Chapter One
PULMONARY HYPERTENSION

1- Introduction

In medicine, pulmonary hypertension (PHT) is an increase in blood pressure in the pulmonary artery, pulmonary vein or pulmonary capillaries (together known as the lung vasculature) leading to shortness of breath, dizziness, fainting and other symptoms, all of which are exacerbated by exertion **(Von Romberg, 1982).**

Pulmonary hypertension can be a severe disease with a markedly decreased exercise tolerance and heart failure. It was first identified by Dr. Ernst von Romberg in 1891 **(Von Romberg, 1982).**

Pulmonary hypertension is classified as primary (idiopathic) or secondary (**Barst, 2001**). There are conditions within the category of secondary pulmonary hypertension that resemble primary pulmonary hypertension in their histo-pathological features and their response to treatment. For this reason, the World Health Organization (WHO) classified pulmonary hypertension into five groups on the basis of mechanisms, rather than associated conditions: arterial, venous, hypoxic, thrombo-embolic or miscellaneous **(Simonneau and Galie et al., 2004).**

2- Definition and classification

Pulmonary arterial hypertension is defined as a sustained elevation of pulmonary arterial pressure to more than 25 mm Hg at rest or to more than 30 mm Hg with exercise **(Harrison and Joseph, 2004).**

Although the pathogenesis of most forms of pulmonary arterial hypertension is unknown, there have been many recent developments, especially pertaining to the molecular genetics and cell biology of idiopathic pulmonary arterial hypertension **(Vallerie and Stephen et al., 2009).**

Classification

A 1973 meeting organized by the World Health Organization (**WHO**) was the first to attempt classification of pulmonary hypertension. A distinction was made between primary and secondary PHT, and primary PHT was divided in the "arterial plexiform", "veno-occlusive" and "thromboembolic" forms **(Simonneau and Galie et al., 2004).**

A second conference in 1998 at Évian-les-Bains also addressed the causes of secondary PHT (i.e. those due to other medical conditions) and in 2003 the 3rd world symposium on pulmonary hypertension was convened in Venice to modify the classification based on new understandings of disease mechanisms. The revised system developed by this group provides the current framework for understanding pulmonary hypertension **(Simonneau and Galie et al., 2004).**

The system includes several improvements over the former 1998 Evian classification system. Risk factor descriptions were updated, and the classification of congenital systemic to pulmonary shunts was revised. A new classification of genetic factors in PHT was recommended, but not implemented because available data were judged to be inadequate **(Simonneau and Galie et al., 2004).**

The Venice 2003 Revised Classification system can be summarized as follows: **(Simonneau and Galie et al., 2004)**

- **WHO Group I** - Pulmonary hypertension (PHT)
  - Idiopathic (IPHT).
  - Familial (FPHT).
  - Associated with other diseases (APHT): collagen vascular diseases (e.g. scleroderma), congenital shunts between the systemic and pulmonary circulation, portal hypertension, HIV infection, drugs, toxins, or other diseases or disorders.
  - Associated with venous or capillary disease.
- **WHO Group II** - Pulmonary hypertension associated with left heart disease.
  - Atrial or ventricular disease.
  - Valvular disease (e.g. mitral stenosis).

- **WHO Group III** - Pulmonary hypertension associated with lung diseases and/or hypoxemia.
  - Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD).
  - Sleep-disordered breathing, alveolar hypoventilation.
  - Chronic exposure to high altitude.
  - Developmental lung abnormalities.
- **WHO Group IV** - Pulmonary hypertension due to chronic thrombotic and/or embolic disease.
  - Pulmonary embolism in the proximal or distal pulmonary arteries.
  - Embolization of other matter, such as tumor cells or parasites.
- **WHO Group V** – Miscellaneous:
  - Inflammatory (Schistosomiasis, Sarcoidosis, Histocytosis X)
  - Lymphangiomatosis
  - Compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

3- Epidemiology

Idiopathic pulmonary arterial hypertension (IPAH) is a rare disease with an incidence of about 2-3 per million per year and a prevalence of about 15 per million. Adult females are almost three times more likely to present with IPHT than adult males. The presentation of IPAH within children is more evenly split along gender lines **(Rudarakanchana and Trembath et al., 2001)**.

Other forms of PAH are far more common. In scleroderma the incidence has been estimated to be 6 to 60% of all patients, in rheumatoid arthritis up to 21%, in systemic lupus erythematosus (SLE) 4 to 14%, in portal hypertension between 2 to 5%, in AIDS (Acquired immune deficiency syndrome**)** about 0.5%, and in sickle cell disease ranging from 20 to 40%. Diet pills such as Fen-Phen (dexfenfluramine and phentermine, which had been taken off from the market) produced an annual incidence of 25-50 per million per year **(Humbert and Sitbon et al., 2006)**.

Pulmonary venous hypertension is exceedingly common, since it occurs in most patients symptomatic with congestive heart failure. Up to 4% of people who suffer a pulmonary embolism go on to develop chronic thromboembolic disease including pulmonary hypertension **(Humbert and Sitbon et al., 2006)**..

Only about 1.1% of patients with COPD develop pulmonary hypertension with no other disease to explain the high pressure. Sleep apnea is usually associated with only very mild pulmonary hypertension, typically below the level of detection. On the other hand Pickwickian syndrome (obesity-hypoventilation syndrome) is very commonly associated with right heart failure due to pulmonary hypertension **(Humbert and Sitbon et al., 2006)**.

4- Pathogenesis

Whatever the initial cause, pulmonary arterial hypertension (**WHO Group I**) involves vasoconstriction or tightening of blood vessels connected to and within the lungs. This makes it harder for the heart to pump blood through the lungs, much as it is harder to make water flow through a narrow pipe as opposed to a wide one. Over time, the affected blood vessels become both stiffer and thicker, in a process known as fibrosis. This further increases the blood pressure within the lungs and impairs their blood flow (**Rich and Kaufmann et al., 1992)**.

In addition, the increased workload of the heart causes hypertrophy of the right ventricle, making the heart less able to pump blood through the lungs, ultimately causing right heart failure (a condition known as cor pulmonale) **(Humbert and Sitbon et al., 2006)**..

As the blood flowing through the lungs decreases, the left side of the heart receives less blood. This blood may also carry less oxygen than normal. Therefore it becomes harder and harder for the left side of the heart to pump to supply sufficient oxygen to the rest of the body, especially during physical activity (**Archer and Rich et al., 2000)**.

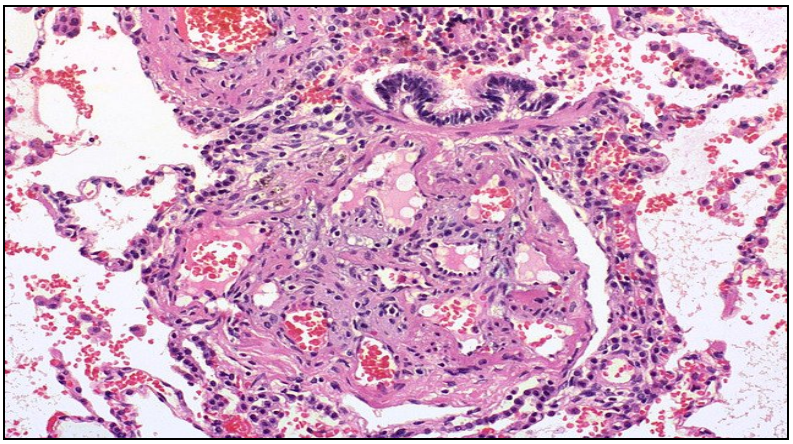

Figure (1): Histopathological criteria of Pulmonary Artery Hypertension. Intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, varying degrees of inflammation, and plexiform arteriopathy **(Vallerie and Stephen et al., 2009).**

Pathogenesis in pulmonary venous hypertension (**WHO Group II**) is completely different. There is no obstruction to blood flow in the lungs. Instead, the left heart fails to pump blood efficiently, leading to pooling of blood in the lungs. This causes pulmonary edema and pleural effusions.

In hypoxic pulmonary hypertension (**WHO Group III**), the low levels of oxygen are thought to cause vasoconstriction or tightening of pulmonary arteries. This leads to a similar

pathophysiology as pulmonary arterial hypertension **(Sitbon and Humbert et al., 2005)**.

In chronic thromboembolic pulmonary hypertension (**WHO Group IV**), the blood vessels are blocked or narrowed with blood clots. Again, this leads to a similar pathophysiology as pulmonary arterial hypertension **(Sitbon and Humbert et al., 2005)**.

5- Etiology and risk factors

1- Idiopathic pulmonary hypertension:

When an underlying cause for high blood pressure in the lungs can't be found, the condition is called idiopathic pulmonary hypertension (IPHT).

Some people with IPHT may have a gene that is a risk factor for developing pulmonary hypertension, but in most people with IPHT there is no recognized cause (**Yigla and Kramer et al., 2004)**.

2- Secondary pulmonary hypertension:

Pulmonary hypertension that is caused by another medical problem is called secondary PHT, this type is more common than IPHT. Causes of secondary PHT include:

- Blood clots in the lungs (pulmonary emboli).

- Chronic obstructive pulmonary diseases, such as emphysema.
- Chronic renal disease on dialysis.
- Connective tissue disorders such as scleroderma or lupus (**Hachulla and Gressin et al., 2005).**
- Sleep apnea and other sleep disorders.
- Congenital heart disease.
- Sickle cell anemia.
- Portal hypertension.
- AIDS **(Mehta and Khan et al., 2000).**
- Lung diseases such as pulmonary fibrosis, a condition that causes scarring in the tissue between the lungs' interstitium.
- Left-sided heart failure.
- Living at high altitudes.
- Use of certain stimulant drugs, such as cocaine **(McLaughlin and Archer et al., 2009).**

Risk factors of pulmonary hypertension:

Although any one can develop either type of pulmonary hypertension, older adults are more likely to have secondary pulmonary hypertension and young people are more likely to have the idiopathic form.

IPHT is also more common in women than it is in men. Another risk factor for pulmonary hypertension is a family history of the disease (**Rich and Kaufmann et al., 1992)**.

Some genes could be linked to IPHT, these genes might cause an overgrowth of cells in the small arteries of the lungs making them narrower. Genetic counselor may recommend for family members for testing the mutation **(Machado and Eickelberg et al., 2009).**

6- Symptomatology and complications

Because symptoms may develop very gradually, patients may delay seeking medical advise for years. Common symptoms include (**Vallerie and Stephen et al., 2009)**:

- Shortness of breath.
- Fatigue .
- Non-productive cough.
- Angina pectoris.
- Fainting or syncope.
- Peripheral edema.
- Hemoptysis.

Pulmonary venous hypertension typically presents with shortness of breath while lying flat or sleeping (orthopnea or

paroxysmal nocturnal dyspnea), while pulmonary arterial hypertension (PAH) typically does not.

According to the severity of Symptomatology; **WHO** classified pulmonary hypertension (**WHO** functional class 1998) into:

Class I:

Patients with pulmonary hypertension but without limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II:

Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III:

Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV:

Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity **(Barst and McGoon et al., 2004).**

Complications of Pulmonary Hypertension

Pulmonary hypertension can lead to a number of complications, including:

- *Right-sided heart failure (cor pulmonale)*

Right ventricle becomes enlarged and has to pump harder than usual to move blood through narrowed or blocked pulmonary arteries. At first, the heart tries to compensate by thickening its walls and expanding the chamber of the right ventricle to increase the amount of blood it can hold. But this thickening and enlarging works only temporarily and eventually the right ventricle fails from the extra strain (**Voelkel and Quaife et al., 2006)**.

- *Blood clots*

Clots help stop bleeding after the injury. But sometimes clots form where they are not needed. A number of small clots or just a few large ones dislodge from these veins and travel to

the lungs leading to a form of pulmonary hypertension that is reversible with time and treatment.

- ***Arrhythmia***

Irregular heartbeats from the upper or lower chambers of the heart are complications of pulmonary hypertension. These can lead to palpitations, dizziness or fainting and can be fatal.

- ***Bleeding***

Pulmonary hypertension can lead to bleeding into the lungs and hemoptysis and this condition could be fatal **(McLaughlin and Archer et al., 2009).**

7- Diagnosis

Pulmonary hypertension is hard to diagnose early because it is not often detected in a routine physical exam. Even when the disease is more advanced, its signs and symptoms are similar to those of other heart and lung conditions. So many tests should be performed to diagnose this condition and distinguish pulmonary arterial hypertension from venous, hypoxic, thromboembolic or miscellaneous varieties **(Rubin and Badesch, 2005)**.

1- Full History:

A detailed family history is established to determine the possibility of the disease to be familial. Also history of

exposure to drugs such as cocaine, methamphetamine, alcohol leading to cirrhosis, and tobacco leading to emphysema are considered significant **(Rubin and Badesch, 2005)**.

2- Clinical Examination:

A physical examination is performed to look for typical signs of pulmonary hypertension. These include altered heart sounds, such as a widely split S_2 or second heart sound, a loud P_2 or pulmonic valve closure sound (part of the second heart sound), parasternal heave, possible S_3 or third heart sound, and pulmonary regurgitation. Other signs include an elevated jugular venous pressure, peripheral edema, ascites, hepato-jugular reflux, and clubbing **(Rubin and Badesch 2005)**.

3- Investigations:

- **Electrocardiography (ECG)**

Manifestations of pulmonary hypertension in ECG include right atrial enlargement, right ventricular hypertrophy and strain, and right axis deviation of the QRS complex **(Tongers and Schwerdtfeger et al., 2007).**

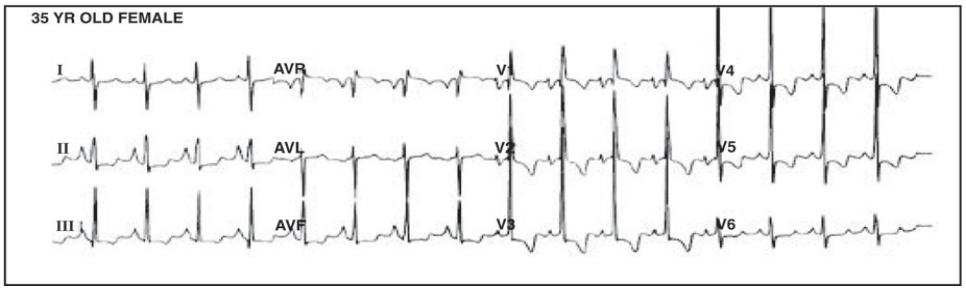

Figure (2): ECG showing pulmonary hypertension criteria **(Vallerie and Stephen et al., 2009)**.

- **Chest X-ray**

This test may be able to check for pulmonary hypertension if pulmonary arteries or the right ventricle of the heart is enlarged. X-ray appears normal in about one-third of pulmonary hypertension cases **(Vallerie and Stephen et al., 2009)**.

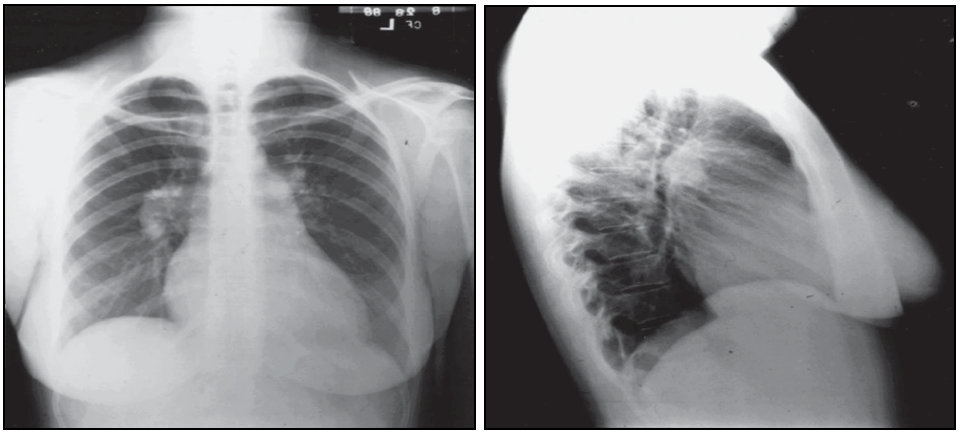

Figure (3): Postero-anterior and lateral chest X-ray shows decreased peripheral lung vascular markings, hilar pulmonary artery prominence, and right ventricular enlargement of a patient with IPAH **(Vallerie and Stephen et al., 2009)**.

Echocardiogram

This noninvasive test uses harmless sound waves. During the procedure, a small, plastic instrument called a transducer is placed on the chest. It collects reflected sound waves (echoes) from the heart and transmits them to a machine that uses the sound wave patterns to compose images of the beating heart on a monitor **(McLaughlin and Sitbon et al., 2005).**