Pulmonary Hypertension: Mechanisms, Investigations and Management

Abstract

Background: Pulmonary hypertension (PH) is a hemodynamic condition characterized by a mean-pulmonary arterial pressure of ≥ 25 mmHg. The most common types of PH are pulmonary arterial hypertension (PAH), chronic thromboembolic pulmonary hypertension (CTEPH), PH caused by left heart disease, and PH due to lung disease. Previously considered incurable, PAH treatment has improved significantly since the introduction of the drug epoprostenol in 1999, with a 3-year survival rate of 30% - 40% to more than 85%. Medications available for the specific treatment of PAH include endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogs, and prostacyclin receptor, agonists. Over the last decade, the management and treatment of CTEPH have improved. Although pulmonary endarterectomy is the only treatment option for CTEPH, newer treatments include the stimulant soluble guanylate cyclase, which is an effective targeted therapy.

Conclusion: The diagnosis and treatment of severe forms of PH, in particular, pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, is complex and best done with close collaboration between local physicians and specialized institutions.

Keywords*: Pulmonary hypertension, pulmonary hypertension (PAH), chronic thromboembolic pulmonary hypertension (CTEPH)*

Introduction

Pulmonary hypertension (PH) is a serious clinical condition characterized by increased pulmonary vascular resistance (PVR) leading to right ventricular failure and premature death. Before the development of epoprostenol, which was first approved in Japan in 1999 as a therapeutic drug. According to PAH, life expectancy for PH patients was less than 3 years. Since 1999, significant improvements have been seen in PH management, especially in its treatment. Early diagnosis is the key to effective PH treatment. However, the initial pulmonary hypertension is often overlooked due to the inaccurate introduction signal. These may include fatigue, weakness, and tiredness. Abnormal fluid accumulation has shown increased high jugular vein pressure, obvious lung components of secondary heart disease, hepatomegaly, ascites, and swelling of the lower extremities may be present. Syncope indicates a life-threatening condition and should not be ignored. Here you will find out the current methods of diagnosis, management, and treatment of PH in Japan (1).

Causes and Risk Factors

Common causes of hypertension include certain types of congenital heart disease, connective tissue disease, coronary artery disease, hypertension, liver cirrhosis, pulmonary thrombosis,

and pulmonary hypertension due to lung disease, such as Chronic emphysema. Heredity also plays a role. High pulmonary hypertension is found in people of all ages, including children, and its frequency increases with age. Pulmonary hypertension is common in women, non-Spanish blacks, and people over the age of 75 (2).

Signs and Symptoms

Symptoms of pulmonary hypertension during the onset of the disease are common in many other medical conditions (e.g., shortness of breath, fatigue). This often causes a delay in diagnosis until more severe symptoms appear, such as dizziness, chest pain, swelling of the ankle, or a feeling of one own's heartbeat (3).

Mechanisms of Pulmonary Hypertension

The pathophysiology of IPAH is not well understood. Inflammation (e.g., hormonal, mechanical, etc.) in the endothelium may occur, possibly in the event of an increase in the incidence of lung damage (i.e., the theory of multiple strokes), leading to a variety of events characterized by vascular scars, endothelial dysfunction, and an increase in intimal and medial (smooth muscles). At least 15-20% of patients previously thought to have IPAH have a familial type of PAH that includes at least one genetic component. The most common genetic factor in these conditions involves the gene BMPR-II. However, only about one-third of affected patients with a PAH family history has significant BMPR-II mutations. This suggests that some unusual genetic factors and/or additional external factors may already be present that put people at the forefront of developing PAH (4).

In 2013, 6 mutations that appear to be associated with PAH and that can be treated with PAH drugs were discovered in a gene, KCNK3, which had never been linked to disease. Each of the 6 mutations was linked to a loss of potassium ion channels. In vitro testing of the investigative agent ONO-RS-082 (2-[p-amylcinnamoyl] amino-4-chlorobenzene acid), a phospholipase A2 inhibitor found that of the 2 variables tested, the drug restores function to inactive potassium. Ion channels. The current NICE Classification PH program now lists the following genetic problems that are known to be associated with PAH: BMPR2, ALK1, ENG, SMAD9, CAV1, KCNK3 (figure 1) (5).

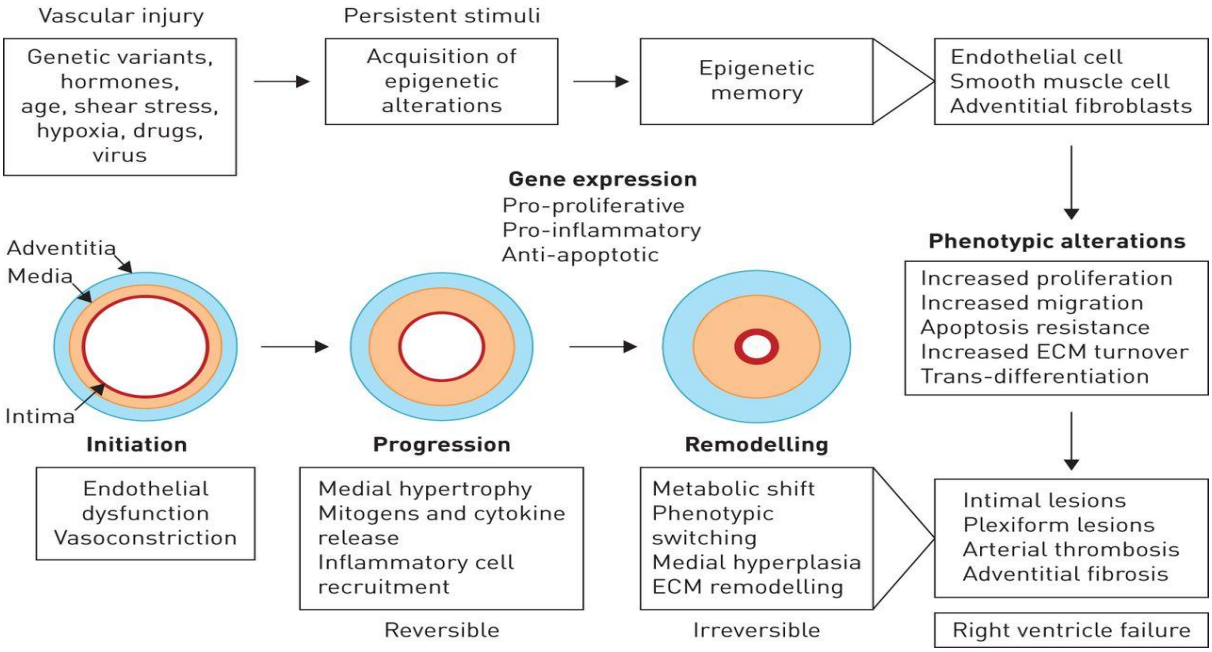

Figure 1 Mechanisms of Pulmonary Hypertension (5)

Classification of Pulmonary Hypertension

Pulmonary hypertension, defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise, is often characterized by a progressive and sustained increase in pulmonary vascular resistance that eventually may lead to right ventricular failure. Left untreated, it can be life-threatening. Because the treatment of pulmonary hypertension is the underlying and its effects on the cardiovascular system, the success rate varies depending on the etiology. New therapeutic agents, such as those tested in prostacyclin and other clinics, have led to the development of specific treatments for previously treatable diseases (figure 2) (6).

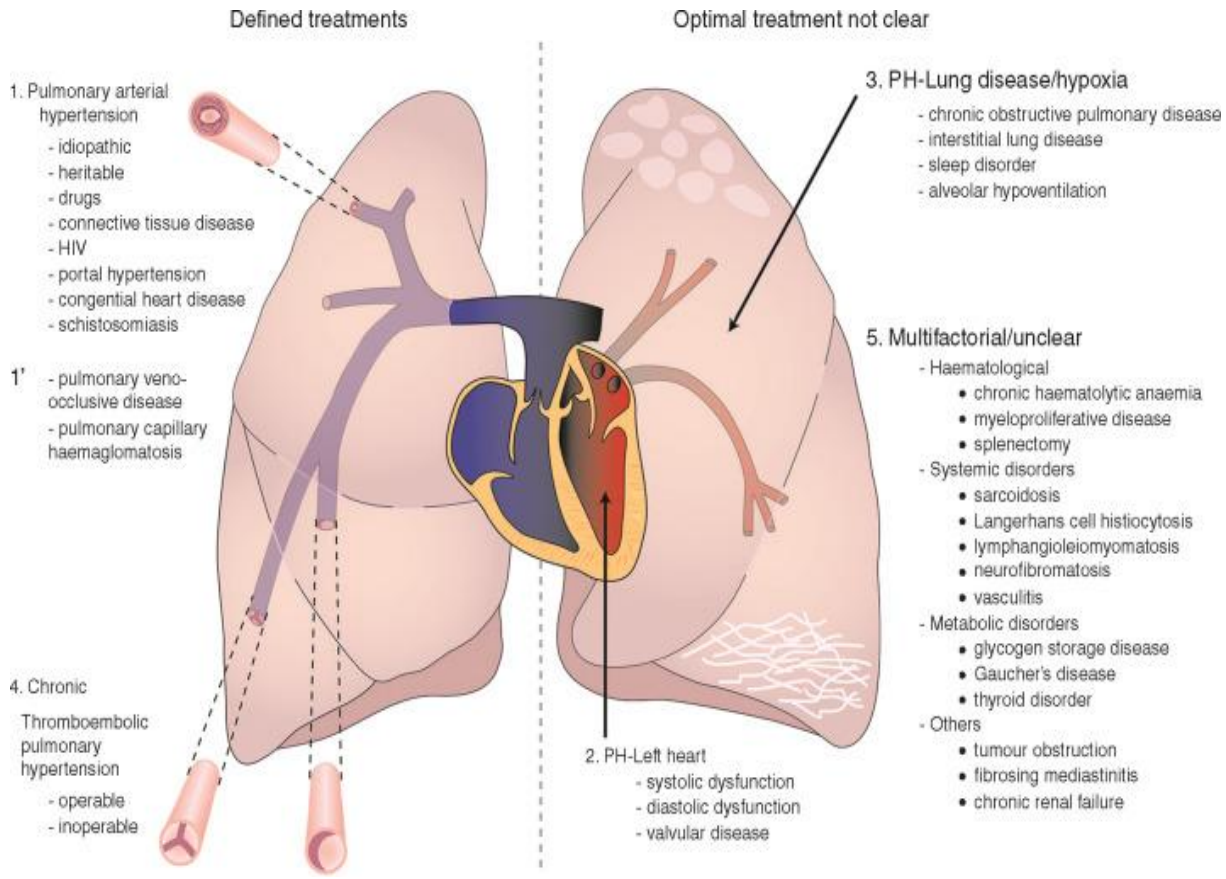

Figure 2 Classification of Pulmonary Hypertension (6)

Group 1: Pulmonary Arterial Hypertension (PAH)

WHO Group 1 refers to pulmonary arterial hypertension (PAH), which is caused when the arteries in the lungs become narrower. The right side of the heart has to work hard to pump blood through these narrow arteries. This increased pressure can cause the heart to lose its ability to pump enough blood to the lungs to meet the needs of the entire body. There are different types of PAH. Idiopathic PAH (IPAH) is PAH that occurs for no apparent reason. Hereditary PAH (HPAH is linked to genes inherited from family members. PAH can also develop in association with other medical conditions, including congenital heart disease, liver disease, HIV, and connective tissue diseases - such as scleroderma and lupus - PAH can even be linked to heart disease There is no known cure for previous or current drug use, such as methamphetamine or certain diet pills. Treatment options for PAH (7).

Group 2: Pulmonary Hypertension Due to Left Heart Disease

WHO group 2 includes PH due to left heart disease. In this PH group, there are problems with contraction or relaxation of the heart, or problems with the valves on the left side of the heart. As a result, the left heart cannot keep up with the blood coming back from the lungs resulting in a "backlog" of blood that increases the pressure in the lungs. WHO group 2 is the most common form of PH (8).

Group 3: Pulmonary Hypertension Due to Lung Disease

WHO group 3 includes pH due to chronic obstructive pulmonary disease and / or hypoxia (low oxygen content). These lung diseases include obstructive pulmonary diseases in which the airways are blocked and it is difficult to breathe (e.g., COPD or emphysema); Obstructive pulmonary disease, in which the lungs develop difficultly when you breathe (e.g., interstitial lung disease or pulmonary fibrosis); Sleep apnea lasts longer in higher positions. The arteries of the lungs constrict so blood flows to the lungs where it gets more oxygen and oxygen. This inertia leads to high blood pressure throughout the lungs (9).

Group 4: Pulmonary Hypertension Due to Chronic Blood Clots in the Lungs

The WHO group 4 is called chronic thromboembolic pulmonary hypertension (CTEPH). This can lead to scarring of the pulmonary arteries, which impedes normal blood flow and makes it harder for the right side of the heart to work. This type of PH is different because it can be treated with pulmonary endarterectomy (PEA).surgery to remove blood clots. However, not all CTEPH patients are eligible for this surgery. The drug is also available to CTEPH patients if the physician determines that the patient is not a candidate for PTE surgery or if PH remains after surgery. Click to learn more about CTEPH (10).

Group 5: Pulmonary Hypertension Due to Unknown Causes

In WHO Group 5, PH is mysteriously the second most common illness. These related conditions include, but are not limited to, sarcoidosis, sickle cell anemia, chronic hemolytic anemia, splenectomy (spleen removal), and certain metabolic disorders (11).

Complications

The most common and gruesome outcome of hypertension is right heart failure. The progressive right heart failure is part of the natural history of pulmonary arterial hypertension (PAH) and is usually somewhat less diagnosed. Registry and institutional data cite PAH patients as the most common cause of death, with sudden cardiac death associated with data suggesting that 44-73% of patients with PAH die from right heart failure or heart failure. In addition to heart attacks on the right side, other causes of death include complications from pulmonary artery enlargement. These include pulmonary artery rupture, severe hemoptysis, and left ventricular artery disease, in which the left main coronary artery is compressed from the pulmonary artery stem. Hemoptysis is caused by anastomoses from bronchial arteries, as hypoxic vasoconstriction in the pulmonary arteries leads to clotting and hypertrophy of the tracheal arteries. Supraventricular arrhythmias and can occur very rarely, resulting in right heart disease (12).

Investigations

Early diagnosis of pulmonary hypertension is difficult because it is rarely diagnosed during regular physical examination. Although the condition is more advanced, its signs and symptoms are similar to those of other cardiovascular conditions. To detect pulmonary hypertension, doctors perform a physical examination and check for any signs and symptoms. You will be asked questions about your medical and family history. Blood tests and imaging tests may help to detect lung hypertension (13).

Blood tests

Blood tests do not help much to diagnose the cause; neither is useful to detect symptoms. Symptoms occur before patient enter diagnostic path. (14).

Chest X-ray

A chest X-ray creates images of the heart, lungs, and chest. It can show enlargement of the right ventricle or the pulmonary arteries. A chest X-ray may also be used to check for other lung conditions that can cause pulmonary hypertension (figure 3) (15).

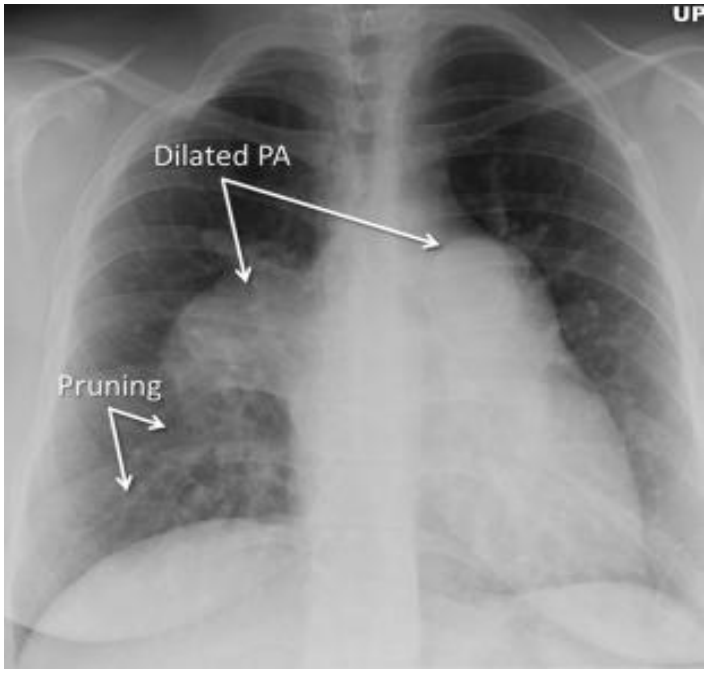

Figure 3 Chest X-ray for Pulmonary Hypertension (15)

Electrocardiogram (ECG)

These non-invasive tests show electrical patterns of the heart and may detect the abnormal heartbeat. An ECG may also reveal signs of enlargement of the right ventricle or ST depression. Right ventricular strain can be caused by pulmonary hypertension, pulmonary embolism (or PE, which itself can cause pulmonary hypertension), RV infarction (a heart attack affecting the RV), chronic lung disease (such as pulmonary fibrosis), pulmonic stenosis, bronchospasm, and pneumothorax (figure 4) (16).

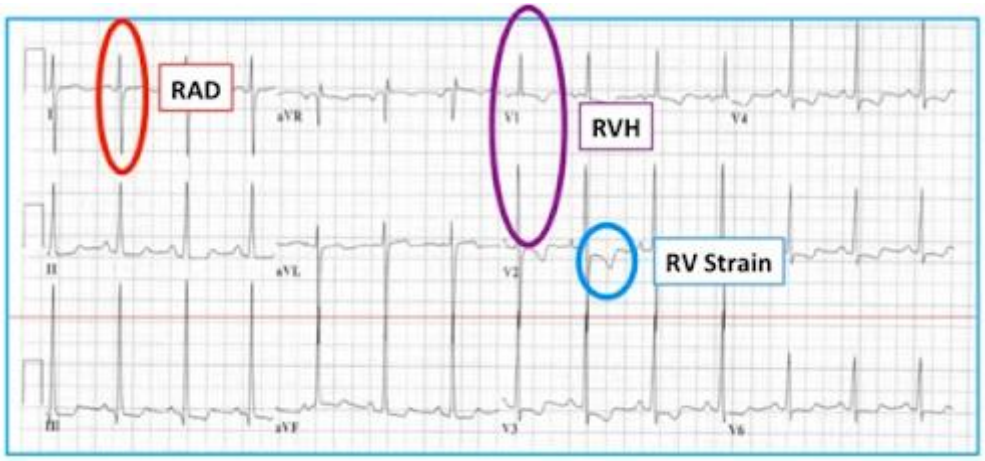

Figure 4 Electrocardiogram (ECG) for Pulmonary Hypertension (16)

Echocardiogram.

Sound waves are used to create dynamic images of the beating heart. This may indicate the size of the right ventricle. Echocardiography is often performed while exercising on an exercise bike or treadmill to understand how the heart works during exercise. Echocardiography can be done after the diagnosis to determine the effectiveness of the treatment (figure 5) (17).

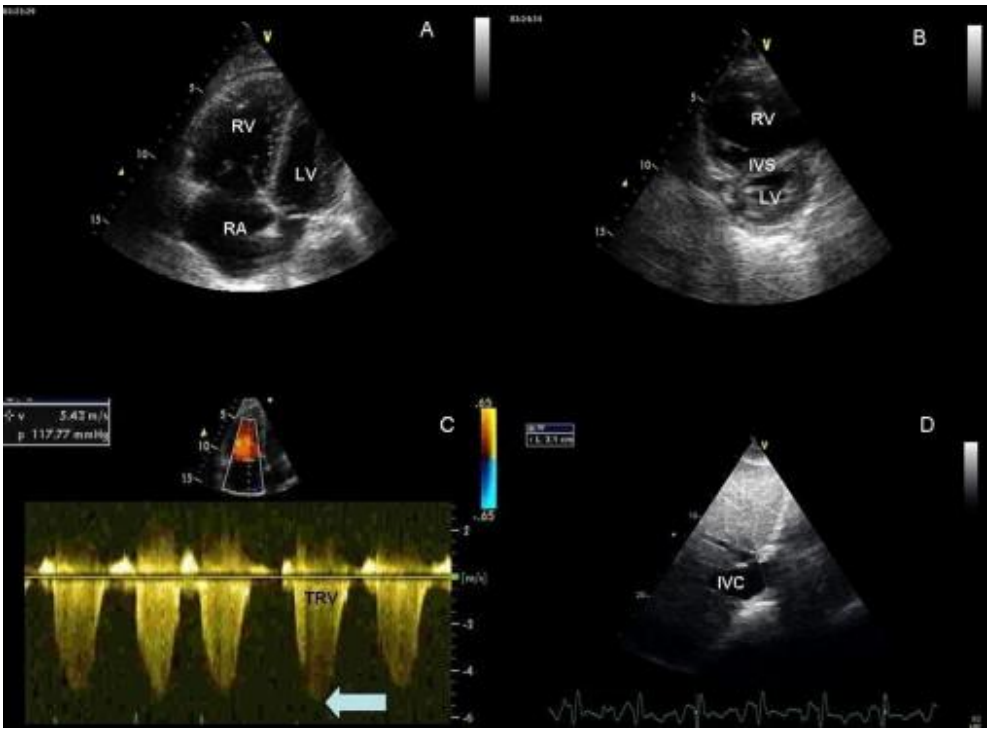

Figure 5 Echocardiogram for Pulmonary Hypertension (17)

Cardiac catheterization

If an echocardiogram shows hypertension in the lungs, you may have a proper cardiac catheterization to confirm the diagnosis. The right heart catheter enables doctors to directly

measure pulmonary pressure and right ventricular pressure. The catheter is gently guided to the right ventricle and pulmonary artery. Tests can also be used to determine how effective drugs are for pulmonary hypertension. If you are diagnosed with hypertension in your lungs, your doctor may also order one or more of the following tests to check your lung condition and determine the cause of the condition (figure 6) (18).

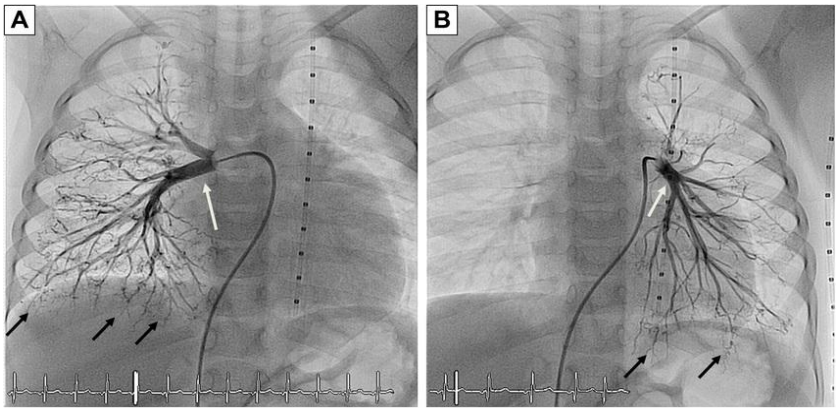

Figure 6 Cardiac Catheterization: Right and Left Pulmonary Arteries (18)

Computerized tomography (CT)

This imaging test creates a variety of images of the bones, blood vessels, and soft tissues in the body. Computed tomography can show the size of the heart and any obstructions in the lungs. This test can be used to closely examine lung diseases that can lead to high levels of pulmonary hypertension, such as COPD or pulmonary fibrosis. A contrast agent (an important difference) can be injected into the blood vessel before the CT scan to visualize embolic material in large arteries (proximal) (figure 7) (19).

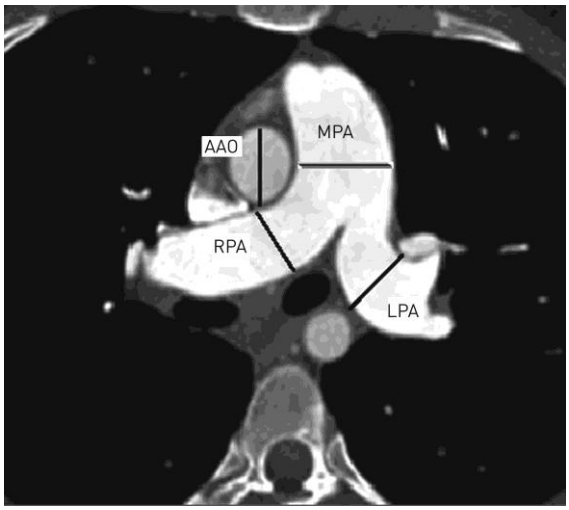

Figure 7 Computerized tomography (CT) for Pulmonary Hypertension (19)

Magnetic resonance imaging (MRI).

MRI scans use magnetic fields and high frequencies to take body images. Your doctor may order a test to measure blood flow to your lungs and determine how well your right ventricle is working (figure 8) (20).

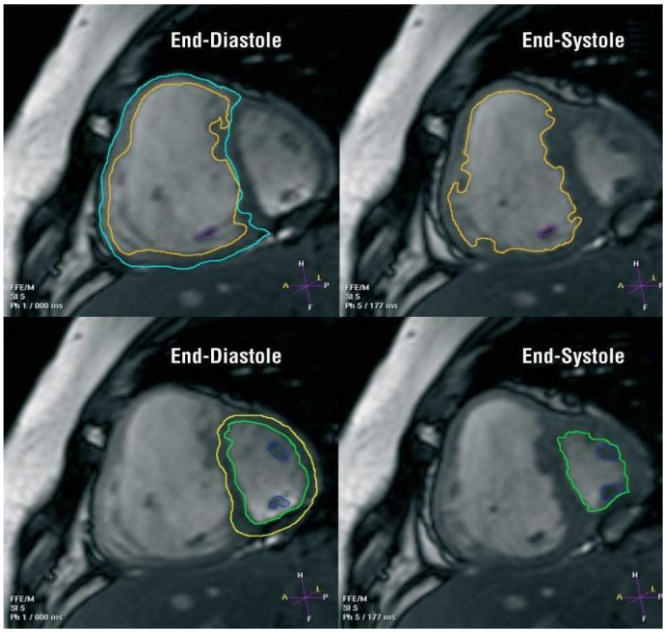

Figure 8 Magnetic resonance imaging (MRI) for Pulmonary Hypertension (20)

Lung (pulmonary) function test

This non-invasive test measures the amount of air the lungs can absorb and the flow of air through the lungs. Testing involves spraying on an object called a spirometer (20).

Sleep study (polysomnogram)

This test measures brain function, heart rate, blood pressure, oxygen levels, and other factors during sleep. It may be helpful to diagnose sleep disorders such as obstructive sleep apnea, which can cause high blood pressure (figure 9) (21).

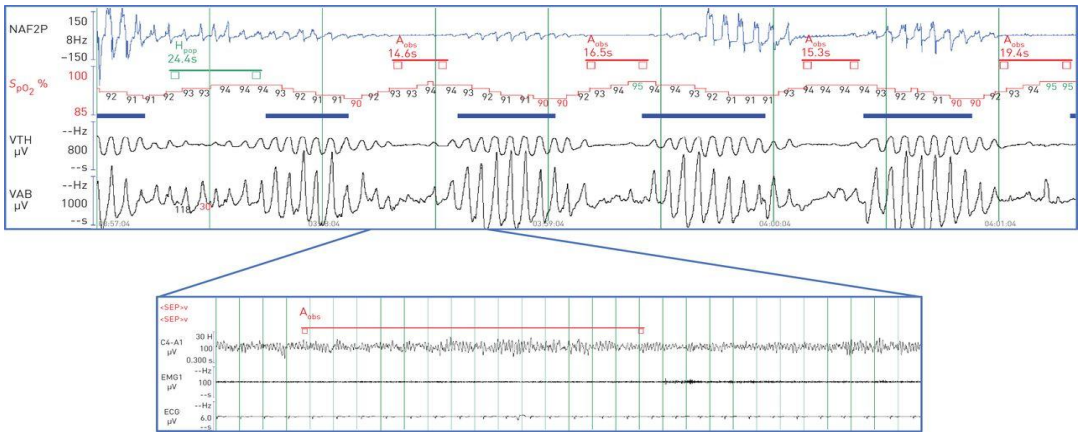

Figure 9 Sleep Study (Polysomnogram) for Pulmonary Hypertension (21)

Ventilation/Perfusion (V/Q) Scan.

In this test, a tracer is injected into a vein in the arm. The tracer shows only blood flow. Then we need the patient to inhale gas to show ventilation scan. A V/Q scan can determine whether blood clots are causing symptoms of pulmonary hypertension (figure 10) (21).

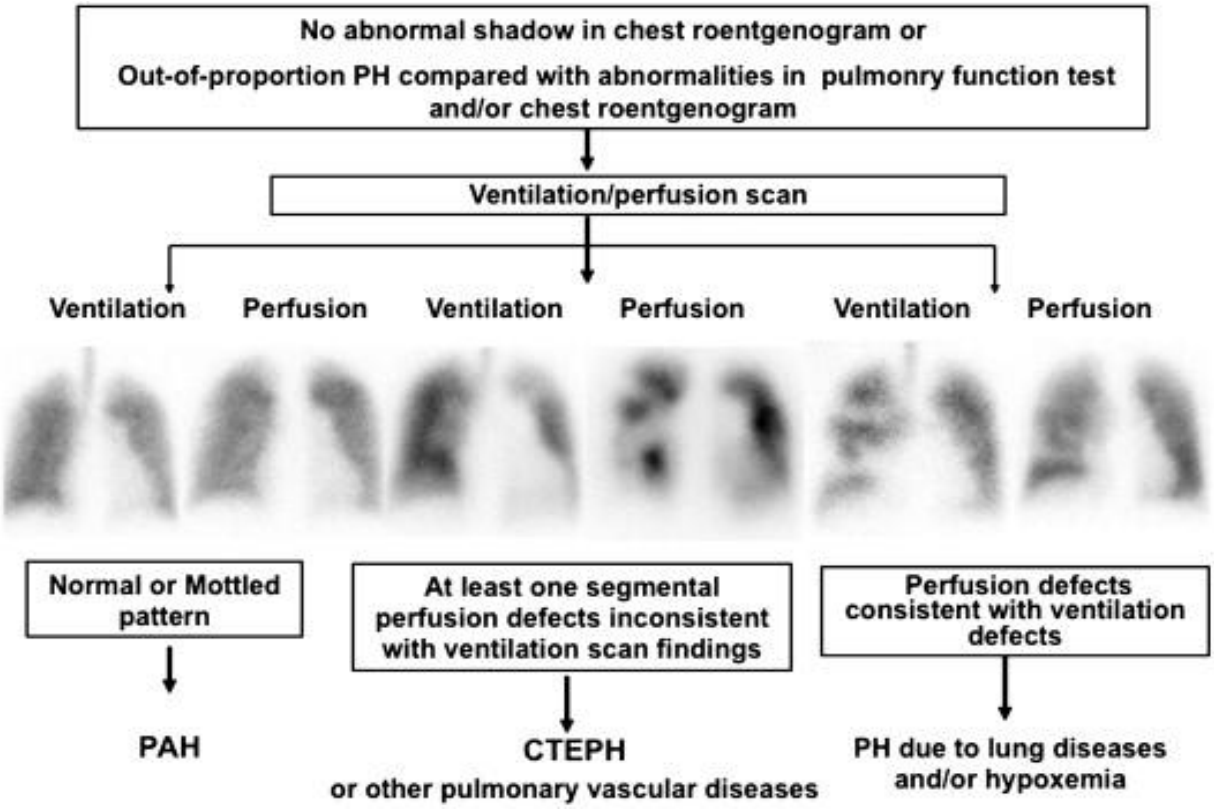

Figure 10 Ventilation/Perfusion (V/Q) Scan for Pulmonary Hypertension (21)

Open-lung biopsy

Lung biopsy is absolutely contraindicated in patient with pulmonary hypertension (22).

Management

Many types of medications are available to help improve the symptoms and signs of pulmonary hypertension and the progression of the disease (22).

PGI analogues

Vasodilators relax and open the small blood vessels, improving blood flow. The most commonly prescribed vasodilator for pulmonary hypertension is epoprostenol. The drug flows continuously with an IV attached to a small pump, which is worn in a pocket on the belt or the shoulder. Potential side effects of epoprostenol include jaw pain, nausea, diarrhea, leg cramps, and pain and infection in the IV area. Other types of vasodilators, including treprostinil, can be taken, injected, or taken orally. The drug iloprost is given while inhaling a nebulizer, a dispenser. Side effects associated with treprostinil include chest pain, often with headaches and nausea, and shortness of breath (22).

Guanylate cyclase (GSC) stimulators

These types of drugs increase the amount of nitric oxide in the body, relax the pulmonary arteries, and reduce the pressure in the lungs. GSC stimulants include riociguat. Side effects include nausea, dizziness, and fainting. Do not take GSC stimulants if you are pregnant (22).

Endothelin receptor antagonists

These drugs block effects of endothelin. Such drugs include bosentan, macitentan, and ambrisentan. These medications may improve energy levels and symptoms. However, they can also damage the liver. You may need a monthly blood test to check your liver function. Endothelin receptor antagonists should not be taken during pregnancy (23).

Sildenafil and tadalafil

Sildenafil and tadalafil are commonly used to treat erectile dysfunction. But they also open the blood vessels in the lungs and allow the blood to flow more easily. Side effects can include stomach upset, headache, and vision problems (23).

High-dose calcium channel blockers.

These drugs help to relax the muscles in the walls of your blood vessels. They include amlodipine, diltiazem, and nifedipine. Calcium channel blockers (CCB) were the first vasodilator agents to gain popular acceptance in the treatment of pulmonary arterial hypertension (PAH). They have been shown to be particularly effective in patients who show a significant immediate hemodynamic response to pulmonary vasodilators (23).

Warfarin

Warfarin may be prescribed to prevent blood clots in the lungs. Blood thinners increase the risk of bleeding, especially in those undergoing surgery. If you are taking warfarin, talk to your doctor about whether you need to stop taking the medicine before the surgery. Many other drugs, supplements, and diets can interact with warfarin. Talk to your doctor about your diet and the medicines you take, including over-the-counter medicines. People taking warfarin need to have regular blood tests to see how well the medicine is working (23).

Digoxin

This medicine slows cardiac rhythm. Mechanism of Action: Digoxin induces an increase in intracellular sodium that will drive an influx of calcium in the heart and cause an increase in contractility. Cardiac output increases with a subsequent decrease in ventricular filling pressures. AV Node Inhibition: Digoxin has vagomimetic effects on the AV node. (23).

Diuretics

These drugs, known as water tablets, help the kidneys pass excess water. Diuretics can be used to reduce the accumulation of water in the lungs, legs, and abdomen (23).

Oxygen therapy

Oxygen therapy can be an important addition to treatment for PH. As well as increasing the amount of oxygen in the blood, oxygen has the additional benefit that it is a vasodilator. This means that it helps to relax the arteries in the lungs, which can reduce the pressure in the pulmonary artery (24).

Surgery and other procedures

Atrial septostomy

It may be recommended if the drug does not control the signs and symptoms of pulmonary hypertension. In an atrial septal defect, the surgeon makes a hole between the left and right atrium (atrial) of the heart to relieve pressure on the right side of the heart. Possible complications include arrhythmias (figure 11) (24).

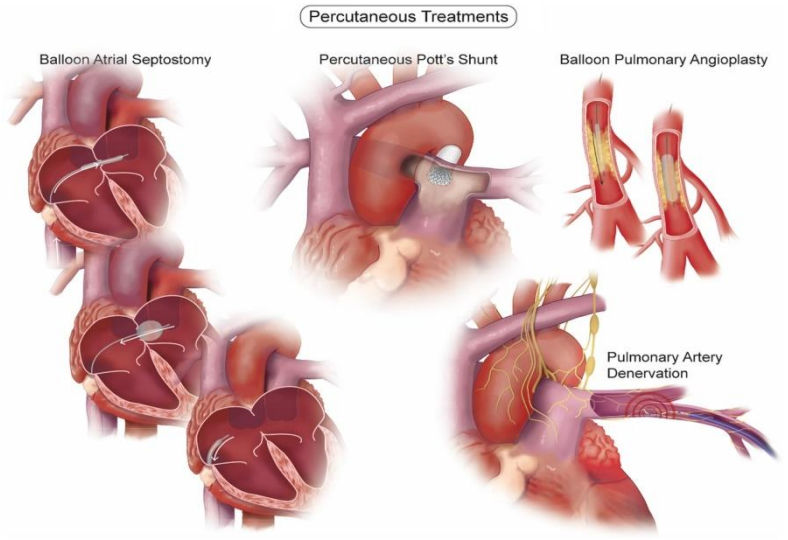

Figure 11 Atrial septostomy (24)

Lung or heart-lung transplant.

Occasionally, pulmonary or heart-lung transplants may be recommended, especially in adolescents with idiopathic pulmonary arterial hypertension (figure 12) (24).

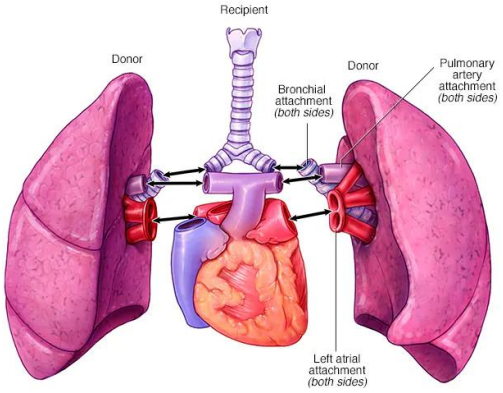

Figure 12 Lung Transplant for Pulmonary Hypertension (24)

Discussion

In recent years, there has been an increase in treatment options and techniques for treating pulmonary arterial hypertension (PAH). However, patients still report delays in obtaining a diagnosis, which is a significant burden associated with the disease and indicates a general lack of knowledge of the disease. This review was written by two PAH patients to describe the patient experience and assess how patients have a say in improving treatment modalities. Since PAH patients live longer, they must work with healthcare professionals to develop treatment strategies that improve and maintain their quality of life. Health professionals should consider a comprehensive approach to disease management, including dietary recommendations, individualized exercise, and counseling options when available, as well as medical treatment. The experience of patients with PAH is important not only in the treatment of each patient but must also be taken into account in the design of the clinical trial and development guidelines. Patient representatives and patient organizations can play an important role in improving the treatment and management of PAH. In this review, we use our experience as patient advocates to describe the current status of PAH patients from initial symptoms to treatment, using two patient cases as examples. We also discuss the role of patient advocacy in improving PAH care and the future roles of patient organizations and patient advocates in the development of clinical trials and the development of new treatment guidelines (25).

Conclusion

Since 1999, PAH has become a treatable cardiovascular disease with improved survival and low morbidity. The exact difference in PH is important because the prognosis and response to treatment vary among different patient populations. Combination therapy should be considered for treatment in patients with newly diagnosed PAH, and reappraisal during follow-up is important. Although CTEPH drugs are now available, PEA is still the treatment option of choice. BPA is another treatment for patients with CTEPH.

Conflict of Interest

There is nothing to disclose

Disclaimer regarding Consent and Ethical Approval:

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors

References

1) Takatsuki S, Ivy DD. Current challenges in pediatric pulmonary hypertension. Semin Respir Crit Care Med. 2013 Oct. 34 (5):627-44.
2) Fernandes CJ, Jardim CV, Hovnanian A, Hoette S, Morinaga LK, Souza R. Schistosomiasis and pulmonary hypertension. Expert Rev Respir Med. 2011 Oct. 5 (5):675-81.

3) Lapa M, Dias B, Jardim C, Fernandes CJ, Dourado PM, Figueiredo M, et al. Cardiopulmonary manifestations of hepatosplenic schistosomiasis. Circulation. 2009 Mar 24. 119 (11):1518-23.
4) Ferreira RC, Domingues AL, Bandeira AP, Markman Filho B, Albuqerque Filho ES, Correiade de Araújo AC, et al. Prevalence of pulmonary hypertension in patients with schistosomal liver fibrosis. Ann Trop Med Parasitol. 2009 Mar. 103 (2):129-43.
5) Sitbon O, Lascoux-Combe C, Delfraissy JF, et al. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. Am J Respir Crit Care Med. 2008 Jan 1. 177(1):108-13.
6) Speich R, Jenni R, Opravil M, Pfab M, Russi EW. Primary pulmonary hypertension in HIV infection. Chest. 1991 Nov. 100(5):1268-71.
7) Battle RW, Davitt MA, Cooper SM, et al. Prevalence of pulmonary hypertension in limited and diffuse scleroderma. Chest. 1996 Dec. 110(6):1515-9.
8) Frost AE, Badesch DB, Barst RJ, Benza RL, Elliott CG, Farber HW, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. Chest. 2011 Jan. 139 (1):128-37.
9) Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest. 2012 Aug. 142 (2):448-456.
10) Sitbon O, Benza RL, Badesch DB, Barst RJ, Elliott CG, Gressin V, et al. Validation of two predictive models for survival in pulmonary arterial hypertension. Eur Respir J. 2015 Jul. 46 (1):152-64.
11) Tonelli AR, Arelli V, Minai OA, Newman J, Bair N, Heresi GA, et al. Causes and circumstances of death in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2013 Aug 1. 188 (3):365-9.
12) D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991 Sep 1. 115 (5):343-9.
13) Demerouti EA, Manginas AN, Athanassopoulos GD, Karatasakis GT. Complications leading to sudden cardiac death in pulmonary arterial hypertension. Respir Care. 2013 Jul. 58 (7):1246-54.
14) Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. Rev Esp Cardiol (Engl Ed). 2016 Feb. 69 (2):177.
15) Soon E, Treacy CM, Toshner MR, MacKenzie-Ross R, Manglam V, Busbridge M, et al. Unexplained iron deficiency in idiopathic and heritable pulmonary arterial hypertension. Thorax. 2011 Apr. 66(4):326-32.
16) Arkles JS, Opotowsky AR, Ojeda J, Rogers F, Liu T, Prassana V, et al. Shape of the right ventricular Doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. Am J Respir Crit Care Med. 2011 Jan 15. 183(2):268-76.
17) Maron BA, Galiè N. Diagnosis, Treatment, and Clinical Management of Pulmonary Arterial Hypertension in the Contemporary Era: A Review. JAMA Cardiol. 2016 Dec 1. 1 (9):1056-1065.

18) Sitbon O, Humbert M, Jagot JL, et al. Inhaled nitric oxide as a screening agent for safely identifying responders to oral calcium-channel blockers in primary pulmonary hypertension. Eur Respir J. 1998 Aug. 12(2):265-70.
19) Wiener RS, Ouellette DR, Diamond E, Fan VS, Maurer JR, Mularski RA, et al. An official American Thoracic Society/American College of Chest Physicians policy statement: the Choosing Wisely top five list in adult pulmonary medicine. Chest. 2014 Jun. 145 (6):1383-1391.
20) Ventetuolo CE, Klinger JR. WHO Group 1 pulmonary arterial hypertension: current and investigative therapies. Prog Cardiovasc Dis. 2012 Sep-Oct. 55 (2):89-103.
21) Taichman DB, Ornelas J, Chung L, Klinger JR, Lewis S, Mandel J, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. Chest. 2014 Aug. 146 (2):449-475.
22) Johnson SR, Granton JT, Mehta S. Thrombotic arteriopathy and anticoagulation in pulmonary hypertension. Chest. 2006 Aug. 130(2):545-52.
23) Johnson SR, Mehta S, Granton JT. Anticoagulation in pulmonary arterial hypertension: a qualitative systematic review. Eur Respir J. 2006 Nov. 28(5):999-1004.
24) Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. N Engl J Med. 2015 Aug 27. 373 (9):834-44.
25) Mathai SC, Girgis RE, Fisher MR, et al. Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. Eur Respir J. 2007 Mar. 29(3):469-75.