

PRIMARY  
PULMONARY  
HYPERTENSION



*Cover:*

*Thickening of muscular  
arterial wall in a patient  
with primary pulmonary  
hypertension.*



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## INTRODUCTION

Primary, or unexplained, pulmonary hypertension (PPH) is a rare lung disorder in which the blood pressure in the pulmonary artery rises far above normal levels for no apparent reason.

The pulmonary artery is the blood vessel carrying oxygen-poor blood from the right ventricle, one of the pumping chambers of the heart, to the lungs. In the lungs, the blood picks up oxygen and then flows to the left side of the heart, where it is pumped by the left ventricle to the rest of the body through the aorta.

Hypertension is the medical term for an abnormally high blood pressure. Normal mean pulmonary-artery pressure is approximately 14 mmHg at rest. In the PPH patient, the mean blood pressure in the pulmonary artery is greater than 25 mmHg at rest and 30 mmHg during exercise. This abnormally high pressure (pulmonary hypertension) is associated with changes in the small blood vessels in the lungs, resulting in an increased resistance to blood flowing through the vessels.

This increased resistance, in turn, places a strain on the right ventricle, which now has to work harder than usual against the resistance to move adequate amounts of blood through the lungs.

## INCIDENCE

The true incidence of PPH is unknown. The first reported case occurred in 1891, when E. Romberg, a German doctor, published a description of a patient who, at autopsy, showed thickening of the pulmonary artery but no heart or lung disease that might have caused the condition. In 1951, when 39 cases were reported by Dr. D.T. Dresdale in the United States, the illness received its name.

Between 1967 and 1973, a 10-fold increase in unexplained pulmonary hypertension was reported in central Europe. The rise was subsequently traced to aminorex fumarate, an amphetamine-like drug introduced in Europe in 1965 to control appetite. Only about 1 in 1,000 people who took the drug developed PPH. When they stopped taking the drug, some improved considerably; in others, the disease kept getting worse. Once aminorex was removed from the market, the incidence of PPH went down to normal levels.

More recently, in the United States and France, several cases of PPH have been associated with the appetite suppressants, fenfluramine and dexfenfluramine.

In the United States it has been estimated that 300 new cases of PPH are diagnosed each year; the greatest number are reported in women between the ages of 21 and 40. Indeed, at one time the disease was thought to occur among young women almost exclusively; we now know, however, that men and women in all age ranges, from very young children to elderly people, can develop PPH. Apparently it also affects people of all racial and ethnic origins equally.

*PPH is most common in young women, but anyone can get it.*

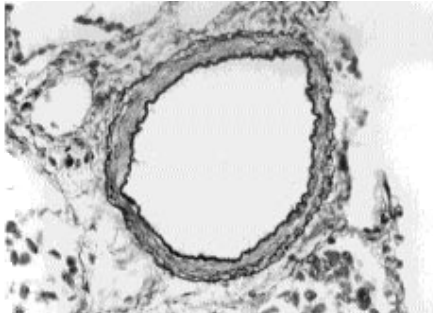
## CAUSE

There may be one or more causes of PPH; however, all remain unknown. The low incidence makes learning more about the disease extremely difficult. Studies of PPH also have been difficult because a good animal model of the disease has not been available.

Researchers think that in most people who develop PPH the blood vessels are particularly sensitive to certain internal or external factors and constrict, or narrow, when exposed to these factors. For example, people with Raynaud's disease seem more likely than others to develop PPH; Raynaud's disease is a condition in which the fingers and toes turn blue when cold because the blood vessels in the fingers and toes are particularly sensitive to cold. Diet suppressants, cocaine, HIV, and pregnancy are some of the factors that are thought to trigger constriction, or narrowing, in the pulmonary artery.

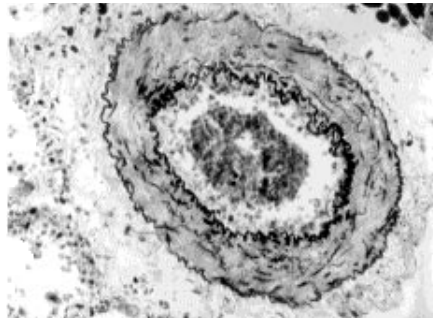
In about 6 to 10 percent of cases, PPH is familial; that is, it is inherited from other family members. The familial form of PPH is similar to the more common form of the disease, sometimes referred to as "sporadic" PPH.

*Normal small pulmonary artery with typically thin muscular wall.*

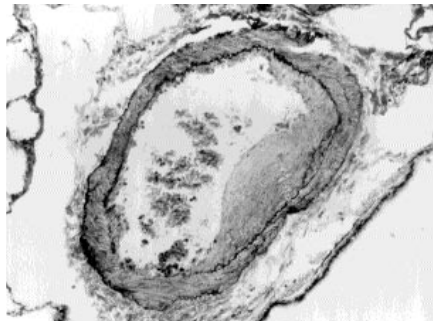


*Some of the changes that can occur in primary pulmonary hypertension:*

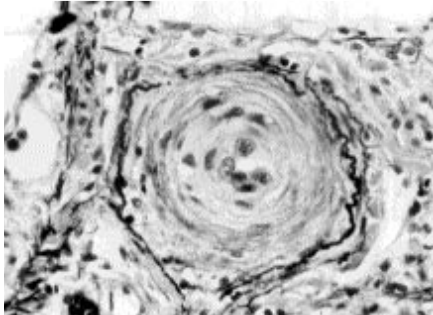
*Wall of small pulmonary artery thickens.*



*Fibrous, or scarred, tissue appears on inner wall of small pulmonary artery.*



*Bands of scarred tissue build up on inner wall of small pulmonary artery, substantially narrowing the blood vessel.*



## COURSE OF THE DISEASE

Researchers believe that one of the ways PPH starts is with injury to the layer of cells (the endothelial cells) that line the small blood vessels of the lungs. This injury, which occurs for unknown reasons, may bring about changes in the way the endothelial cells interact with smooth muscle cells in the vessel wall. As a result, the smooth muscle contracts more than normal and thereby narrows the vessel.

The process eventually results in the development of extra amounts of tissue in the walls of the pulmonary arteries. The amount of muscle increases in some arteries, and muscle appears in the walls of arteries that normally have no muscle. With time, scarring, or fibrosis, of the arteries takes place, and they become stiff as well as thickened. Some vessels may become completely blocked. There is also a tendency for blood clots to form within the smaller arteries.

In response to the extra demands placed on it by PPH, the heart muscle gets bigger, and the right ventricle expands in size. Overworked and enlarged, the right ventricle gradually becomes weak and loses its ability to pump enough blood to the lungs. Eventually, the right side of the heart may fail completely, resulting in death.



## SYMPTOMS

In general, researchers find there is no correlation between the time PPH is thought to have started, the age at which it is diagnosed, and the severity of symptoms. In some patients, especially children, the disease progresses fairly rapidly.

The first symptom is frequently tiredness, with many patients thinking they tire easily because they are simply out of shape. Difficulty in breathing (dyspnea), dizziness, and even fainting spells (syncope) are also typical early symptoms. Swelling in the ankles or legs (edema), bluish lips and skin (cyanosis), and chest pain (angina) are among other symptoms of the disease.

Patients with PPH may also complain of a racing pulse; many feel they have trouble getting enough air. Palpitations, a strong throbbing sensation brought on by the increased rate of the heartbeat, can also cause discomfort.

*Early symptoms usually include tiredness, shortness of breath, and fainting.*

Some people with PPH do not seek medical advice until they can no longer go about their daily routine. The more severe the symptoms, the more advanced the disease. In these more advanced stages, the patient is able to perform only minimal activity and has symptoms even when resting. The disease may worsen to the point where the patient is completely bedridden.

## DIAGNOSIS

PPH is rarely picked up in a routine medical examination. Even in its later stages, the signs of the disease can be confused with other conditions affecting the heart and lungs. Thus, much time can pass between the time the symptoms of PPH appear and a definite diagnosis is made.

PPH remains a diagnosis of exclusion. This means that it is diagnosed only after the doctor finds pulmonary hypertension and excludes or cannot find other reasons for the hypertension, such as a chronic obstructive pulmonary disease (chronic bronchitis and emphysema), blood clots in the lung (pulmonary thromboemboli), or some forms of congenital heart disease.

The first tests for PPH help the doctor determine how well the heart and lungs are performing. If the results of these tests do not give the doctor enough information, the doctor must perform a cardiac catheterization. The procedure, discussed below, is the way the doctor can make certain that the patient's problems are due to PPH and not to some other condition.

#### ■ **Electrocardiogram**

The electrocardiogram (ECG) is a record of the electrical activity produced by the heart. An abnormal ECG may indicate that the heart is undergoing unusual stress.

In addition to the usual ECG performed while the patient is at rest, the doctor may order an exercise ECG. This ECG helps the doctor evaluate the performance of the heart during exercise, for example, walking a treadmill in the doctor's office.

#### ■ **Echocardiogram**

In an echocardiogram, the doctor uses sound waves to map the structure of the heart by placing a slim device that looks like a microphone on the patient's chest. The instrument sends sound waves into the heart, which then are reflected back to form a moving image of the beating heart's structure on a TV screen. A record is made on paper or videotape. The moving pictures show how well the heart is functioning. The still pictures permit the doctor to measure the size of the heart and the thickness of the heart muscle; in the patient with severe pulmonary hypertension,

the still pictures will show that the right heart is enlarged, while the left heart is either normal or reduced in size. Echocardiograms are helpful in excluding some other causes of pulmonary hypertension and can be useful in monitoring the response to treatment.

#### ■ **Pulmonary Function Tests**

A variety of tests called pulmonary function tests (PFTs) evaluate lung function. In these procedures, the patient, with a nose clip in place, breathes in and out through a mouthpiece. The patient's breathing displaces the air held in a container suspended in water. As the container rises and falls in response to the patient's breathing, the movements produce a record, or spirogram, that helps the doctor measure lung volume (how much air the lungs hold) and the air flow in and out of the lungs. Some devices measure air flow electronically.

*A variety of tests are needed to diagnose PPH.*

A mild restriction in air movement is commonly seen in patients with PPH. This restriction is thought to be due, in part, to the increased stiffness of the lungs resulting from both the changes in the structure and the high blood pressure in the pulmonary arteries.

#### ■ **Perfusion Lung Scan**

A perfusion lung scan shows the pattern of blood flow in the lungs; it can also tell the doctor whether a patient has large blood clots in the lungs. In the perfusion scan, the doctor injects a radioactive substance into a vein. Immediately after the injection, the chest is scanned for radioactivity. Areas in the lung where blood clots are blocking the flow of blood will show up as blank or clear areas.

Two patterns of pulmonary perfusion are seen in patients with PPH. One is a normal pattern of blood distribution; the other shows a scattering of patchy abnormalities in blood flow.

A major reason for doing a perfusion scan is to distinguish patients with PPH from those whose pulmonary hypertension is due to blood clots in the lungs.

#### ■ **Right-Heart Cardiac Catheterization**

In right-heart cardiac catheterization, the doctor places a thin, flexible tube, or catheter, through an arm, leg, or neck vein in the patient, and then threads the catheter into the right ventricle and pulmonary artery. Most important in terms of PPH is the ability of the doctor to get a precise measure of the blood pressure in the right side of the heart and the pulmonary artery with this procedure. It is the only way to get this measure, and must be performed in the hospital by a specialist.

During catheterization, the doctor can also evaluate the right heart's pumping ability; this is done by measuring the amount of blood pumped out of the right side of the heart with each heartbeat.

#### ■ **Functional Classification**

Once PPH is diagnosed, most doctors will classify the disease according to the functional classification system developed by the New York Heart Association. It is based on patient reports of how much activity they can comfortably undertake.

**Class 1**—Patients with no symptoms of any kind, and for whom ordinary physical activity does not cause fatigue, palpitation, dyspnea, or anginal pain.

**Class 2**—Patients who are comfortable at rest but have symptoms with ordinary physical activity.

**Class 3**—Patients who are comfortable at rest but have symptoms with less-than-ordinary effort.

**Class 4**—Patients who have symptoms at rest.

## TREATMENT

Some patients do well by taking medicines that make the work of the right ventricle easier. Anticoagulants, for example, can decrease the tendency of the blood to clot, thereby permitting blood to flow more freely. Diuretics decrease the amount of fluid in the body, further reducing the amount of work the heart has to do.

Until recently, nothing more could be done for people who have PPH. However, today doctors can choose from a variety of drugs that help lower blood pressure in the lungs and improve the performance of the heart in many patients.

Some patients also require supplemental oxygen delivered through nasal prongs or a mask if breathing becomes difficult; some need oxygen around the clock. In severely affected cases, a heart-lung, single lung, or double lung transplantation may be appropriate.

*Some people do well on drugs; others may need a transplant.*

### ■ Drugs

Doctors now know that PPH patients respond differently to the different medicines that dilate, or relax, blood vessels and that no one drug is consistently effective in all patients. Because individual reactions vary, different drugs have to be tried before chronic or long-term treatment begins. During the course of the disease, the amount and type of medicine may also have to be changed.

To find out which medicine works best for a particular patient, doctors evaluate the drugs during cardiac catheterization. This way they can see the effect of the medicine on the patient's heart

and lungs. They can also adjust the dose to reduce the side effects that may occur—for example, systemic low blood pressure (hypotension); nausea; angina; headaches; or flushing.

To determine whether a drug is improving a patient's condition, both the pulmonary pressure and the amount of blood being pumped by the heart (the cardiac output) must be evaluated. A decrease in pulmonary pressure alone, for example, does not necessarily mean that the patient is recovering; cardiac output must either increase or remain unchanged. The most desirable response is a decrease in pressure and an increase in cardiac output. Once the patient has reached a stable condition, he or she can go home, returning every few weeks or months to the doctor for followup.

At present, approximately one-quarter to one-half of patients can be treated with calcium channel blocking drugs given by mouth. By relaxing the smooth muscle in the walls of the heart and blood vessels, these calcium channel blockers improve the ability of the heart to pump blood.

A vasodilator, prostacyclin, is helping some severely ill patients who are unresponsive to treatment with calcium channel blockers. The drug, which has been studied in clinical trials, imitates the natural prostacyclin that the body produces on its own to dilate blood vessels. Prostacyclin also seems to help prevent blood clots from forming.

Prostacyclin is administered intravenously by a portable, battery-operated pump. The pump is worn attached to a belt around the waist or carried in a small shoulder pack. The medication is then slowly and continuously pumped into the body through a permanent catheter placed in a vein in the neck.

Prostacyclin seems to improve pulmonary hypertension and permit more physical activity. It is sometimes used as a bridge to help those patients waiting for a transplant, while in other cases it is used for long-term treatment.

*A battery-powered pump, attached to a waistband, is used to deliver continuous infusions of prostacyclin to PPH patients through a catheter inserted in a neck vein.*



## ■ Transplantation

The first heart-lung transplant was performed in this country in 1981. Many of these operations were performed for patients with PPH. The survival rate is the same as for other patients with heart-lung transplants, about 60 percent for 1 year, and 37 percent for 5 years.

The single lung transplant is the most common method of transplant used in cases of PPH. This procedure, in which one lung—either the left or right—is replaced, was first performed in 1983 in patients with pulmonary fibrosis. Double lung transplants are also done to treat PPH, but are less common than the single lung transplant for treatment of PPH.

There are fewer complications with the single lung transplant than with the heart-lung transplant, and the survival rate is on the order of 70 to 80 percent for 1 year. A surprising finding is the remarkable ability of the right ventricle to heal itself. In patients with lung transplants, both the structure and function of the right ventricle markedly improve. Complications of transplantation include rejection by the body of the transplanted organ, and infection. Patients take medications for life to reduce their body's immune system's ability to reject "foreign" organs.



## THE PRIMARY PULMONARY HYPERTENSION PATIENT REGISTRY

### 1981-1988

In 1981, the National Heart, Lung, and Blood Institute (NHLBI) established the first PPH-patient registry in the world. The registry followed 194 people with PPH over a period of at least 1 year and, in some cases, for as long as 7.5 years. Much of what we know about the illness today stems from this study.

At the time the patients enrolled in the registry, 75 percent were in functional classes 3 or 4. They had an average mean pulmonary artery pressure three times the normal, an abnormally high pressure in the right side of the heart, and a reduced cardiac output. In making the diagnosis of PPH, investigators found no complications arising from cardiac catheterization.

The study findings show that pulmonary artery pressure in patients who had symptoms for less than 1 year was similar to that in patients who had symptoms for more than 3 years. Researchers also found that patients whose only symptom was difficulty in breathing upon exercise already had very high pulmonary artery pressure. This suggests that the pulmonary artery pressure rises to high levels early in the course of the disease.

No correlations could be found between the cause of PPH and cigarette smoking, occupation, place of residence, pregnancy, use of appetite suppressants, or use of prescription drugs, including oral contraceptives. This study was designed to serve only as a registry, so it was not possible to evaluate the effectiveness of treatment.

Because we still do not understand the cause or have a cure for PPH, NHLBI remains committed to supporting basic and clinical studies of this illness. Basic research studies are focusing on the possible involvement of immunologic and genetic factors in the cause and progression of PPH, looking at agents that cause narrowing of the pulmonary blood vessels, and identifying factors that cause growth of smooth muscle and formation of scar tissue in the vessel walls. Most important is finding a reliable way to diagnose PPH early in the course of the disease that does not require cardiac catheterization.

## LIVING WITH PRIMARY PULMONARY HYPERTENSION

With the cause of primary pulmonary hypertension still unknown, there is at present no known way to prevent or cure this disease. However, many patients report that by changing some parts of their lifestyle, they can go about many of their daily tasks. For example, they do relaxation exercises, try to reduce stress, and adopt a positive mental attitude.

People with PPH go to school, work at home or outside the home part-time or full-time, and raise their children. Indeed, many patients with PPH do not look sick, and some feel perfectly well much of the time as long as they do not strain themselves physically.

Walking is good exercise for many patients. Some patients with advanced PPH carry portable oxygen when they go out; patients who find walking too exhausting may use a wheelchair or motorized scooter. Others stay busy with activities that are not of a physical nature.

For the patient who lives at a high altitude, a move to a lower altitude—where the air is not so thin, and thus the amount of oxygen is higher—can be helpful. Medical care is important, preferably by a doctor who is a pulmonary vascular specialist. These specialists are usually located at major research centers.

PPH patients can also help themselves by following the same sensible health measures that everyone should observe. These include eating a healthy diet, not smoking, and getting plenty of rest. Pregnancy is not advised because it puts an extra load on the heart. Oral contraceptives are not recommended, and other methods of birth control should be used.

Most doctors and patients agree that it is important for both patient and family to be as informed as possible about PPH. In this way everyone can understand the illness and apply that information to what is happening. In addition to family and close friends, support groups can help the PPH patient.

**FOR MORE INFORMATION**

If you have questions on PPH, contact:

Office of the Director  
Division of Lung Diseases  
National Heart, Lung, and Blood Institute  
II Rockledge Centre  
6701 Rockledge Drive, MSC 7952  
Bethesda, MD 20892-7952  
(301) 435-0233

**For additional copies, write or call:**

NHLBI Information Center  
P.O. Box 30105  
Bethesda, MD 20824-0105  
(301) 592-8573

**Other information can be obtained from:**

Pulmonary Hypertension Association (PHA)  
817 Silver Spring Ave.  
Suite No. 303  
Silver Spring, MD 20910  
1(800) 748-7274

## GLOSSARY

**Angina:** Chest pain that originates in the heart.

**Aorta:** Blood vessel that delivers oxygen-rich blood from the left ventricle to the body; it is the largest blood vessel in the body.

**Atrium:** One of the two receiving chambers of the heart. The right atrium receives oxygen-poor blood from the body. The left atrium receives oxygen-rich blood from the lungs. The plural of atrium is atria.

**Blood pressure:** The pressure of blood against the walls of a blood vessel or heart chamber. Unless there is reference to another location, such as the pulmonary artery or one of the heart chambers, it refers to the pressure in the systemic arteries, as measured, for example, in the forearm.

**Cardiac output:** Total amount of blood being pumped by the heart over a particular period of time.

**Catheter:** Thin, flexible medical tube; one use is to insert it into a blood vessel to measure blood pressure.

**Clinical trials:** Medical studies of patients that evaluate the effectiveness of treatment.

**Constrict:** Tighten; narrow.

**Cyanosis:** A bluish color in the skin because of insufficient oxygen.

**Diastolic pressure:** The lowest pressure to which blood pressure falls between contractions of the ventricles.

**Dilate:** Relax; expand.

**Dyspnea:** A sensation of difficulty in breathing.

**Edema:** Swelling due to the buildup of fluid.

**Endothelial cells:** The delicate lining, only one cell thick, of the organs of circulation.

**Fibrosis:** Process by which inflamed tissue becomes scarred.

**Heartbeat:** One complete contraction of the heart.

**Hyperreactive:** Describes a situation in which a body tissue is especially likely to have an exaggerated reaction to a particular situation.

**Hypertension:** Abnormally high blood pressure.

**Hypotension:** Abnormally low blood pressure.

**Lung volume:** The amount of air the lungs hold.

**Mean blood pressure:** The average blood pressure, taking account of the rise and fall that occurs with each heartbeat. It is often estimated by multiplying the diastolic pressure by two, adding the systolic pressure, and then dividing this sum by three.

**Palpitation:** The sensation of rapid heartbeats.

**Perfusion:** Flow.

**Pulmonary artery:** Blood vessel delivering oxygen-poor blood from the right ventricle to the lungs.

**Pulmonary hypertension:** Abnormally high blood pressure in the arteries of the lungs.

**Smooth muscle:** Muscle that performs automatic tasks, such as constricting blood vessels.

**Spirogram:** A record of the amounts of air being moved in and out of the lungs.

**Syncope:** Fainting; temporary loss of consciousness.

**Systemic:** Relating to a process that affects the body generally; in this instance, the way in which blood is supplied through the aorta to all body organs except the lungs.

**Systolic pressure:** The highest pressure to which blood pressure rises with the contraction of the ventricles.

**Vasodilator:** An agent that widens blood vessels.

**Ventricle:** One of the two pumping chambers of the heart. The right ventricle receives oxygen-poor blood from the right atrium and pumps it to the lungs through the pulmonary artery. The left ventricle receives oxygen-rich blood from the left atrium and pumps it to the body through the aorta.



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