Pulmonary Hypertension (PH) — Categories, Causes and Treatment

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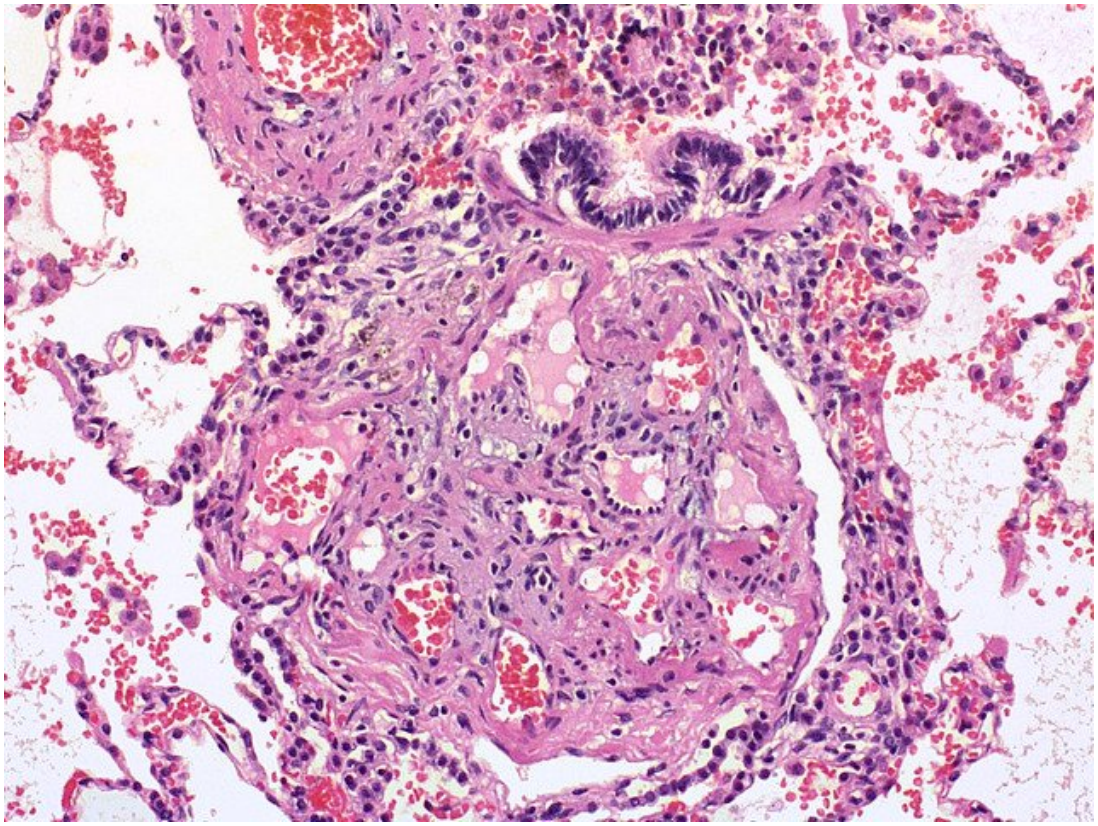
Pulmonary hypertension (PH) is a clinical condition that is characterized by elevated pulmonary arterial pressure. It can lead to serious clinical consequences, thus early detection and treatment are important before it becomes advanced and less responsive to therapy. PH is a feature of advanced underlying disease that is usually caused by cardiac, pulmonary, or intrinsic vascular diseases. Therefore, suspected cases will undergo diagnostic testing to confirm the condition and identify the underlying cause. The definition, epidemiology, classification and etiologies, pathophysiology, clinical features, diagnostic evaluation, and treatment all will be discussed in this article.



Definition of Pulmonary Hypertension

Pulmonary hypertension is an abnormal rise of mean pulmonary arterial pressure above the upper limit of normal (that is more than or equal to 25 mmHg at rest). The mean pulmonary pressure of 21-24 mmHg is considered as the borderline. The definition, however, is not based on the systolic pulmonary artery pressure.

In pulmonary hypertension, there is enlarged proximal pulmonary arteries, right ventricular hypertrophy, and right atrial dilation.

Classification of Pulmonary Hypertension

Pulmonary Hypertension is classified as:

Idiopathic pulmonary arterial hypertension (IPAH)

It is defined as pulmonary hypertension in the absence of underlying diseases of the lungs or the heart. It is an extremely **rare condition**, with an estimated incidence of two cases per million. It develops **most commonly in women** in their fourth or fifth decades (middle-aged women).

Secondary pulmonary hypertension

Hypoxemia of is the main pathophysiological trigger that results in pulmonary arterial vasoconstriction which leads to pulmonary hypertension.

It has been revealed that some types of pulmonary hypertension closely resemble idiopathic pulmonary arterial hypertension (IPAH) in their histopathology and response to treatment. Therefore, World Health Organization (WHO) has classified the pulmonary hypertension into **5 categories** based upon mechanism:

Category 1: Pulmonary arterial hypertension (PAH)

Key feature: Elevation in pulmonary arterial pressure (PAP) with normal pulmonary capillary wedge pressure (PCWP). It includes:

Idiopathic (IPAH):

- Sporadic
- Familial
- Exposure to drugs or toxins
- Persistent pulmonary hypertension of the newborn
- Pulmonary capillary hemangiomatosis (PCH)

Associated with other active conditions:

- Collagen vascular disease
- Congenital systemic-to-pulmonary shunts
- Portal hypertension
- HIV infection

Category 2: Pulmonary venous hypertension

Key feature: Elevation in PAP with elevation in PCWP

Pulmonary hypertension owing to left heart disease, and includes:

- Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease
- Pulmonary venous obstruction
- Pulmonary venoocclusive disease (PVOD)

Category 3: Pulmonary hypertension associated with hypoxemic lung disease

Key feature: Chronic hypoxia with mild elevation of PAP

Includes:

- Chronic obstructive lung disease
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Category 4: Pulmonary hypertension due to chronic thromboembolic disease

Key feature: Elevation of PA pressure with documentation of pulmonary arterial obstruction for over 3 months

Includes:

- Chronic pulmonary thromboembolism
- Nonthrombotic pulmonary embolism (tumor, foreign material)

Category 5: Miscellaneous

Key feature: elevation in PAP in association with a systemic disease where a causal relationship is not clearly understood.

Includes:

- Sarcoidosis
- Chronic anemias
- Histiocytosis X
- Lymphangiomatosis
- Schistosomiasis

Pulmonary arterial hypertension (PAH) refers to category 1 PAH, while **Pulmonary hypertension (PH)** refers to any of from the 2nd to the 5th categories. Sometimes, the term “Pulmonary Hypertension” is also used when referring to all 5 categories.

Epidemiology of Pulmonary Hypertension

Spread of pulmonary hypertension

The prevalence of Pulmonary Arterial Hypertension (PAH) in the general population is about **5 to 15 cases per one million adults**. The prevalence of other categories appears to vary widely in the population. The annual death rate from pulmonary hypertension increased from 5.2 to 5.4 per 100,000 population. The **greatest rate of death was in African-Americans and women**. The most common cause of death from 1980 to 1999 was a chronic lower respiratory disease. Thereafter, Pulmonary hypertension (PH) was the most common cause of death. Heart failure was the most common cause of hospitalization after 1994.

Pathophysiology of Pulmonary Hypertension

The hemodynamic factors that contribute to pulmonary artery pressure can be described using **Ohm’s Law:**

Ppa = (Q x PVR) + PCWP

Ppa is mean pulmonary arterial pressure. **Q** is right-sided cardiac output. **PVR** is pulmonary vascular resistance. **PCWP** is pulmonary capillary wedge pressure.

If you looked at this equation, you'll find that the mean **pulmonary arterial pressure is determined by the pulmonary vascular resistance**, right-sided cardiac output, and mean pulmonary venous pressure which is estimated by the pulmonary capillary wedge pressure.

Increased follow through pulmonary vessels as a result of increased right-sided cardiac output is not enough to cause pulmonary hypertension because the pulmonary vessels vasodilate and recruit vessels in response to increased blood flow. Also, increased pulmonary venous pressure alone doesn't cause pulmonary hypertension. Therefore, the main cause of pulmonary hypertension is almost always increased pulmonary vascular resistance. However, a chronic increase in both increased blood flow and pulmonary venous pressure may increase pulmonary vascular resistance.

Causes of increased pulmonary vascular resistance

Conditions associated with occlusive vasculopathy of the small pulmonary arteries and arterioles:

- Idiopathic PAH
- Connective tissue disease
- HIV infection
- Congenital heart disease

Conditions that decrease the area of the pulmonary vascular bed:

- Pulmonary emboli
- Interstitial lung disease

Conditions that induce hypoxic vasoconstriction:

- Hypoventilation syndromes
- Parenchymal lung disease

Causes of increased flow through the pulmonary vasculature

Congenital heart defects with left-to-right shunt:

- Atrial septal defects
- Ventricular septal defects
- Patent ductus arteriosus

Liver cirrhosis

Causes of increased pulmonary venous pressure

- Mitral valve disease
- Left ventricular systolic or diastolic dysfunction
- Constrictive pericarditis
- Restrictive cardiomyopathy

- Pulmonary venous obstruction (eg, pulmonary veno-occlusive disease)

Regardless of the cause of pulmonary hypertension, the right-side heart tries to overcome the high pressure in the pulmonary vascular beds by right ventricular hypertrophy and increasing right ventricular systolic pressure to maintain adequate cardiac output.

Chronic increase in pulmonary vascular resistance may cause remodeling of pulmonary vasculatures causing sustained pulmonary hypertension even if the triggering cause is removed, that is why early detection and prompt treatment of pulmonary hypertension and the underlying cause is important.

Several factors affect the ability of the right ventricle to overcome the increase in vascular resistance, such as:

Age: The older the patient, the less ability of the heart to adopt the increased vascular resistance.

The rapidity of the development of pulmonary hypertension: Acute pulmonary embolism can increase the load on the right ventricle and lead to right heart failure and shock. Chronic pulmonary thromboembolism of the same severity may result only in mild symptoms, such as exercise intolerance!

Right ventricular hypertrophy increases the myocardial demands as the enlarged muscle needs more blood flow and oxygen to contract efficiently, resulting in myocardial ischemia with subsequent RV failure.

Chronic hypoxia can cause vasoconstriction of pulmonary vasculatures by a variety of partially reversible mechanisms:

1. Decreased production of nitric oxide synthase (eNOS) enzyme by the vascular endothelial cells results in a diminished **nitric oxide**, the natural endogenous vasodilator.
2. Impaired the functional of the voltage-gated potassium channels in pulmonary artery smooth muscle cells can alter the membrane resting action potentials resulting in an increase in the intracellular influx of calcium and contraction of the smooth muscles of the pulmonary artery.
3. The activity of phospholipase A2 increases, resulting in a release of the arachidonic acid from phospholipid membranes. The metabolism of Arachidonic acid by cyclooxygenases can lead to different vasoactive compounds, such as prostaglandins, thromboxanes, and leukotrienes.
4. Expression of endothelin increases.

Clinical Features of Pulmonary Hypertension

Signs and symptoms of pulmonary hypertension are **non-specific**, therefore it is difficult to recognize the condition, especially if it is obscured by the manifestations of the underlying cause.

History

The most prominent feature of pulmonary hypertension is **dyspnea** that initially on exertion but later occurs also at rest. There are several causes for the dyspnea:

1. Dyspnea can be a manifestation of the **underlying disease** (eg,

pulmonary embolus, chronic obstructive pulmonary disease).
2. Right ventricular failure can be associated with **congestion of hepatic veins** and the formation of ascites that may result in mechanical compression on the diaphragm leading to the sensation of dyspnea.
3. Decreased right-side cardiac output alone can cause **acidosis and hypoxia** with compensatory tachypnea.

The patient may present with **dull, retrosternal chest pain** (i.e. angina) due to increased oxygen demand and myocardial hypoperfusion that is caused by hypertrophy and the increased stress on the right ventricle. Exertional syncope due to an inability of increased cardiac output with activity or exercise. Anorexia, nausea, vomiting and right hypochondrial abdominal pain due to hepatic congestion cause by right side heart failure.

Examination

If pulmonary hypertension progressed into pulmonary hypertension with right-sided heart failure, characteristic physical signs can be detected by examination:

Inspection:

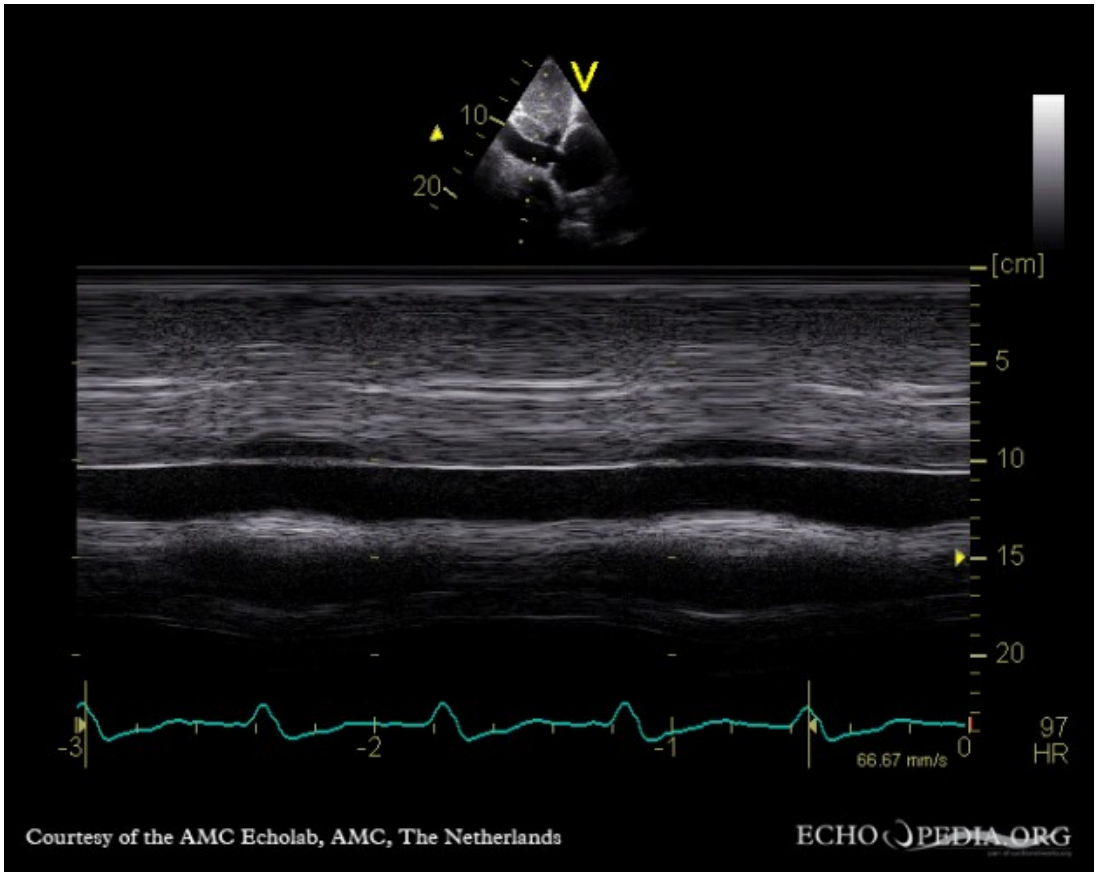
- Prominent A wave may be seen when assessing jugular venous pulsation (JVP).
- Cyanosis can be seen in late stages due to the systemic increase in vascular resistance as a result of markedly reduced cardiac output.

Palpation:

- Right ventricular hypertrophy can cause left parasternal heave.
- Systolic pulsation can be felt in the pulmonary area (left intercostals space) due to a dilated pulmonary artery.

Auscultation:

- Increased intensity of the pulmonic component of the 2^{nd} heart sound (P2), maybe the initial finding of pulmonary hypertension
- Right-sided fourth heart sound (S4)
- Systolic ejection click and flow murmur in pulmonary area
- In severe cases, tricuspid and pulmonary regurgitation and signs of right heart failure (Cor pulmonale)



Investigations of Pulmonary Hypertension

Diagnostic testing is mandatory when pulmonary hypertension is suspected. The purpose of diagnostic testing is to confirm the diagnosis of pulmonary hypertension, determine its severity and identify the underlying cause.

Chest X-ray

- The lung field may show the underlying pathology.
- It may show enlargement of central pulmonary arteries and the main branches. Enlarged proximal pulmonary arteries taper rapidly not reaching to the periphery.
- It may show cardiomegaly with right ventricular enlargement and right atrial dilatation.

Electrocardiogram

It may show right ventricular hypertrophy with axis deviation.

Echocardiography

- It may show enlargement of the right atrium and ventricle with a thickened interventricular septum, with a reduction in a reduction in left ventricular (LV) cavity size.
- Echo can reveal the tricuspid regurgitant jet that can be used to estimate the

right ventricle (RV) systolic pressure by Doppler.
- Right ventricular pressure overload may result in abnormal septal motion.
- Echo is helpful in the evaluation of the suspected underlying cause.

Cardiac catheterization

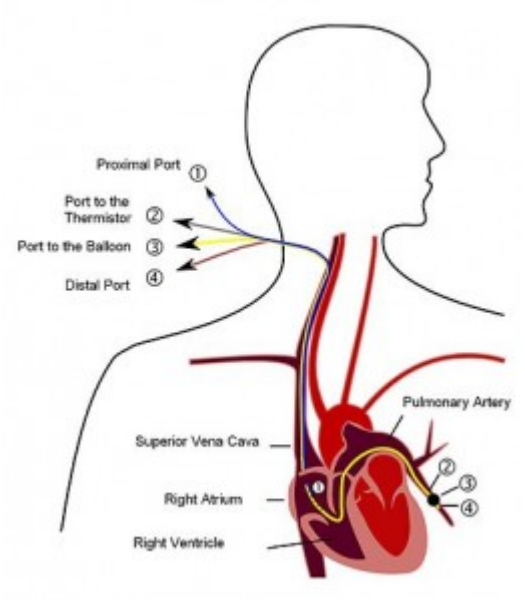


Image: "Pulmonary artery catheter" by Tariq Abdulla.
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It is used for confirming the diagnosis and the accurate assessment of pulmonary artery pressure, cardiac output, and left ventricle filling pressure as and any underlying cardiac shunt.

Pulmonary function tests

They can reveal the underlying obstructive airway disease. (Note that high-resolution chest computed tomography (CT) is preferred to identify the restrictive lung diseases). They may show reduced vital capacity.

Laboratory tests

They include complete blood Count (CBC), Liver Function Tests (LFTs), HIV testing and antinuclear antibody (ANA) tests. It has been found that thyroid abnormalities are frequently associated in patients with idiopathic pulmonary hypertension, therefore thyroid-stimulating hormone levels should be assessed periodically.

Differential Diagnosis of Pulmonary Hypertension

Early pulmonary hypertension should be differentiated from other causes of **exertional dyspnea,** which is the most common initial symptom.

Once pulmonary hypertension caused right ventricular failure with its characteristic manifestations (peripheral edema, exertional chest pain, exertional syncope, and right upper quadrant pain) , the differential diagnosis involves:

Left-sided heart failure	Left ventricular systolic and diastolic heart failure can cause: 1. Peripheral edema 2. Right upper quadrant pain due to hepatic congestion, 3. Syncope due to arrhythmias or inadequate cardiac output. 4. Exertional chest pain. It can be distinguished from pulmonary hypertension using echocardiography or right and left heart catheterization.
Coronary artery disease	Myocardial ischemia is one of the most common causes of exertional chest pain, and also can cause exertional syncope if it is complicated by arrhythmia. Coronary artery disease can be identified simply by ECG stress test.
Hepatic disease	Acute or chronic hepatic disease can affect the production of albumin and the pressure inside the portal vein which may result in hypoalbuminemia or portal hypertension, leading to peripheral edema. It also may cause right upper quadrant pain. Liver disease can be detected by liver function tests (LFTs) and Rt. upper quadrant ultrasound (U/S).
Budd-Chiari syndrome	Budd-Chiari syndrome occurs due to thrombosis of the hepatic veins or the intrahepatic or suprahepatic inferior vena cava, resulting in venous outflow obstruction. Patient presents with peripheral edema and right upper quadrant pain due to hepatic congestion. Budd-Chiari syndrome can be identified by Doppler ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), or venography.

Treatment of Pulmonary Hypertension

Secondary pulmonary hypertension

Early detection and treatment of the underlying cause may reverse the condition because the advanced disease is less responsive to the treatment.

Continuous supplementation of oxygen:

- For at least 15 hours/day has been found to slow the progression of pulmonary hypertension in patients with category 3 pulmonary PH, such as Chronic Obstructive Pulmonary Disease (COPD).
- It also should be considered for all patients with pulmonary hypertension plus hypoxemia.
- Pulse oximetry should be monitored to identify any reduction in oxygen saturation.

Inhaled nitric oxide is a natural vasodilator that is effective in lowering the pulmonary artery pressure in patients with category 1 pulmonary hypertension, and critically ill patients.

Anticoagulation:

- Patients with pulmonary hypertension are at increased risk of for intrapulmonary thromboembolism.
- Warfarin is indicated to be given with INR maintained at 2–3 to patients with hereditary pulmonary artery hypertension (PAH), drug-induced PAH, or category 4 pulmonary hypertension.

Digoxin is effective in patients with right ventricular failure from pulmonary hypertension:

- It improves the right ventricular ejection fraction in patients with category 3

pulmonary hypertension due to COPD and biventricular failure.
- The effect on digoxin on patients with category 1 PAH is not known.

Vasodilator therapy: Chronic vasodilator therapy decreases pulmonary hypertension, and include **Calcium channel blockers:**

- Nifidipine, diltiazem in high doses may produce a dramatic reduction in pulmonary artery pressure and associated with improved symptoms.
- CCBs haven't been approved for the treatment of pulmonary arterial hypertension (PAH) by the U.S Food and Drug Administration.

Idiopathic pulmonary arterial hypertension (IPAH)

There is no satisfactory treatment for primary pulmonary hypertension. And the prognosis is generally poor. The supportive measure is the following:

Lifestyle changes: It includes **exercise** like bike riding or swimming, which appears to be beneficial for patients with pulmonary hypertension. Weight lifting and climbing upstairs (isometric activities) should be avoided because they can lead to syncope. Pregnancy should not be allowed as it may worsen the disease leading to mortality of mother or the child.

Oxygen supplementation if patient is hypoxemic at rest.

Diuretics: Patients with advanced primary pulmonary hypertension can have increased left ventricular filling pressure that contributes to the symptoms of dyspnea and orthopnea, therefore, diuretics improve dyspnea. Diuretics are also the first choice for right ventricular failure. If necessary, fluid can also be removed by dialysis or ultrafiltration.

Inhaled nitric oxide may helpful.

Anticoagulants: Significant survival benefit is seen with warfarin maintaining INR 2–3.

Vasodilator therapy: Chronic vasodilator therapy decreases pulmonary hypertension, and include:

- **Phosphodiesterase inhibitors:** Sildenafil (Viagra) and tadalafil are potent pulmonary vasodilators, which are approved for the treatment of pulmonary arterial hypertension (PAH).
- **Continuous intravenous infusion of epoprostenol (prostacyclin)** is approved as a chronic IV treatment of pulmonary arterial hypertension (PAH). It has been shown to improve quality of life, exercise tolerance and survival. It is administered through a central venous catheter that is surgically implanted and delivered by an ambulatory infusion system.

Lung transplantation is considered for patients who continue experiencing manifestations of right heart failure while on intravenous prostacyclin. Acceptable results have been achieved with heart-lung, bilateral lung, and single-lung transplantation.

Prognosis of Pulmonary Hypertension

The natural course of idiopathic pulmonary arterial hypertension is uncertain, and the disease is usually diagnosed late after changes become partially reversible. Before the current therapies, the mean survival rate was **two to three years once the disease is diagnosed**. The main cause of death is right ventricular failure.

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Notes