

Pulmonary Arterial Hypertension

*Understanding your options
for evaluation and treatment*



Introduction

Pulmonary hypertension (PH) is a simplified name for a complex health problem: high blood pressure in the lungs. Although it is rare, it is a disease that can affect people of all ages and ethnic backgrounds.

There are several different kinds of PH; this brochure will describe them and explain how they are different. You will also learn about the different tools your healthcare team can use to make a rapid, accurate diagnosis—and about the newest treatments that show great promise for today's patients. The focus of the information will be on pulmonary arterial hypertension (PAH) because of its unique treatment options.

Understanding a complex disease

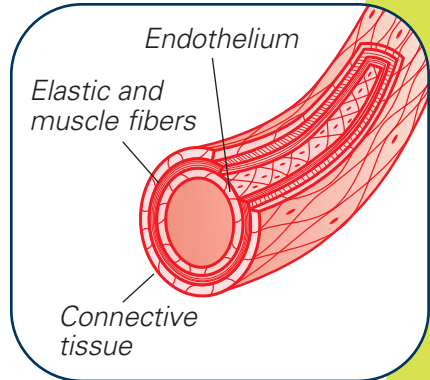
PAH starts when the small vessels that supply blood to the lungs constrict, or tighten up. This makes it more difficult for blood to get through to the lungs, and as a result the heart must pump harder. Over time, scarring (*fibrosis*) of the blood vessels makes them stiffer and thicker, and some may become completely blocked. The extra stress causes the heart to enlarge and become less flexible.

As this cycle continues, less and less blood is able to flow out of the heart, through the lungs, and into the body, and more and more symptoms begin to appear.

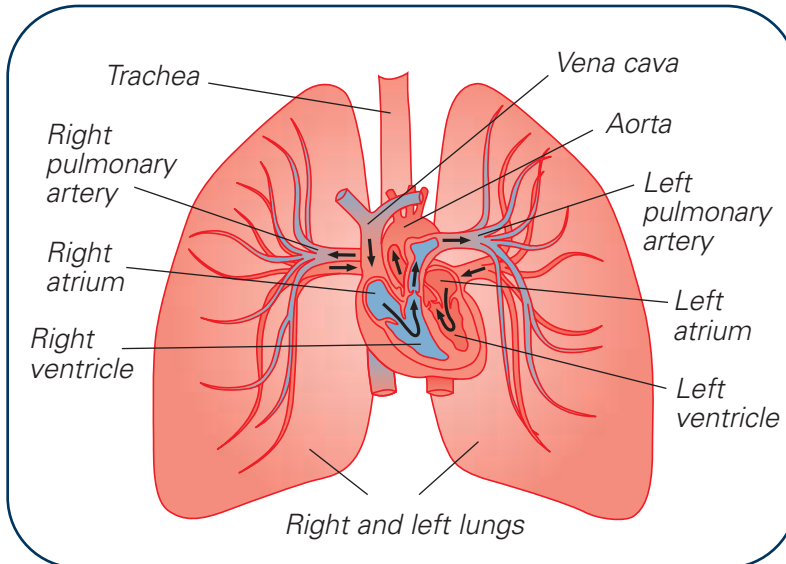
The role of endothelin

Endothelin (*en-do-THÉE-lin*) is a chemical that occurs naturally in the human body. It is mainly produced by endothelial cells, which form a thin lining on the inside of blood vessels. In normal amounts, endothelin plays a role in blood flow. However, abnormal amounts of endothelin are produced in diseases such as PAH. This contributes to the constriction of blood vessels and can affect the blood pressure in the lungs and the severity of other problems associated with PAH.

Normal blood vessel



Blood circulation through the heart and lungs



The different types of pulmonary hypertension

In 1998, the World Health Organization (WHO)* sponsored a meeting of PH specialists with the goal of creating a standardized system for defining different kinds of PH. The committee proposed that the disease be divided into the following five categories:

1. Pulmonary arterial hypertension (PAH)

The pulmonary artery is the large vessel that carries blood from the heart into the lungs so it can pick up oxygen. All cases of PAH affect this artery and the hundreds of tiny blood vessels that branch off from it. This category includes two types:

Primary pulmonary hypertension (PPH), which can occur at random, without an apparent cause. Other times, the disease can be inherited; it is estimated that at least 10 percent of PPH cases occur in families where at least one other person has had it.

PAH related to other causes, which appears to be similar to PPH, but is actually associated with exposure to toxins or the effects of other diseases. These can include

- Use of diet drugs such as fenfluramine or dexfenfluramine (Fen-Phen or Redux)
- Use of cocaine, methamphetamine, or other street drugs
- Exposure to toxins in contaminated foods or the environment
- Human immunodeficiency virus (HIV)
- Collagen vascular disease (scleroderma, lupus, rheumatoid arthritis)
- Chronic liver disease or portal vein obstruction

2. Pulmonary hypertension associated with disorders of the respiratory system

Diseases such as emphysema and asthmatic bronchitis can cause this kind of PH, as can conditions including sleep apnea and chronic exposure to high altitude.

3. Pulmonary hypertension due to chronic thrombotic or embolic disease

Patients at risk for this type of PH may have blood clots in the pulmonary artery, sickle cell disease, or pulmonary embolism caused by a clot, tumor, or foreign matter in the lungs.

4. Pulmonary hypertension due to disorders directly affecting the pulmonary blood vessels

This includes inflammatory diseases such as schistosomiasis or sarcoidosis, or pulmonary capillary disease.

5. Pulmonary venous hypertension (PVH)

PVH is caused by diseases of the left side of the heart, such as mitral valve disease or a poorly performing left ventricle. This can cause increased pulmonary artery pressures but rarely leads to severe pulmonary arterial hypertension.

As mentioned above, this brochure is mainly about the diagnosis and treatment of the first type of PH, pulmonary arterial hypertension (PAH).

*The World Health Organization is considered the international authority on health definitions and disease information. Visit the WHO website at www.who.int.

PAH is often not recognized until the disease is quite advanced. Early symptoms are often similar to those of other diseases, and as a result, many people may have PAH without knowing it. Higher awareness and earlier diagnosis can help people get earlier treatment.

The symptoms of PAH

The symptoms of PAH are caused by a lack of oxygen and increased stress on the heart. These symptoms may not be obvious at first, but over time they become more severe and begin to limit daily life. As the disease progresses, patients experience constant breathlessness and fatigue, so that even simple tasks such as getting dressed and walking short distances become difficult.

Some of the early symptoms of PAH include

- Dyspnea (breathlessness or shortness of breath)
- Chronic fatigue (feeling tired all the time)
- Dizziness, especially when climbing stairs or upon standing up
- Fainting (often the symptom that gets people to see their doctors)
- Edema (swollen ankles and legs)
- Chest pain, especially during physical activity



The importance of accurate diagnosis

PAH is often not diagnosed in a timely manner. It is a rare disease with early symptoms that are easily confused with those of other conditions, such as asthma. Thus, patients may receive treatment for their symptoms, but not for the underlying disease that causes them. As a result, the path to a confirmed diagnosis can take several years while other possibilities are eliminated.

To establish a formal diagnosis of PAH, a series of tests show how well a person's heart and lungs are working. These tests may include

- Echocardiogram
- Six-minute walk test
- Electrocardiogram (ECG)
- Assessment of function in tasks of daily living
- Right heart catheterization

If these tests show that a person has PAH, other kinds of diagnostic tests may be ordered to aid in identifying the cause. These tests include

- A computed tomography (CT or CAT) scan to rule out a pulmonary embolism or lung disease
- A pulmonary function test to rule out obstructive lung disease
- A formal sleep study to rule out sleep apnea
- Laboratory tests to rule out hepatitis, collagen disease, HIV, or other conditions

When no cause can be found, the diagnosis is primary pulmonary hypertension (PPH). Earlier diagnosis and treatment may help people maintain their level of activity longer.



A comprehensive treatment plan

Although there is no cure for PAH, there are several treatments available—and because PAH is a complicated disease, treatment can be complex. You will work closely with your doctor to develop a treatment plan that meets your needs.

Most of the current treatments for PAH are prescribed for specific problems caused by the disease. If you have a combination of symptoms, you may receive different types of medication alone or along with others, including

- Anticoagulants—to prevent blood clots in the lungs
- Calcium channel blockers—to relieve constriction in the pulmonary artery (however, these drugs are effective in only a small percentage of people who take them for PAH)
- Digoxin—to help the heart pump more effectively (however, this drug has no effect on constricted blood vessels)
- Diuretics—to reduce fluid in the body and reduce swelling to make more oxygen available to the blood in the feet and legs
- Inhaled oxygen—to make more oxygen available to the blood

Although none of these therapies has been approved by the FDA to treat PAH, they are used to provide relief from symptoms in some patients.

Epoprostenol (brand name Flolan^{®*}), which helps to open up constricted blood vessels, is approved by the FDA to treat PAH. This medication is delivered continuously to the body through a catheter and has been shown to prolong the lives of people with PAH. Until recently Flolan was the only therapy proven effective in PAH.

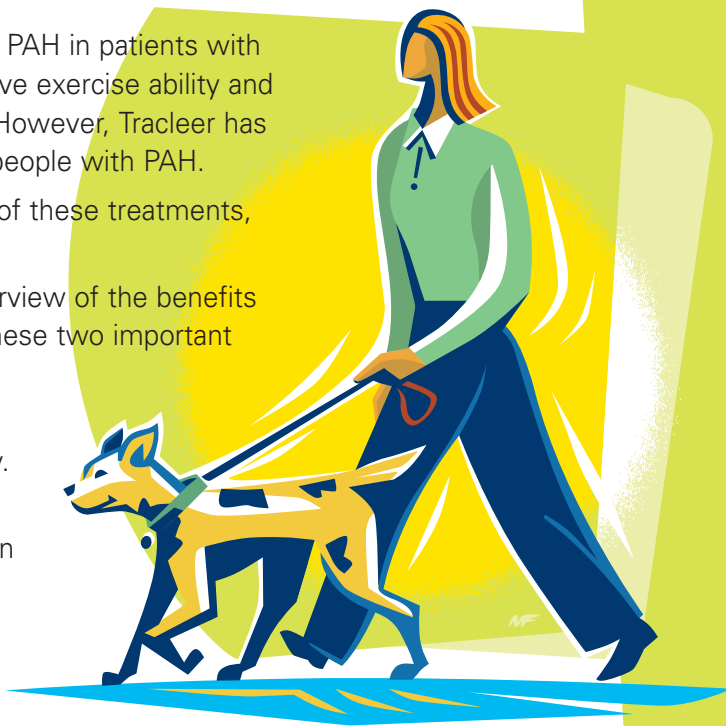
The newest PAH medication is called Tracleer[™] (bosentan), and it can be taken in a simple pill form. Tracleer works in a way different from any other drug; it is an *endothelin receptor antagonist*, which means it helps to prevent endothelin from causing harmful effects.

Tracleer is approved for the treatment of PAH in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. However, Tracleer has not been proven to prolong the lives of people with PAH.

For patients who do not respond to any of these treatments, a lung transplant may be recommended.

The next two pages will give you an overview of the benefits and risks of Tracleer therapy, including these two important issues that every patient must know:

- Tracleer may cause liver damage; therefore, liver monitoring is necessary.
- Tracleer may cause birth defects; therefore, it is essential that patients on Tracleer are not pregnant and don't become pregnant. Monthly pregnancy tests must be obtained.



*Flolan is a registered trademark of GlaxoSmithKline, Inc. Please see accompanying full prescribing information for Tracleer.

A unique treatment option

As discussed earlier in these pages, abnormal amounts of endothelin are produced in PAH, which contributes to worsening symptoms. As the first in a new class of drugs—endothelin receptor antagonists, or ERAs—Tracleer may help to prevent the harmful effects of endothelin in PAH patients with WHO Class III or IV symptoms.

It has been shown to offer several important benefits to patients with PAH:

- Tracleer can improve symptoms and improve patients' ability to perform normal activities
- Tracleer can slow the worsening of symptoms
- Tracleer can lower high blood pressure in the lungs
- Tracleer can enable the heart to pump blood more effectively

Each person will respond in a different way to Tracleer, but effects are usually seen after 4 to 8 weeks of therapy.

Although Tracleer does have important benefits, it does not cure PAH and does not relieve all symptoms of PAH.

As with any medication, the optimal benefit is experienced by patients who take Tracleer as directed by their physicians. Patients should know how to recognize side effects and report them promptly.

Tracleer should *not* be taken with cyclosporine A (used for psoriasis and rheumatoid arthritis, and to prevent rejection of heart or kidney transplants) or glyburide (used for diabetes). These medicines can cause too much Tracleer to stay in your blood and increase your chance of liver damage.

Potential for liver damage: *Tracleer™ (bosentan) may cause liver damage if liver enzyme elevations (measured by blood tests of liver function) are left undetected; therefore, it is very important that you have monthly liver function tests. In addition, Tracleer generally should not be used by patients with moderate or severe liver impairment.*

Before starting Tracleer therapy, patients must receive a liver function test and women of childbearing potential must have a negative pregnancy test. When taking Tracleer, follow-up urine or serum pregnancy tests should be obtained monthly in women of childbearing potential. See “Potential for liver damage” and “Potential for birth defects” for further details.

Working as a team

Whether you are reading this brochure because you think you or a loved one might have PAH, or because you are living with PAH now, you should know that today you have more choices—and more opportunities—than ever. Be proactive about making the right choices; work closely with your loved ones and your healthcare providers to make sure you have the emotional support you need, as well as the most appropriate treatment.

You can be an effective advocate for yourself by

- Asking questions to make sure you understand instructions for taking Tracleer
- Discussing with your doctor what you can realistically expect from your therapy
- Identifying side effects and alerting your doctor to them
- Keeping your healthcare providers informed about how you feel

Potential for birth defects: *Tracleer has the potential to cause birth defects; therefore, pregnancy must be excluded before the start of treatment and prevented thereafter by the use of reliable contraception (e.g., condoms, diaphragms). Hormonal contraceptives, including oral, injectable, or implantable contraceptives, should not be relied upon as a sole means of contraception since these may not work when used with Tracleer. Ask your doctor about effective contraceptive options. Tell your doctor immediately if you become pregnant or suspect that you are pregnant.*

Finding information and support

If you have any questions about the information in this brochure, don't hesitate to ask your healthcare providers. You can also find reliable and helpful information from national organizations:

Pulmonary Hypertension Association

Patient HELP-LINE: **800-748-7274**

PHA office: **301-565-3004**

Website: **www.phassociation.org**

Scleroderma Foundation

Information line: **800-722-HOPE**

Office line: **978-463-5843**

Website: **www.scleroderma.org**

www.TRACLEER.com

Please see accompanying full prescribing information.

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