Pulmonary hypertension

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Anatomy

The vessels supplying the lungs include the pulmonary arteries, pulmonary veins, and bronchial arteries

- ***Pulmonary Arteries***

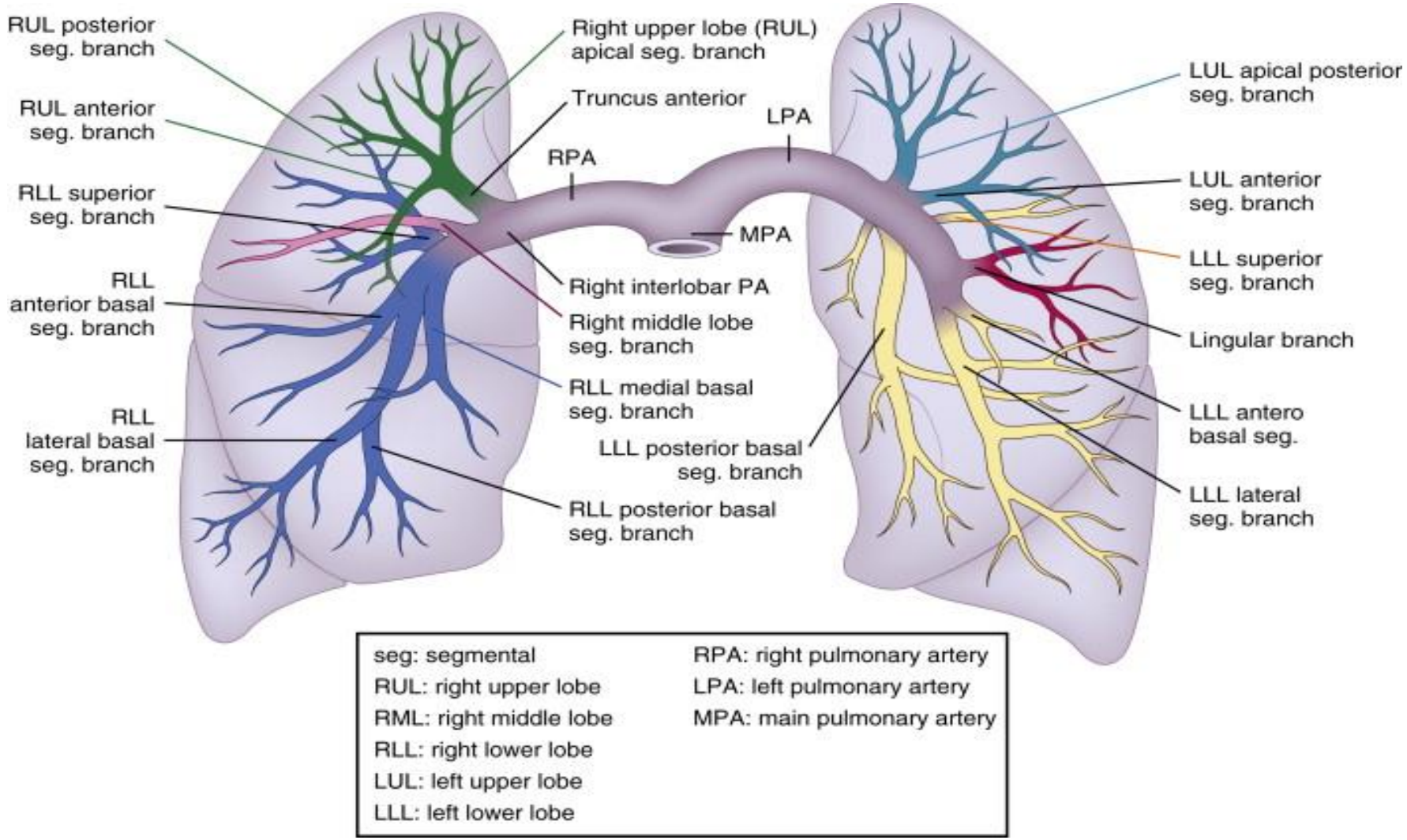
◆ The main pulmonary artery arises from the right ventricle distal to the pulmonary valve and it divides into right and left pulmonary arteries.

◆ The right pulmonary artery divides into three lobar arteries, one for each lobe of the right lung

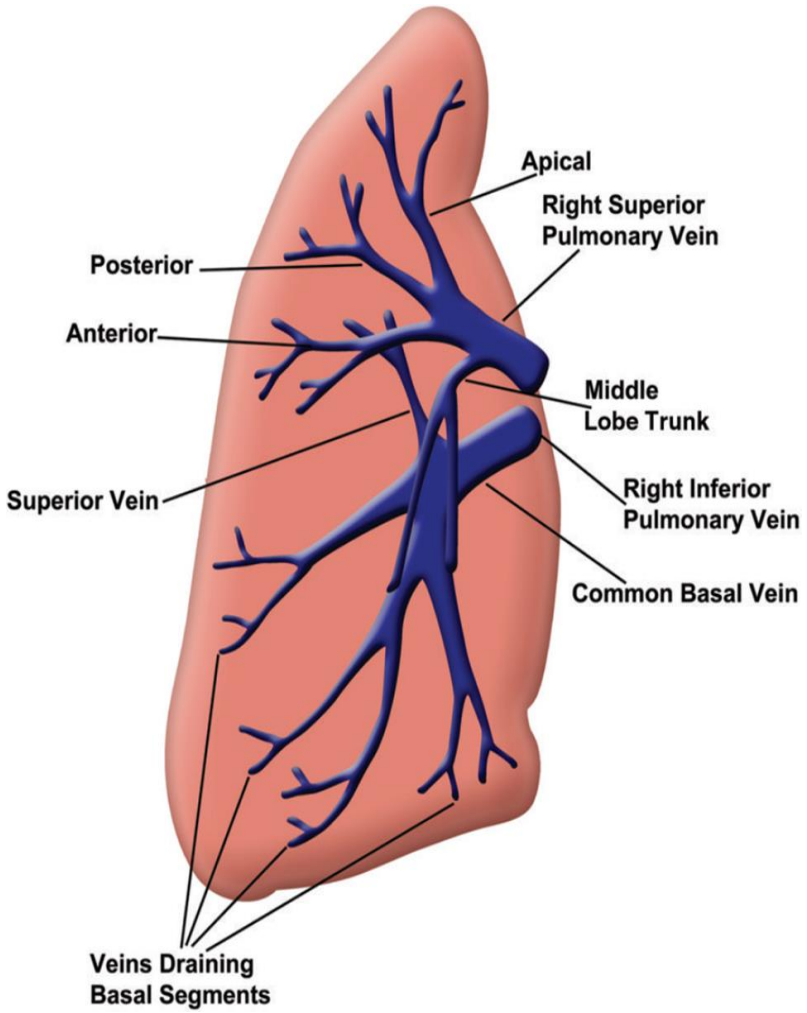
◆ The left pulmonary artery divides into two lobar arteries, one for each lobe of the left lung.

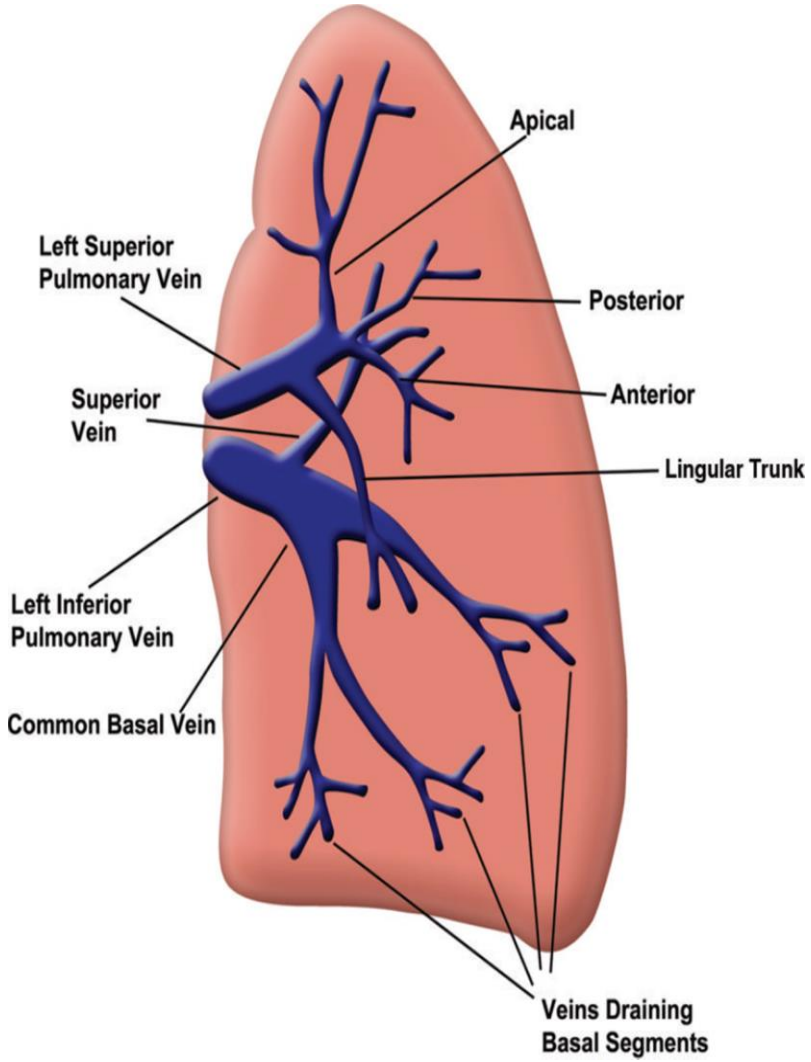
◆ The segmental arteries are adjacent to their accompanying bronchi, situated medial to the bronchi in the upper lobes and laterally in the lingual and middle and lower lobes.

Pulmonary artery anatomy



Pulmonary Veins





Pulmonary Veins

- The pulmonary veins are the veins that transfer oxygenated blood from the lungs to the heart. There are four main pulmonary veins, two from each lung that drain into the left atrium of the heart. The pulmonary veins are part of the pulmonary circulation.

Pulmonary Veins

Anatomic Variations

- The right superior pulmonary vein draining the right upper lobe and right middle lobe.
- The right inferior pulmonary vein draining the right lower lobe
- The left superior pulmonary vein draining the left upper lobe and lingula.
- The left inferior pulmonary vein draining the left lower lobe.

Bronchial Arteries

- The bronchial arteries arise from the descending thoracic aorta at the level of the left main bronchus and supply the trachea, bronchi, esophagus, and lymph nodes.

Pulmonary arteries

a-Thinner than systemic arteries

b-Have proportionately more elastic tissue in their walls.

c-The diameter of the arterioles, was a less than 100 µm

d-Low pressure system

e-Low incidence of atherosclerosis

f-Low vascular resistance

g-More distensible than systemic

Pulmonary hypertension

Definition

Normal pressure in the pulmonary artery system is 20/8 mmHg.

The mean pulmonary artery pressure is 12–15 mmHg.

Pulmonary hypertension

is defined as a mean pulmonary artery pressure (PAP) of greater than 25 mmHg at rest or greater than 30 mmHg on exercise as assessed by right heart catheterization (RHC).

Pulmonary Hypertension

A systolic pulmonary artery pressure (sPAP) greater than 35 to 40 mm Hg on echocardiogram should prompt further workup for PH

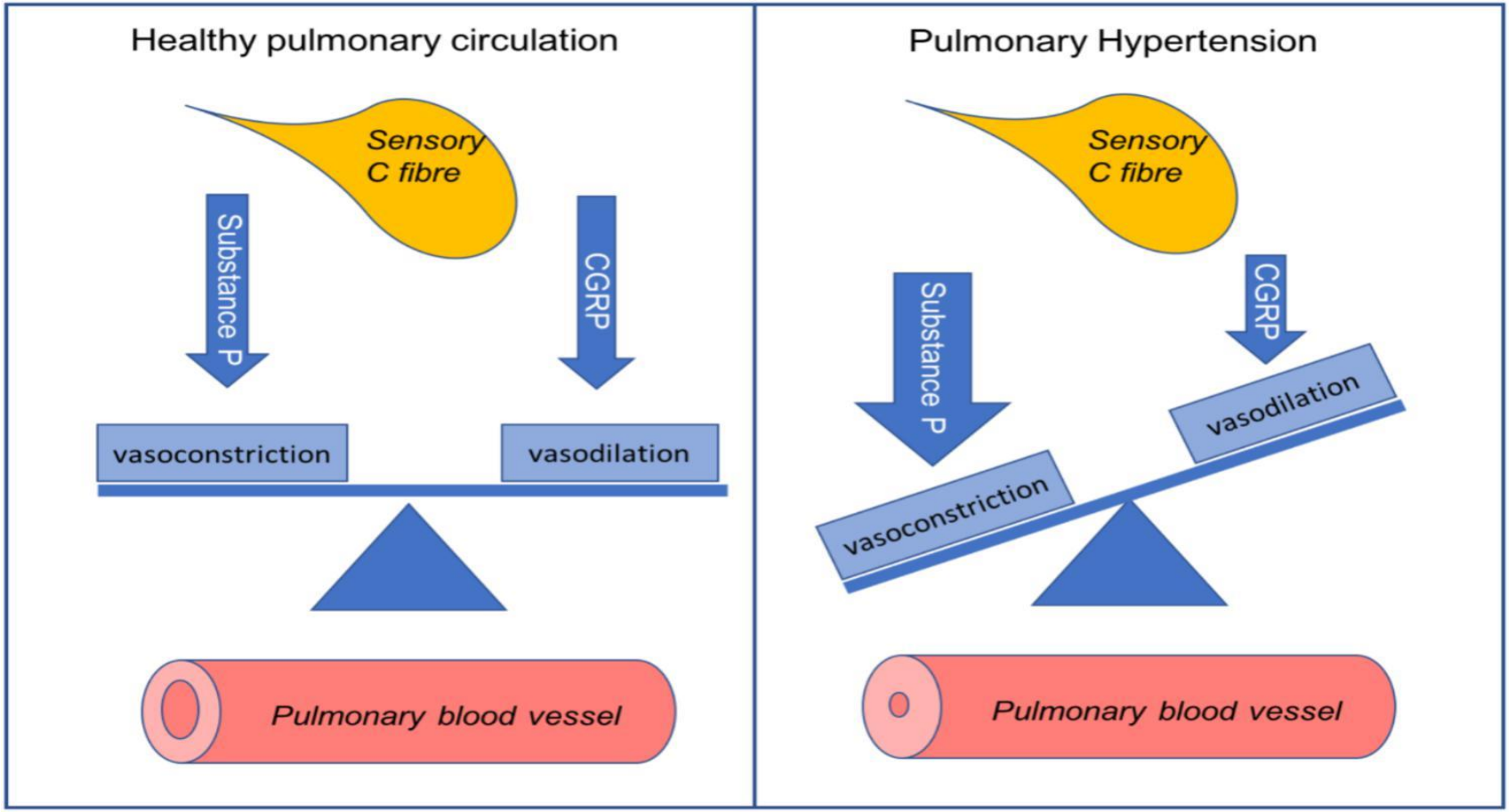
Pulmonary hypertension can occur due to pulmonary arterial hypertension alone or occur due to pulmonary venous hypertension.

Regulation of Vascular Tone

Pulmonary vascular tone is dependent on the balance of vasoconstrictors and vasodilators

Oxygen is a potent vasodilator, therefore hypoxia results in vasoconstriction.

Regulation of Vascular Tone



Regulation of Vascular Tone

Vasodilator

Prostacyclin (i.e., prostaglandin I2 [PGI2]) is a product of endothelial cells

Nitric oxide is a potent vasodilator that is produced by endothelial cells

Vasoconstrictor

Serotonin

Thromboxane A2

Angiopoietin-1

Plasminogen activator inhibitor-1

Endothelin-1 is synthesized and secreted by endothelial cells

Epidemiology

a-Pulmonary hypertension can affect patients of

all ages and ethnicities but occurs more commonly

in African-Americans.

b-The prevalence of pulmonary hypertension is estimated to be around 5–7/100 000 of population.

c-Pulmonary hypertension has a poor prognosis if not diagnosed and treated promptly.

Table 4 Updated clinical classification of pulmonary hypertension (Dana Point, 2008[1])

1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/or hypoxaemia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

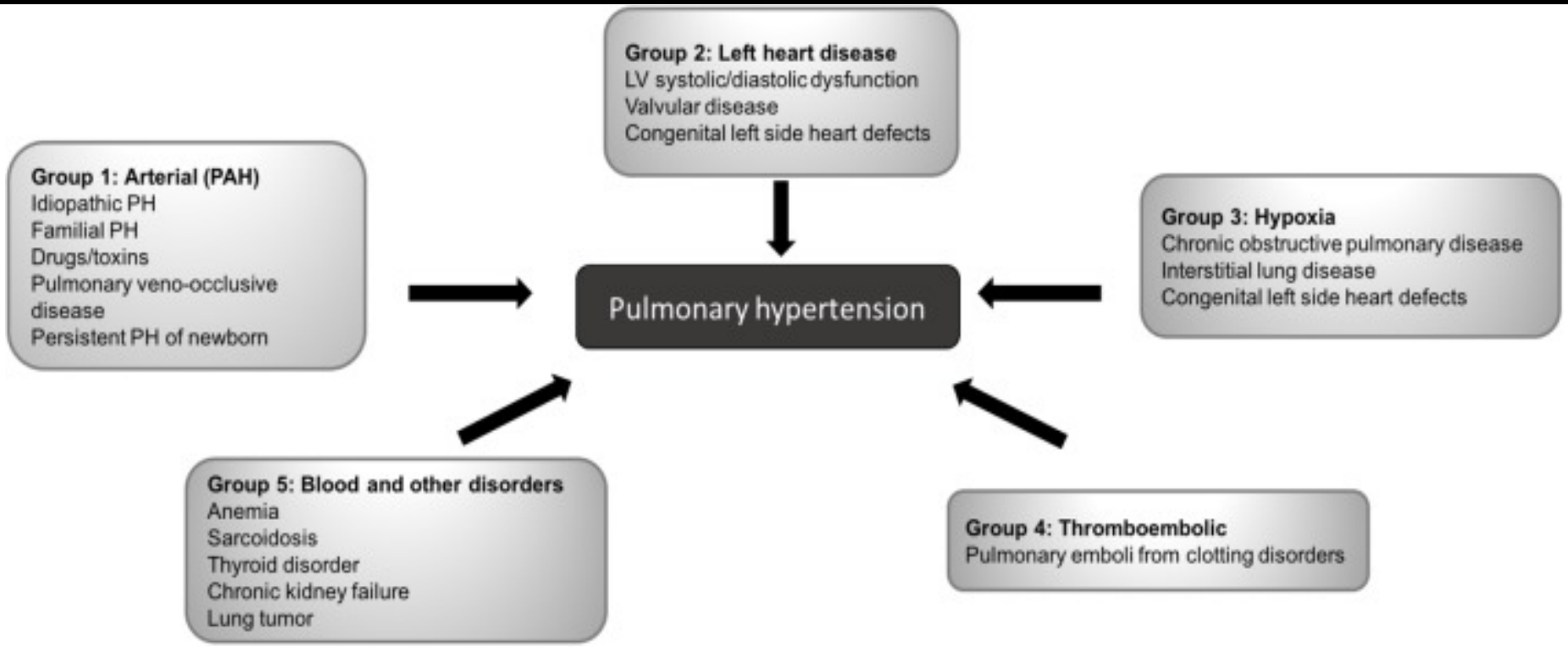
4 Chronic thromboembolic pulmonary hypertension

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 = activin receptor-like kinase 1 gene; APAH = associated pulmonary arterial hypertension; BMPR2 = bone morphogenetic protein receptor, type 2; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Galiè N et al. Eur Heart J 2009; 30:2493–537

Pulmonary Hypertension Disease Classifications



Functional Class	Symptom / Level of disease
Class I	Symptom-free when physically active or at rest
Class II	No symptoms at rest, discomfort/shortness of breath on mild exertion
Class III	Shortness of breath / tiredness with light activities
Class IV	Symptoms at rest and severe symptoms with activity

Pulmonary Hypertension Disease Classifications

a- PAH can be induced by drugs as some anti-depressants and appetite suppressant drugs.

b- For all PH subtypes, patients are also classified into functional classes indicating disease severity .

c- Patients tend to be diagnosed in functional class II-III and progressively worsen.

Histopathology

- Regardless of the cause of PH, there is common histopathology to all five groups includes:

1-hypertrophy of vascular smooth muscle cells

2-fibrosis

3-vascular wall remodeling and vessel obstruction.

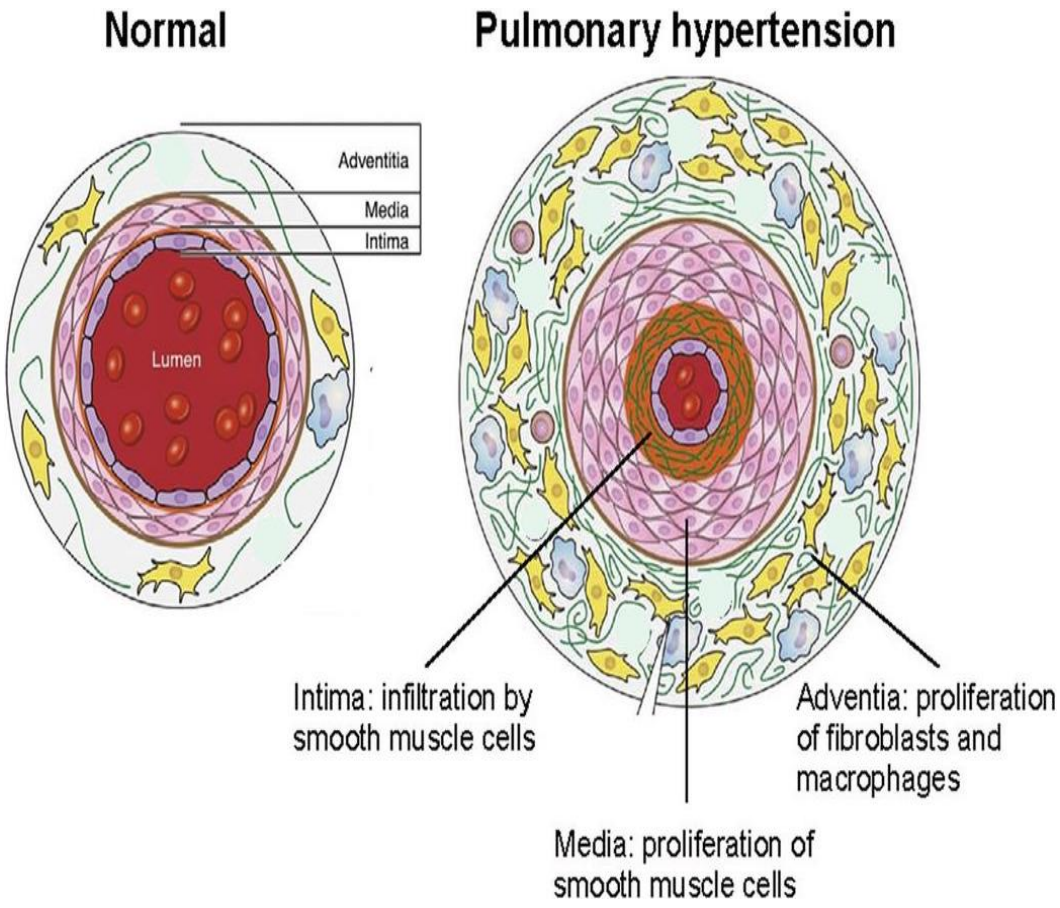


Table 58-2 Recommendation for Screening for Pulmonary Arterial Hypertension

Risk Factor	Recommendation
Family history of PAH	Yes
Connective tissue disease	
Scleroderma	Yes
Other	No
Congenital heart disease	
Large ASD, nonoperated	Yes
Large VSD, nonoperated	Yes
HIV infection	No
Portal hypertension	No
Consideration for liver transplantation	Yes
Use of appetite-suppressant drugs	No
Previous pulmonary embolism	No
Increasing dyspnea	Yes
Massive/submassive PE	Yes

DIAGNOSTIC APPROACH

SYMPTOMS AND SIGNS *:*

A diagnosis of PH should be considered in any patient who presents with:

1-Breathlessness in the absence of specific cardiac or pulmonary disease,

2-Patients who have underlying cardiac or pulmonary disease and present with increasing dyspnea that is not explained by the underlying disease

SYMPTOMS

1-Fatigue

2-Progressive dyspnea on exertion

3-Palpitation

4-Chest pain

5-Dizziness

6-Cough

7-The mean duration of symptoms before diagnosis reported in most registries approaches 2 years.

SIGNS

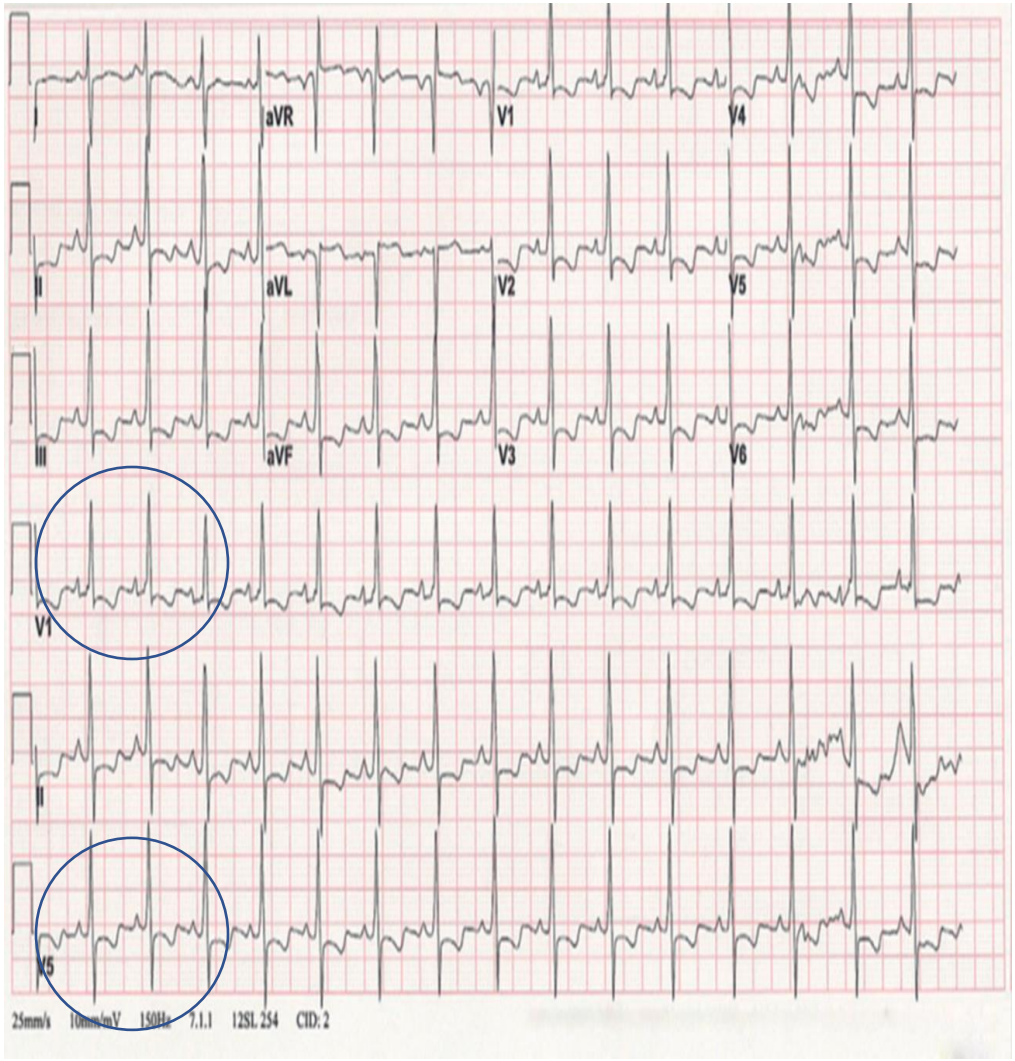
1-Tachypnoea

2-Tachycardia

3- Loud second heart sound (P2, the pulmonary component).

4-In severe pulmonary hypertension there will be signs of right heart failure, which includes(a parasternal heave, raised JVP, peripheral edema, tricuspid regurgitation, and Hepatomegaly).

ELECTROCARDIOGRAM



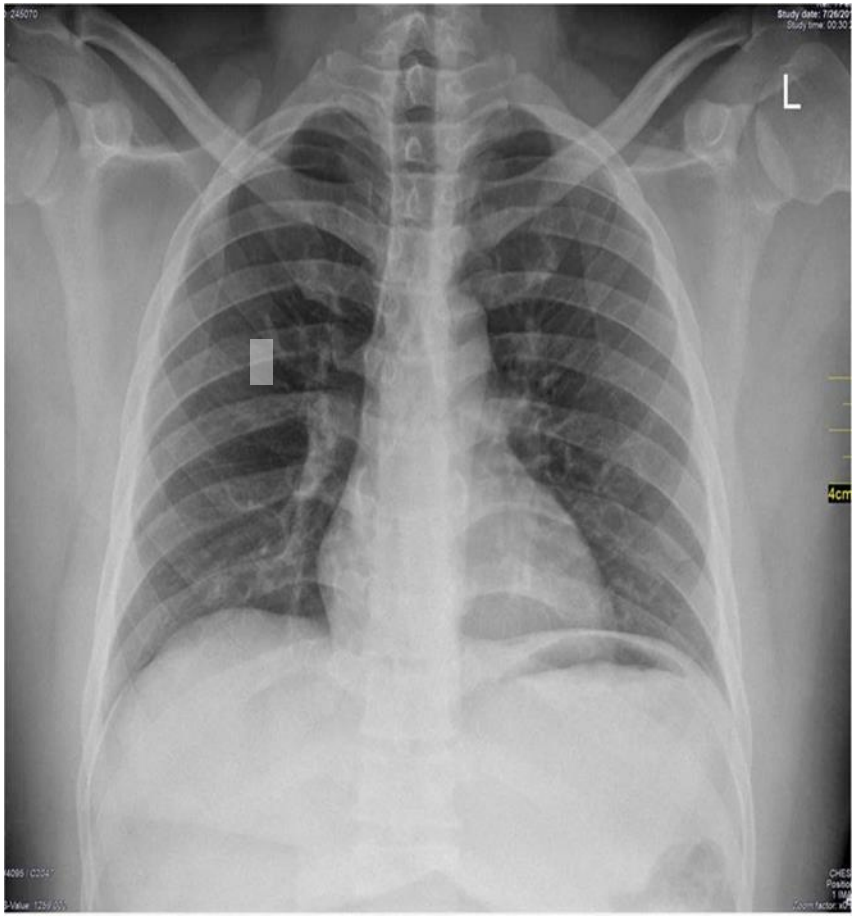
(1) a tall R wave and small S wave with R/S ratio greater than 1 in lead V1,

(2) qR complex in lead V1,

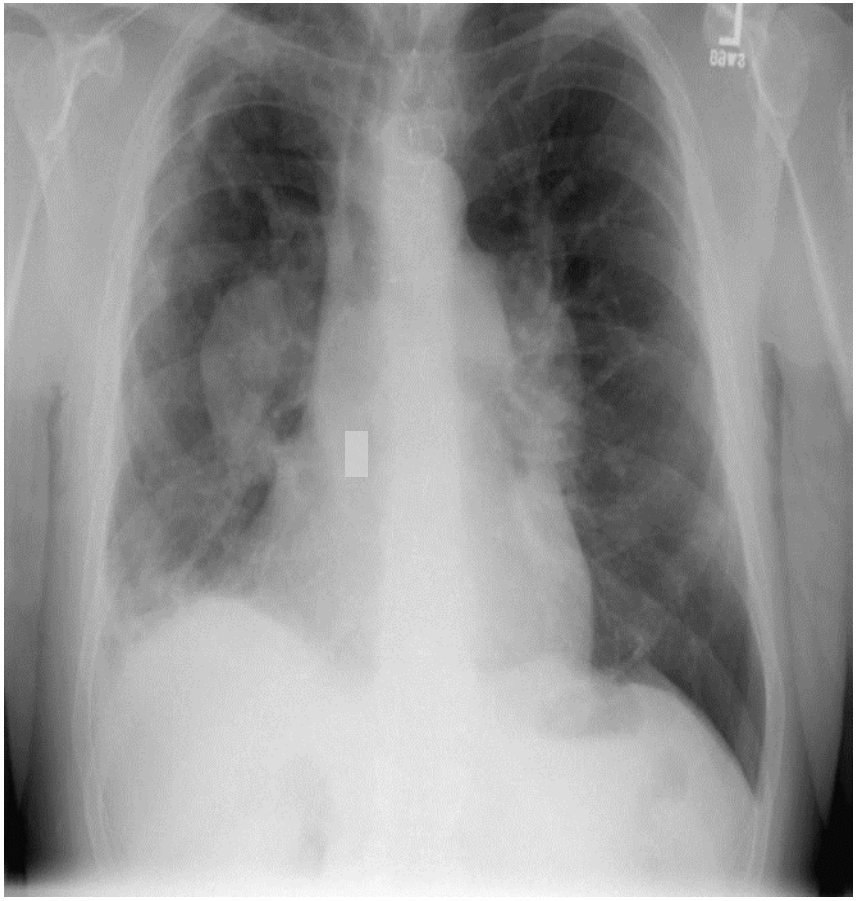
(3) a large S wave and small R wave with R/S ratio less than 1 in lead V5 or V6

CHEST RADIOGRAPH

- normal



- Pulmonary hypertension



CHEST RADIOGRAPH

1- Enlarged hilar pulmonary arterial shadows (right descending greater than 1.6 cm, left greater than 1.8 cm)

2- Concomitant attenuation of peripheral pulmonary vascular markings (“pruning”)

3- Right ventricular hypertrophy

PULMONARY FUNCTION TESTING

Patients with IPAH and CTEPH typically exhibit a mild to moderate restrictive ventilatory defect, a reduction in diffusion capacity.

No correlation has been observed between the severity of PH and the reduction in diffusion

Arterial blood gas analysis typically shows hypoxemia, hypocapnia secondary to alveolar hyperventilation

ECHOCARDIOGRAM

1-Estimates PA systolic pressure

2-Assesses RV size, thickness, and function

3-Evaluates RA size, LV systolic and diastolic function, valve function

4-Detects pericardial effusions and intra cardiac shunts

5- define the cause of PH.

CHEST COMPUTED TOMOGRAPHY

High-resolution CT (HRCT) scanning, however, is required to exclude parenchymal lung disease (ILD) as the cause of PH.

Computed tomography pulmonary angiography

A CTPA can confirm an acute pulmonary embolus and a VQ scan will be required to diagnose chronic pulmonary emboli

Right-sided heart catheterization

1- Right-sided heart catheterization is required to confirm the presence of PH and to determine the severity and prognosis of PH.

2- Assess the elevation of right atrial pressure and a depressed cardiac output that they are associated with worse prognosis and decreased survival.

Right-sided heart catheterization

3- Used for evaluation of vaso reactivity and to guide therapy; a favorable acute response to a vasodilator (intravenous epoprostenol, adenosine, or inhaled nitric oxide) is defined as a fall in mPAP of at least 10 mm Hg to 40 mm Hg or less, with an increased or unchanged cardiac output. These “responders” have an improved survival

Treatment

The recommended approach for treatment can be divided into two categories:

a. General care

b. PAH-specific therapy.

GENERAL THERAPY

1-Supplemental oxygen to maintain oxygen saturation above 90%

2-Careful diuresis is indicated in patients with evidence

of right ventricular failure.

3-Digoxin may produce a modest increase in cardiac output in patients with PH and right ventricular failure.

4-Oral anticoagulation in patients with idiopathic PAH.

DISEASE-TARGETED THERAPIES

A- Oral therapies are considered first-line treatment for

PAH in patients of functional classes II and III, whereas

parenteral therapy should be considered in patients of

functional class IV

B-Reevaluate patients every 3 to 4 months by functional

class, 6-minute walk testing, echocardiography and right-sided

heart catheterization.

Pharmacologic Agents for PAH
3 Pathways

- Endothelin pathway
  - Selective endothelin receptor antagonists (ambrisentan)
  - Dual endothelin receptor antagonists (bosentan, macitentan)
- Nitric oxide pathway
  - PDE-5 inhibitors (sildenafil, tadalafil)
  - sGC stimulators (riociguat)
- Prostacyclin pathway
  - PGI2 analogues (epoprostenol, treprostinil, iloprost
  - Non-prostanoid receptor agonists (selexipag)

Humbert M, et al. *Circulation* 2014;130:2189-2208.

Endothelin Receptor Antagonists

(1) Endothelin-1 is a potent vasoconstrictor that is overexpressed in the plasma and lung tissue of patients with PAH.

(2) Bosentan is an oral nonselective endothelin receptor antagonist

(3) Ambrisentan is an oral selective endothelin type A receptor antagonist.

(4) Both of these agents have been shown to improve exercise capacity, functional class

Phosphodiesterase Type-5 Inhibitors

- Nitric oxide is a potent vasodilator that is produced by endothelial cells from arginine by nitric oxide synthase and acts on the vascular smooth muscle cells via cyclic guanosine monophosphate(cGMP).
- Phosphodiesterase-5 degrades cGMP, thus counteracting this vasodilatory pathway.
- Patients with PAH have decreased plasma levels of nitric oxide metabolites; likewise, endothelial nitric oxide synthase (eNOS) expression is reduced in the pulmonary arteries.
- sildenafil, tadalafil inhibit phosphodiesterase type 5, thus enhancing relaxation and growth inhibition of vascular smooth muscle cells. Both have demonstrated improvement in exercise capacity and functional class.

Prostanoids

(1)Prostacyclin is a potent vasodilator and inhibitor of platelet activation and smooth muscle proliferation.

(2) Three prostanoids that have been shown to improve exercise capacity, quality of life, functional class, and hemodynamics are epoprostenol, treprostinil, and iloprost.

(3) Regimens proven effective include:

a. Intravenous epoprostenol therapy

b. Inhaled, subcutaneous, intravenous treprostinil therapy

c. Inhaled iloprost

Thank you