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☛ To promote public awareness and education through patient and health professional seminars, literature, and publicity campaigns.

☛ To stimulate and support research to improve treatment and ultimately find the cause and cure of scleroderma and related diseases.

**SCLERODERMA  
FOUNDATION**

12 Kent Way, Suite 101

Byfield, MA 01922

Phone: 978-463-5843

Fax: 978-463-5809

Info Line: 800-722-HOPE

Email: [sfinfo@scleroderma.org](mailto:sfinfo@scleroderma.org)

Website: [www.scleroderma.org](http://www.scleroderma.org)

# *Pulmonary Arterial Hypertension (PAH) in Scleroderma*

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## *What is pulmonary arterial hypertension (PAH)?*

Pulmonary arterial hypertension (PAH) is high blood pressure in the arteries that take blood from the right side of the heart to the lungs.

When the blood pressure inside the pulmonary arteries is high, the right side of the heart has to pump harder to move blood into the lungs to pick up oxygen. This can lead to failure of the right side of the heart.

Patients with scleroderma are at increased risk for developing PAH.

## *What types of PAH occur in scleroderma?*

Patients with limited scleroderma (the CREST syndrome) are more likely to have PAH without significant interstitial lung disease (ILD).

It is not known what causes PAH in this group of patients. It may be the same processes that cause damage to small blood vessels in the systemic circulation. The lining cells of the blood vessels (endothelial cells) are injured and excessive material is laid down inside the blood vessel walls. This stiffens the blood vessels, and the muscle that constricts the blood vessel may overgrow and narrow the blood vessel.

Other patients have PAH because they have significant ILD (lung inflammation and scarring). The ILD reduces the blood oxygen level, which in turn, may cause a reflex increase in blood pressure in the pulmonary arteries.

## *What are the symptoms of PAH?*

Patients with mild PAH may have no symptoms. Patients with moderate or severe PAH usually notice shortness of breath (dyspnea), especially with exercise.

Patients may also notice unusual chest pains and symptoms of right-sided heart failure. Right-sided heart failure occurs when the contraction of the right ventricle of the heart is not strong enough to pump blood through the stiff, thick pulmonary arteries. The muscle of the right ventricle may initially thicken, but then dilates (stretches out) as the heart fails. Blood that would normally be pumped from the right side of the heart into the lungs backs up into the rest of the body. The patient may have worsening shortness of breath, swelling of the veins in the neck, swelling of the belly, and swelling of the feet. This is like water backing up behind a nearly clogged pipe in a plumbing system.

## *What tests might be done to diagnose PAH?*

In a patient with scleroderma, the development of unexplained shortness of breath should lead to consideration of possible PAH.

Physical examination of the heart is insensitive for detecting PAH. A laboratory clue that you might have PAH is a reduced diffusing capacity (DLCO) on your pulmonary function tests (PFTs). The diffusing capacity measures the ability of gas to move from the air, across the lung tissue and blood vessel wall, into your blood. In the absence of interstitial lung disease (ILD), if the diffusing capacity is less than 50% of its predicted value, this is a clue that PAH may be present.

The test most commonly used to diagnose PAH is the echocardiogram. It can estimate the pulmonary artery pressure fairly well, in a noninvasive manner.

Your physician may order a cardiac catheterization to measure the actual pressure in the pulmonary arteries. This invasive test is done if the results will change the therapy you receive. A small tube is inserted through the jugular vein in the neck or the femoral vein in the groin, and passed through the central veins and the right side of the heart, and into the lungs. Cardiac catheterization enables measurement of the pulmonary artery pressure, cardiac output (the amount of blood flow generated by the heart),

and resistance to blood flow in the lungs.

A six-minute walk test is often helpful in assessing exercise capacity in patients with PAH. In addition, a Functional Class is often assigned to patients based on their activity tolerance, ranging from Class I to IV (with I being best and IV the worst).

## *What is the natural course of PAH in scleroderma?*

It was previously thought that the development of PAH in patients with scleroderma was often associated with a poor prognosis. However, ongoing educational efforts regarding the risk of PAH in scleroderma may lead to earlier diagnosis.

Within the last few years, the echocardiogram has been widely used to identify mild or moderate PAH in scleroderma patients. The natural course of mild or moderate PAH in scleroderma patients is unknown.

It is possible that mild or moderate PAH will persist unchanged for long periods of time. However, if a patient develops severe PAH and right-sided heart failure, the prognosis may be poor.

## *What is the treatment of PAH?*

First, your doctor will try to determine whether your PAH occurs with or without significant interstitial lung disease (ILD). Pulmonary function tests will be helpful. If there is evidence of active inflammation in the lungs (which might cause ILD to worsen), treatment for ILD may be indicated.

Supplemental oxygen, anticoagulation, and diuretics are often important parts of treatment for PAH. If your oxygen level at rest, with exercise, or during sleep is low, home oxygen therapy may be given.

The decision to treat with anticoagulation is made on an individual basis by the patient and physician.

If right-heart failure is present, it is treated with a variety of medications. Diuretics may be given to remove some fluid (edema) that develops.

Calcium channel blockers (such as diltiazem, nifedipine, or amlodipine) can help a small proportion

of patients. Such treatment usually follows an assessment of vasoreactivity during cardiac catheterization.

### **New Drugs for Treating PAH**

The past decade has seen three new drugs for treating PAH: epoprostenol (brand name Flolan®), treprostinil (brand name Remodulin®), and bosentan (brand name Tracleer®). Each will be briefly reviewed below.

#### **1. Epoprostenol**

Epoprostenol (Flolan®) is a potent vasodilator, which must be given by a constant intravenous infusion. This requires an indwelling central venous catheter and an infusion pump.

Epoprostenol was first studied in primary pulmonary hypertension (PPH; pulmonary hypertension occurring in the absence of an associated disease like scleroderma). In a multicenter, randomized, controlled clinical trial in patients with PPH, continuously infused epoprostenol plus conventional therapy (oral vasodilators, anticoagulation, etc.) was compared to conventional therapy alone.

The epoprostenol-treated group showed improved exercise tolerance, increased cardiac output, decreased pulmonary vascular resistance, and improved survival.

A later study of chronic intravenous epoprostenol showed improvement in exercise capacity and hemodynamics in patients with PAH occurring in association with scleroderma.

In this study, patients receiving epoprostenol demonstrated better exercise capacity and cardiopulmonary hemodynamics at 12 weeks compared to the control group. A survival difference between groups was not seen in this population over the period of study, but the study was not designed to detect a difference in survival.

Common side effects of epoprostenol therapy include headache, flushing, jaw pain with initial mastication, diarrhea, and foot/bone pain. Other side effects include the potential for serious infection associated with the catheter in the chest wall.

Chronic intravenous epoprostenol has been

approved by the Food and Drug Administration (FDA) for the treatment of Functional Class III and IV PPH and PAH related to scleroderma.

## 2. Treprostinil

Due to the complexity of chronic intravenous epoprostenol therapy, studies have since been undertaken with various analogues of prostacyclin being administered via the subcutaneous (under the skin), oral, and inhaled routes.

Continuous subcutaneous infusion of treprostinil (Remodulin®) resulted in a slight improvement in exercise capacity, which was greater in sicker patients, and was dose-related.

The use of treprostinil may be somewhat limited, however, by infusion site pain and redness.

Treprostinil has recently been approved by the FDA for the treatment of Functional Class II, III, and IV PAH.

## 2. Bosentan

Endothelin receptor antagonists (ERAs) have recently garnered attention in the treatment of PAH. Bosentan (Tracleer®) is an oral endothelin receptor antagonist.

In a pilot study, bosentan was shown to improve exercise capacity and cardiopulmonary hemodynamics in patients with functional class III and IV PAH. A larger international study (the BREATHE-1 study) confirmed improvement in exercise capacity and showed a reduction in clinical worsening.

While oral bosentan therapy is clearly simpler than chronic intravenous epoprostenol or subcutaneously infused treprostinil, there is a potential for liver injury with bosentan, and monthly blood tests are required while receiving treatment. Bosentan is likely to produce major birth defects if used by pregnant women. Pregnancy must be prevented, and monthly pregnancy tests are required while taking bosentan. Other side effects of bosentan therapy may include headache, flushing, edema (fluid retention), and anemia. Although there are no data on the effects of bosentan or other ERAs on testicular function in man, many ERAs have

profound effects on the structure and function of the testes in animals.

Bosentan has been approved by the FDA for the treatment of Functional Class III and IV PAH.

## Lung Transplantation

Lung transplantation is reserved for patients with severe PAH who do not respond to aggressive medical therapy. Due to the relatively high operative and perioperative risks associated with lung transplantation for PAH, as well as the significant long-term risks of infection and rejection, lung transplantation should not be considered a cure for PAH.

Whether single-lung, bilateral-lung, or heart-lung transplantation is the procedure of choice, is still the subject of controversy. Some experts tend to prefer bilateral-lung transplantation for patients with PAH, and reserve heart-lung transplantation for patients with PAH occurring in association with uncorrectable congenital heart disease, or patients having significant left ventricular dysfunction or valvular disease.

Not all patients are suitable candidates for lung transplantation. Gastro-esophageal reflux disease (GERD), or esophageal dysmotility, occurs frequently in scleroderma, and may be a reason not to attempt lung transplantation due to the risk of aspiration.

Due to the complexity of the diagnosis and treatment of PAH, strong consideration should be given to referral of patients to physicians with expertise in the management of PAH.

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