Pulmonary hypertension- Pathophysiology (RN)

Goal: The goal of this artcle is to discuss pathophysiology, classification and hemodynamic changes in pulmonary hypertension patients.

Objective: After completion of this activity, the candidate should be able to

1. Describe various types of pulmonary hypertension
2. Describe grading of pulmonary hypertension
3. Describe pathophysiology of pulmonary hypertension
4. Describe hemodynamic changes in pulmonary hypertension

Pulmonary circulation, unlike systemic circulation, is a low resistance circulation (Kumar et al., 2017, p. 517). Pulmonary hypertension (PH) is a pulmonary vascular disease which is often characterized by a progressive and sustained increase in pulmonary vascular resistance that eventually may lead to RVF. PH is defined as an increase in the pulmonary arterial pressure with a mean pulmonary arterial pressure greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise (Kumar et al., 2017; Nader Kamangar, 2016, p. 517). Thorough understanding of the pathogenesis of PH is very important as it helps in the administration of proper therapy to the patient even if primary cause is known.

PH is a disease of complex pathology. There are multiple factors responsible for the development of pulmonary hypertension. There is no single factor which can be held responsible for the disease. The factors can be a genetic mutation, acquired state or it can be an exogenous exposure. PH involves the complex interaction of multiple vascular effectors at all anatomic levels of the arterial wall. The pathophysiology of PH can be explained by multiple hit hypothesis (Gan, 2012, pp. 1-6).

There are many studies published to classify PH. On the basis of the vessels involves the PH can be divided into Pulmonary Arterial Hypertension (PAH), Pulmonary Venous Hypertension (PVH), PH associated with disorders of respiratory system or hypoxemia, PH caused by chronic thromboembolic disease and other causes.

Simonneau et al. (2013), while taking into consideration **'WHO classification of PH'** updated classification of PH as following:-

I. **Pulmonary arterial hypertension**
   a. Idiopathic PAH
   b. Heritable PAH
      i. BMPR2
      ii. ALK-1, ENG, SMAD9, CAV1, KCNK3
      iii. Unknown
   c. Drug and toxin-induced
   d. Associated with:

i. Connective tissue disease
ii. HIV infection
iii. Portal hypertension
iv. Congenital heart diseases
v. Schistosomiasis

I' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

I" Persistent pulmonary hypertension of the newborn (PPHN)

II. Pulmonary hypertension due to left heart disease

a. Left ventricular systolic dysfunction
b. Left ventricular diastolic dysfunction
c. Valvular disease
d. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

III. Pulmonary hypertension due to lung diseases and/or hypoxia

a. Chronic obstructive pulmonary disease
b. Interstitial lung disease
c. Other pulmonary diseases with mixed restrictive and obstructive pattern
d. Sleep-disordered breathing
e. Alveolar hypoventilation disorders
f. Chronic exposure to high altitude (In HAPE) (Brian R. Walker et al., 2014, p. 104)
g. Developmental lung diseases

IV. Chronic thromboembolic pulmonary hypertension (CTEPH)

V. Pulmonary hypertension with unclear multifactorial mechanisms

a. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
b. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
c. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
d. Others: obstruction by tumor, fibrosing mediastinitis, chronic renal failure, segmental PH

Though after reading this chapter you will be able to understand all the terminologies related to PH, the above-mentioned classification doesn't give adequate clinical and research-based ease in the evaluation of PH to the physicians. So, American Thoracic Society has put in a great effort in dividing PH into following phenotypes, to better understand the disease:- (Dweik et al., 2014)

I. Mixed Pre- and Post-capillary PH
II. Severe PH in Respiratory Disease
III. Maladaptive RV Hypertrophy
IV. Connective Tissue Disease–associated PH
V. Porto pulmonary Hypertension
VI. HIV-associated PAH
VII. PH in Elderly Individuals
VIII. PAH in Children
IX. Metabolic Syndrome

1. Etiology

WHO grouping of PH is not followed by ATS and ACC, so Kumar et al. (2017, p. 517), as well as Lewis J Rubin and William Hopkins (2017), separately explained the most common causes of PH keeping in mind the WHO classification of PH into five groups according to the cause as :-

- Autoimmune diseases **(group 1)**
  Changes in pulmonary vasculature and interstitium leading to PH.
- Idiopathic pulmonary hypertension **(also group 1)**
  This terminology often considered as a misnomer as it has been proved that 80% of the patients diagnosed with idiopathic pulmonary hypertension has an autosomal dominant trait. So primary PH is a more appropriate name.
- Antecedent congenital or acquired heart disease **(group 2)**
  The increase left atrial pressure which later on transfers to the pulmonary side.
- Chronic obstructive or interstitial lung diseases **(group 3)**

  Increase in pulmonary resistance and obliterates alveolar capillaries. According to Maron (2016, p. 84), lung diseases play a major role in the formation of PH.

- Obstructive sleep apnea **(also group 3)**
  PH has been found to associated with obstructive sleep apnea as a result of obesity and hypoxemia.
- Recurrent thromboemboli **(group 4)**
  Decrease functional cross-sectional area of the pulmonary vascular bed.
- Idiopathic PH **(group 5)**

1. Heath & Edwards Grading of PH in Congenital Heart Diseases

Heath & Edwards classify pathology underlying PH in congenital heart disease in 1958. According to them PH can be divided into 6 grades: - (Lewis J Rubin & William Hopkins, 2017)

Heath-Edwards Grade I and II (Reversible)

Muscularization of the small pulmonary arterioles, followed by medial hypertrophy and intimal hyperplasia

Heath-Edwards Grade III (Reversible)

Collagenous replacement of intimal cells, leading to an "onion-skin" appearance

Heath-Edwards Grade IV, V & VI (Irreversible)

Abnormalities overlap and they can be considered as a single grade. Notable changes can be

- Progressive dilatation of small arteries
- Plexiform and angiomatoid lesions with intra-alveolar hemosiderin-filled macrophages
- Necrotizing arteritis with thrombosis
- Fibrinoid necrosis of the arterial wall with a transmural infiltrate of polymorphonuclear leukocytes and eosinophils

2. Pathology

The most common primary cause of PH is chronic hypoxia and the main factor leading to PH is increased pulmonary vascular resistance. Increased blood flow alone causes a little increase in the pressure in significant pulmonary hypertension as the pulmonary vascular bed vasodilates in response to increase in flow and recruit new vessels. Similarly, increased pulmonary venous pressure alone does not usually cause significant PH. However, a chronic increase in both increased flow and increased pulmonary venous pressure can increase pulmonary vascular resistance (Lewis J Rubin & William Hopkins, 2017). Death may occur from PH as a result of decompensated cor pulmonale.

Following mechanisms are involved in the development of PH (Gan, 2012; Kumar et al., 2017).

a) Pathogenic Mechanisms

According to Gan (2012, p. 5), three main pathogenic processes involved in pulmonary artery vasoconstriction and subsequent development of pulmonary hypertension are:- (Gan, 2012, pp. 2-17)

- Vasoconstriction
- Vascular remodeling
- Thrombosis in situ

Vasoconstriction

An imbalance between vasoconstrictors and vasodilators is the basic reason behind vasoconstriction (Gan, 2012, p. 5).

Vascular remodeling

This results from the proliferation of vascular smooth muscle and endothelial cells (Gan, 2012, p. 5).

Thrombosis in situ

Thrombosis develops as a result of coagulation abnormalities and a reason behind the increase in PVR (Gan, 2012, p. 5).

b) Cellular Mechanism

The multifactorial pathophysiology of PH is characterized by pulmonary vascular remodeling in all three layers of the vessel wall. Endothelial cells, smooth muscles, fibroblast, platelets and inflammatory cells play important role in the vascular remodeling.

Endothelial Cells of the Intima

Though the exact mechanism of endothelial injury is unknown, it is believed to include genetic susceptibility along with hypoxia, stress, inflammation, drugs or toxins. Endothelial cell injury also affects the proliferation, apoptosis and homeostatic function of the endothelium (Gan, 2012, pp. 6-8). Endothelial cells of the **Intima** promotes vasoconstriction by a decrease in production of NO (a potent vasodilator) and increase in the production of endothelin, serotonin, leukotrienes, pro-inflammatory (IL1, IL6, IL8), pro-mitogenic (VEGF-1, endothelin-1, thromboxane, PDGF-B, CX3CL1) and anti-thrombic mediators (increased tissue factor, decreased thrombomodulin), as well as increased expression of inflammatory cell adhesion molecules (VCAM, ICAM, P-selectin) (Maron, 2016, p. 84). Endothelin-1 has a potent role in vasoconstriction and mitogenesis (Gan, 2012, pp. 11-12). It will be described in detail later.

Smooth Muscle Cells of the Media

In PH there is an alteration in the rate of proliferation and apoptosis of smooth muscle cells besides upregulation of metalloproteinase (MMP2 and MMP9). The main pathology at the cellular level is an extension of smooth muscle into peripheral nonmuscular vessels (Gan, 2012, pp. 6-8). It is believed that chronic hypoxia plays a significant role in the proliferation of smooth muscle cells. Changes in media are marked by the thickening of media at all levels of the pulmonary vasculature, from large muscular to small non-muscular ones. As small arteries make the majority of surface area of lung vasculature, the result is an increase in the pulmonary resistance (Maron, 2016, p. 84). There is also formation neointima; a new layer of myofibroblasts and EC matrix between endothelium and internal elastic lamina (Gan, 2012, pp. 6-8).

Fibroblast and immune cells of The Adventitia

As a result of hypoxia, there is a significant increase in collagen and ECM protein deposition, marked expansion of the vasa vasorum, proliferation of resident fibroblasts and possibly macrophages, activation of resident progenitor cells, as well as recruitment of circulating immune and progenitor cells in adventitia in PH. This leads to substantial thickening of adventitia (Maron, 2016, p. 85).

Inflammatory Cells

In PH patients there is seen an elevated level of ANA, proinflammatory cytokines IL-1 and IL-6, inflammatory infiltrates (macrophages and lymphocytes), and increased expression of chemokine RANTES and fractalkine (Gan, 2012, pp. 6-8). Though it was believed earlier that inflammation leads to thickening of vessels from “inside out”, but now the fibroblast proliferation along with inflammation has affirmed the “outside-in hypothesis” (Maron, 2016, p. 85).

Platelet and Thrombotic Lesions

In PH platelets release procoagulants, vasoactive and mitogenic mediators, TXA2, PAF, serotonin, PDGF, TGF- β, and VEGF (Gan, 2012, pp. 6-8). These along with the release of vasoconstrictors and decrease in NO from endothelium contribute to procoagulant state (McLaughlin et al., 2009, p. 1579).

c) Molecular Mechanism

The molecular mechanism is important in understanding idiopathic PH. Grade I and II changes are characterized by muscularization of the small pulmonary arterioles, followed by medial hypertrophy and intimal hyperplasia. Grade III abnormalities are characterized by collagenous replacement of intimal cells, leading to an "onion-skin" appearance. Grade IV through VI abnormalities overlap and can be considered one stage. These changes are irreversible and associated with a poor outcome after repair of a congenital lesion (Lewis J Rubin & William Hopkins, 2017).

Genetic Predisposition to PH

In PH there are mutations in BMPR2 gene which is a member of TGF- β receptor superfamily. (Gan, 2012, p. 9). Kumar et al. (2017, p. 518) have also explained the association of BMPR2 gene with primary hypertension.

Acquired/Exogenous Factors

Chronic hypoxia, hemoglobinopathies, autoimmune vascular disease, viral infections, congenital heart disease with systemic- to- pulmonary shunt, and “serotoninergic” anorexigen use, thrombocytosis, central nervous system stimulants, portal hypertension, persistent PH of the newborn, and female gender predilection human immunodeficiency virus (HIV)

Vascular Effectors

As mentioned earlier there is an increase in vasoconstriction and PVR in PH. There is a long list of vasoconstrictors that are released in PH.

There is an increase in the **serotonin** released by platelets which is a potent vasoconstrictor (Gan, 2012, p. 11).

VIP is also a vasoconstrictor in pulmonary vasculature and it’s also increased in PH (Gan, 2012, p. 11).

As we know that **NO** is a very potent vasodilator which acts via cGMP pathway (McLaughlin et al., 2009, p. 1579). There is dysregulation of vasoconstriction due to reduced eNOS. There is also evidence suggesting of a decrease in production of endogenous vasodilators like **CO** and **H2S** (Gan, 2012, p. 11).

As discussed earlier the production of **TXA2** also play its role in vasoconstriction. Even biochemical analysis of urine of PH patients have shown decrease prostacyclin and increase TXA2 in PH patients (Gan, 2012, p. 11).

Endothelin-1 (ET-1) expressed by endothelial cells, acts as a potent pulmonary arterial vasoconstrictor and smooth muscle cell mitogen. Endothelin-1 binds to the endothelin receptor A on vascular smooth muscle. This result in an increase in the IC calcium which activates protein kinase C, mitogen-activated protein kinase and early growth response genes c-fos and c-jun. All this results in vasoconstriction, mitogenesis, and vascular remodeling ultimately leading to PH (Gan, 2012, pp. 11-12). Level of ET-1 help in determining the prognosis of PH (McLaughlin et al., 2009, p. 1579).

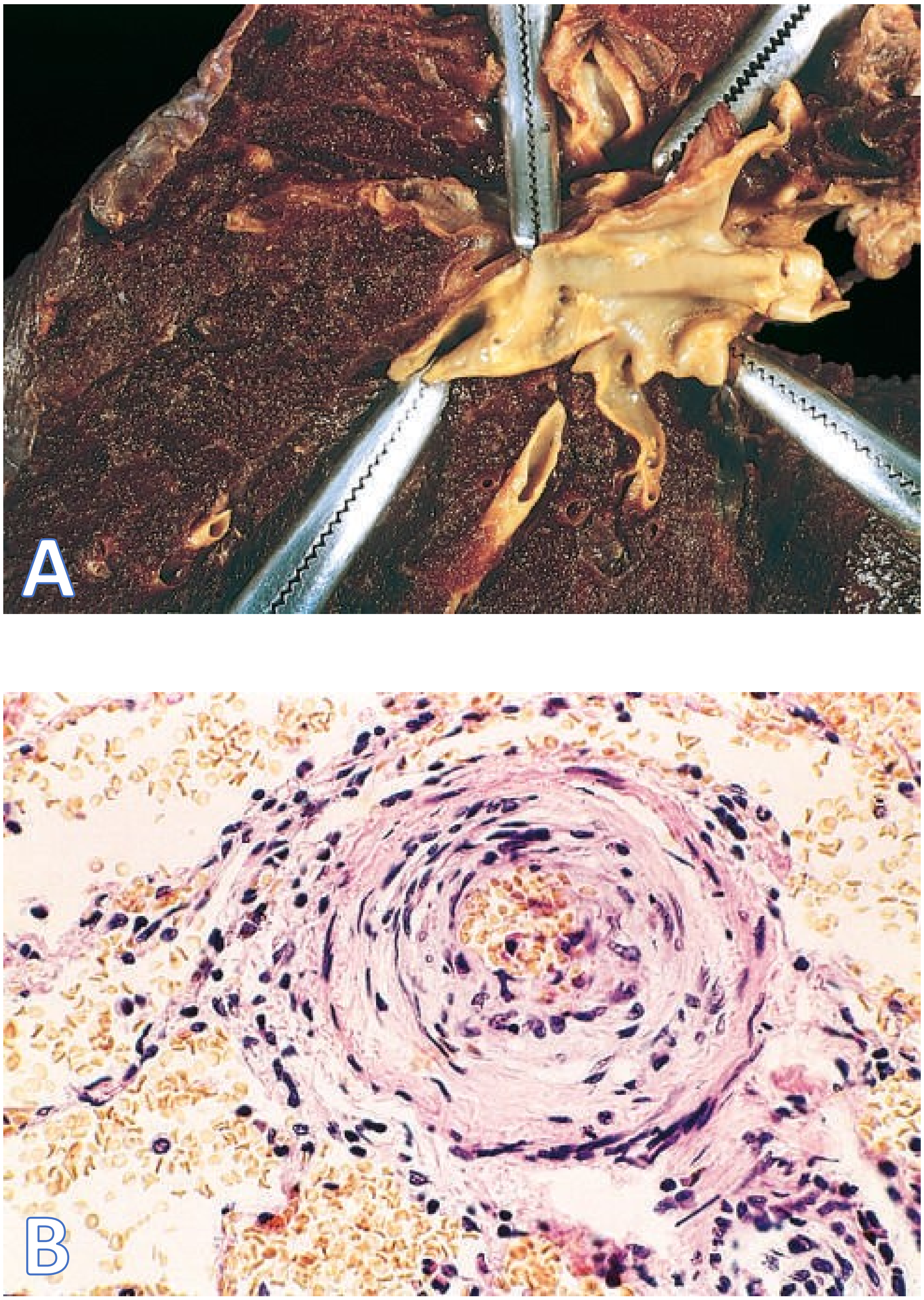
Expression **of Vascular endothelial growth factor (VEGF)** is also increased in the PH which is known for its role in vascular remodeling, endothelial survival, proliferation and apoptosis (Gan, 2012, pp. 11-13).

3. Histology

As discussed earlier chronic hypoxia is the major factor in the pathophysiology of pulmonary hypertension. Though PH is considered a panvasculopathy but histological findings in PH are as following (McLaughlin et al., 2009, p. 1578)

- Intimal hyperplasia
- Medial hypertrophy
- Adventitial proliferation
- Thrombosis in situ
- Plexiform arteriopathy
- Inflammation (inflammatory infiltrates e.g. macrophages and lymphocytes) (Gan, 2012, pp. 6-8)

These finding may be diffuse or focal and a patient can present with all of these abnormalities. In some cases, there is seen an increase in the level of proinflammatory cytokines, autoantibodies, and inflammatory infiltrate in PAH suggesting the role of inflammation in PH (McLaughlin et al., 2009, p. 1579). The histology of pulmonary hypertension can be summarized as medial hypertrophy of pulmonary arteries (muscular and elastic), pulmonary artery atherosclerosis, and right ventricular hypertrophy (Figure 1) (Kumar et al., 2017, p. 518).



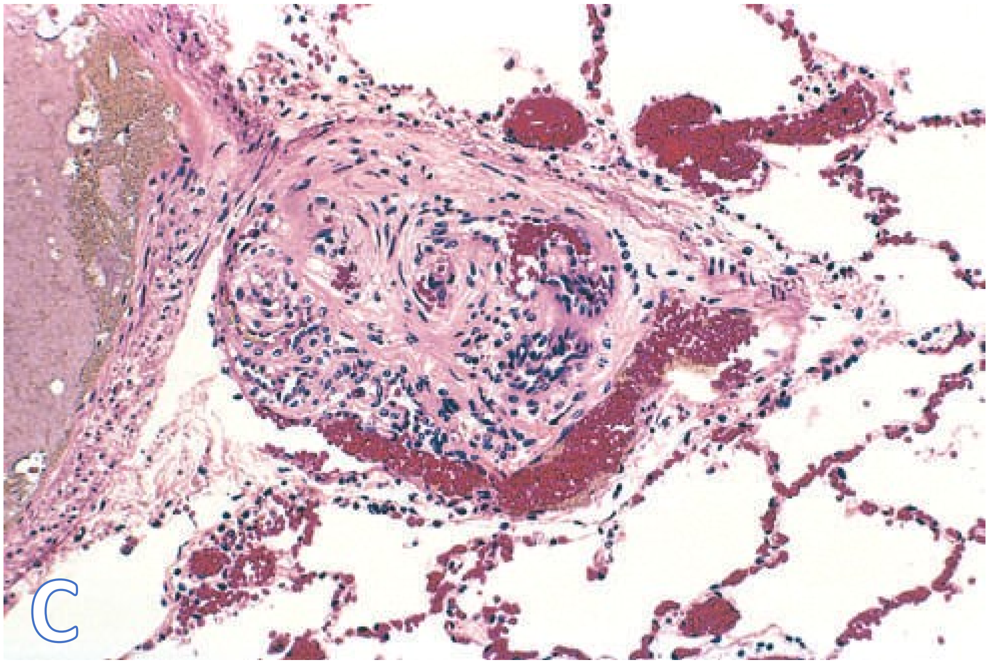


Figure 1: Vascular changes in pulmonary hypertension. (A) Atheroma formation, a change usually limited to large pulmonary arteries. (B) Marked medial hypertrophy. (C) Plexiform lesion characteristic of advanced pulmonary hypertension seen in small arteries. (Courtesy: Robbins basic pathology (10 ed.), p. 518)

Another rare pathological finding in PH is “plexiform lesion” which is the formation of a tuft of capillaries that spans across thin-walled, small arteries to even outside vessel (Kumar et al., 2017, p. 518).

4. Right Ventricle

In PH due to increase in the PVR, there is an increase in the RV afterload which leads to RV hypertrophy and dilatation. So a physician can predict the prognosis of PH by determining the functional capacity of RV (McLaughlin et al., 2009, p. 1578). Right ventricular dysfunction and overload also affect left ventricular functions by distorting Frank-Starling Mechanism. This phenomenon of leftwards bowing of interventricular septum due to right ventricle overload thereby decreasing the left ventricular chamber size, compliance and contractility are called “Reverse Bernheim Effects” (Hsia & Haddad, 2012).

5. Hemodynamic Changes

Before describing hemodynamic changes, it should be kept in mind that nowadays the definition of pulmonary hypertension is no longer based upon the systolic pulmonary artery pressure or exercise derived values but a multifactorial approach is important (Lewis J Rubin & William Hopkins, 2017). As discussed in detail that in PH there is mean pulmonary artery pressure > 25 mmHg at rest or 30 mmHg with exercise. Moreover, PAH also requires the presence of a PCWP (pulmonary capillary wedge pressure) ≤ 15 mmHg and a PVR ≥ 240 dynes/s/cm5. Hemodynamic variables that contribute to pulmonary arterial pressure can be identified using a variation of Ohm's Law,

Change in pressure = flow x resistance

Ppa - Ppv = Q x PVR

$$Ppa = (Q \times PVR) + Ppv$$

where Ppa is mean pulmonary arterial pressure, Ppv is mean pulmonary venous pressure, Q is right-sided cardiac output, and PVR is pulmonary vascular resistance. The Ppv is estimated by the pulmonary capillary wedge pressure (PCWP) as

$$Ppa = (Q \times PVR) + PCWP$$

From this equation, it is apparent that the mean pulmonary arterial pressure is determined by the pulmonary vascular resistance, right-sided cardiac output, and mean pulmonary venous pressure.

6. ABBREVIATION

ATC= American Thoracic Society

BMPR2 = Bone Morphogenetic Protein Receptor Type 2

EC= Extracellular

eNOS= endothelial isoform NO synthase

HAPE= High Altitude Pulmonary Edema

PCWP= pulmonary capillary wedge pressure

PH= Pulmonary Hypertension

Ppa= mean pulmonary arterial pressure

Ppv= mean pulmonary venous pressure

PVR= Pulmonary Vascular Resistance

Q= right-sided cardiac output

TXA2= Thromboxane A2

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