilator is required, or if further information is required for surgical intervention.

- **Chronic thromboembolic pulmonary hypertension**
  - Chronic thromboembolic pulmonary hypertension occurs in a minority of patients following acute embolism. Approximately 0.1% of survivors develop progressive pulmonary hypertension. Less than 1% of these patients have deficiencies of antithrombin 3, protein C, or protein S. No consistent defect in fibrinolytic activity has been identified.
  - Pathologically, these patients have a full range of pulmonary hypertensive lesions, including plexogenic lesions in the small pulmonary arteries. These patients present with progressive dyspnea and exercise intolerance. Physical examination findings demonstrate right ventricular failure and pulmonary hypertension.
  - Diagnostic confirmation of this disorder requires right heart catheterization for pulmonary angiography. The angiographic features in these patients are quite different from the features observed in patients with acute embolism. Marked narrowing of central pulmonary arteries is observed, as compared to the intraluminal filling defects observed in patients with acute embolism.
  - Pulmonary angioscopy findings have proven valuable for confirming the presence of chronic thromboembolic obstruction and determining whether it is accessible to surgical intervention. The pulmonary angioscope is a fiberoptic device that allows visualization of the pulmonary arteries to the segmental level.

- **Pulmonary thromboendarterectomy**
  - Chronic thromboembolic pulmonary hypertension is a potentially treatable form of pulmonary hypertension.
  - Pulmonary thromboendarterectomy is capable of restoring severely compromised patients to a healthy hemodynamic and symptomatic status.
  - The procedure is performed during cardiopulmonary bypass and periods of circulatory arrest. Careful dissection of chronically endothelialized material from the native intima is performed to restore pulmonary arterial patency.
  - Postoperative complications include pulmonary artery steal, which is the redistribution of pulmonary arterial blood flow away from previously well-perfused segments into the newly operated segments. Reperfusion pulmonary edema is another complication and may vary in severity from a mild form that results in hypoxemia to a more severe form that results in hemorrhage and fatal complications.
  - A published series reported a perioperative mortality rate of 8.6% in 1200 patients. Among survivors of thromboendarterectomy, marked reductions in pulmonary artery pressures and pulmonary vascular resistance have been observed. Most patients who were New York Heart Association (NYHA) class III or IV returned to NYHA class I or II status. This procedure is performed in a few centers where surgical teams have gained sufficient experience in the perioperative care of these patients.

**MULTIMEDIA**

<table>
<thead>
<tr>
<th>Authors and Editors</th>
<th>Introduction</th>
<th>Clinical</th>
<th>Differentials</th>
<th>Workup</th>
<th>Treatment</th>
<th>Medication</th>
<th>Follow-up</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multimedia</td>
<td>References</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Media file 1:** Gross pathology on a patient who died from severe pulmonary hypertension secondary to persistent patent ductus arteriosus.

![View Full Size Image](http://www.emedicine.com/med/topic2946.htm)

**Media type:** Photo

**Media file 2:** Another view (of picture in Media File 1) of gross pathology on a patient who died from severe pulmonary hypertension secondary to persistent patent ductus arteriosus.

![View Full Size Image](http://www.emedicine.com/med/topic2946.htm)

**Media type:** Photo

**Media file 3:** During a pulmonary arterial thromboendarterectomy, a bilateral proximal thrombus was carefully dissected and extracted, leading to the resolution of secondary pulmonary artery hypertension.

![View Full Size Image](http://www.emedicine.com/med/topic2946.htm)

**Media type:** Photo
Media file 4: Chest radiograph of a patient with secondary pulmonary hypertension shows enlarged pulmonary arteries. This patient had an atrial septal defect.

Media file 5: A 54-year-old woman with history of scleroderma (CREST variety, ie, calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia) developed dyspnea that worsened upon exertion. Images from a high-resolution CT scan of the lungs showed no parenchymal disease. The patient was found to have severe pulmonary arterial hypertension.

Media file 6: A 54-year-old woman with history of scleroderma (CREST variety, ie, calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia) developed dyspnea that worsened upon exertion. Spiral CT scan image showed enlarged pulmonary arteries but no evidence of thromboembolism (same patient as in Media File 5).

Media file 7: A ventilation/perfusion scan of bilateral mismatched segmental and subsegmental defects, suggesting chronic thromboembolic hypertension.
This left pulmonary arterial angiogram shows large central pulmonary arteries and attenuation of peripheral vessels, but thrombosis cannot be identified because it has organized along the vessel walls.

Bilateral angiogram should be performed in patients suggested to have chronic thromboembolic pulmonary arterial hypertension. This right pulmonary arterial angiogram from the patient in Media File 8 again shows no evidence of a filling defect, therefore excluding acute thrombosis. Angioscopy is a potentially useful procedure in this setting.


---

**Pulmonary Hypertension, Secondary excerpt**

Article Last Updated: Jun 23, 2006

We subscribe to the HONcode principles of the Health On the Net Foundation

Medicine is a constantly changing science and not all therapies are clearly established. New research changes drug and treatment therapies daily. The authors, editors, and publisher of this journal have used their best efforts to provide information that is up-to-date and accurate and is generally accepted within medical standards at the time of publication. However, as medical science is constantly changing and human error is always possible, the authors, editors, and publisher or any other party involved with the publication of this article do not warrant the information in this article is accurate or complete, nor are they responsible for omissions or errors in the article or for the results of using this information. The reader should confirm the information in this article from other sources prior to use. In particular, all drug doses, indications, and contraindications should be confirmed in the package insert. FULL DISCLAIMER

**Privacy Policy Changes**

**Important Announcement:**

WebMD, Inc. ("WebMD Health"), a leader in online health information services to the medical professional community has acquired eMedicine. This acquisition was completed January 18, 2006. As we become more fully integrated, eMedicine users are now eligible to utilize the services available to physicians through WebMD Health’s professional portals, including Medscape.com, theheart.org and Medsite.com. Your eMedicine account information will now be accessible to WebMD Health where it will be maintained in accordance with the WebMD Professional Services Privacy Policy. **Click here** to view the WebMD Professional Services Privacy Policy.

If you desire to remove your account information from WebMD Health, please send an email to PrivacyPolicyNotice@emedicine.com.