Pulmonary hypertension

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Anatomy

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

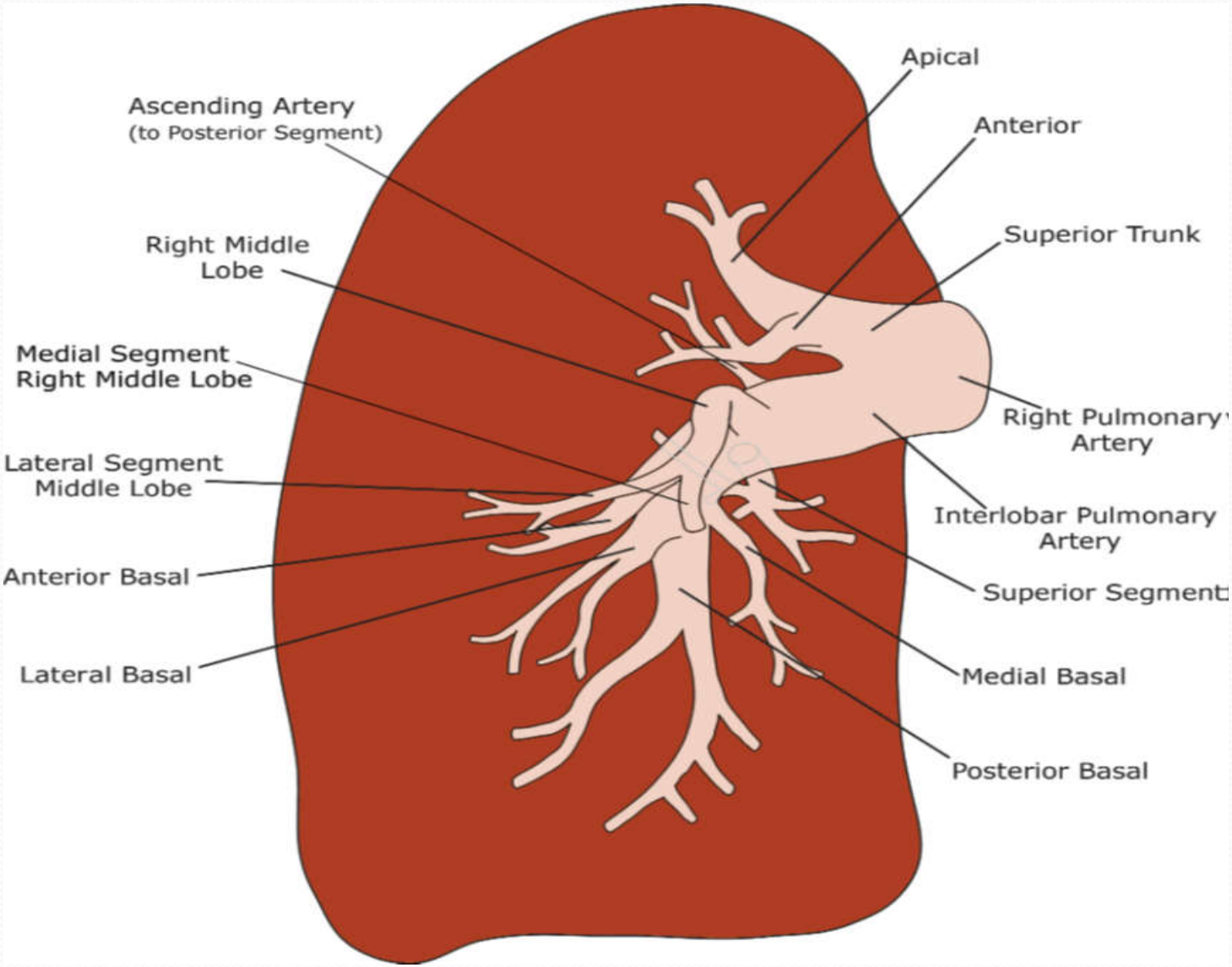
- **Pulmonary Arteries**

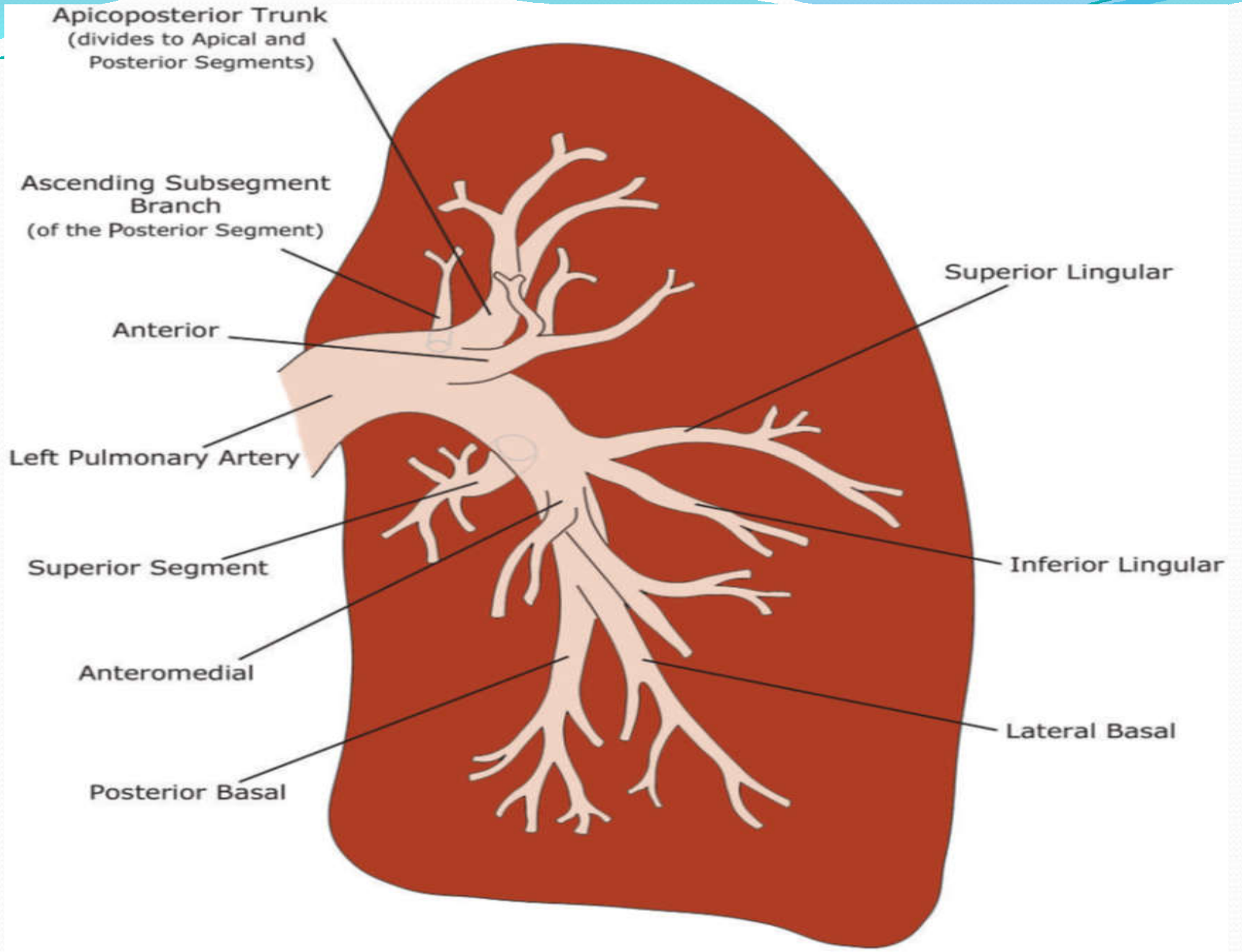
◆ The main pulmonary artery arises from the right ventricle distal to the pulmonary valve and it divides into right and left pulmonary arteries.

◆ The right pulmonary artery divides into the trunks anterior (superior trunk) and the inter lobar pulmonary artery.

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

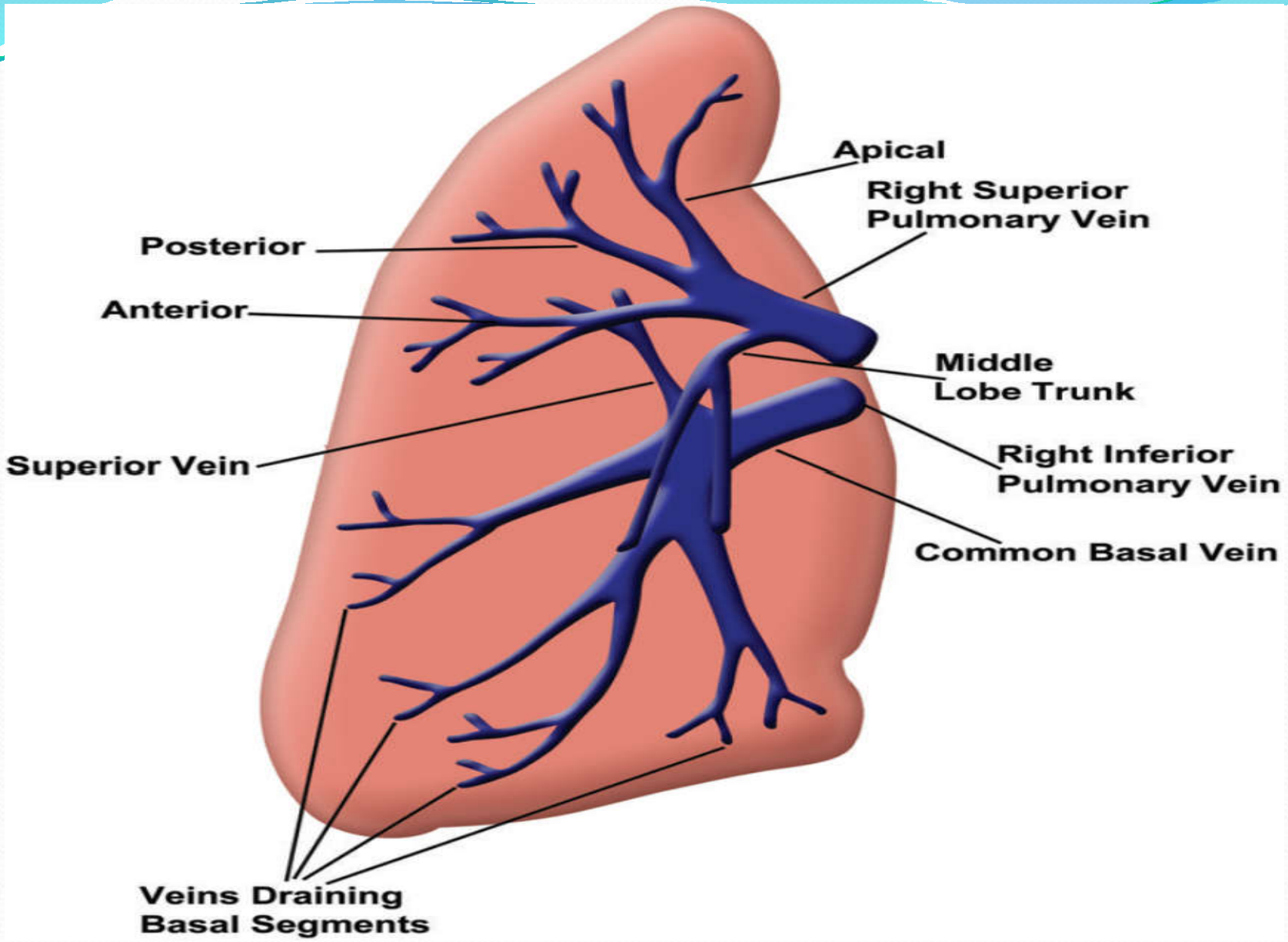
◆ The segmental arteries are adjacent to their accompanying bronchi, situated medial to the bronchi in the upper lobes and laterally in the lingual and middle and lower lobes.

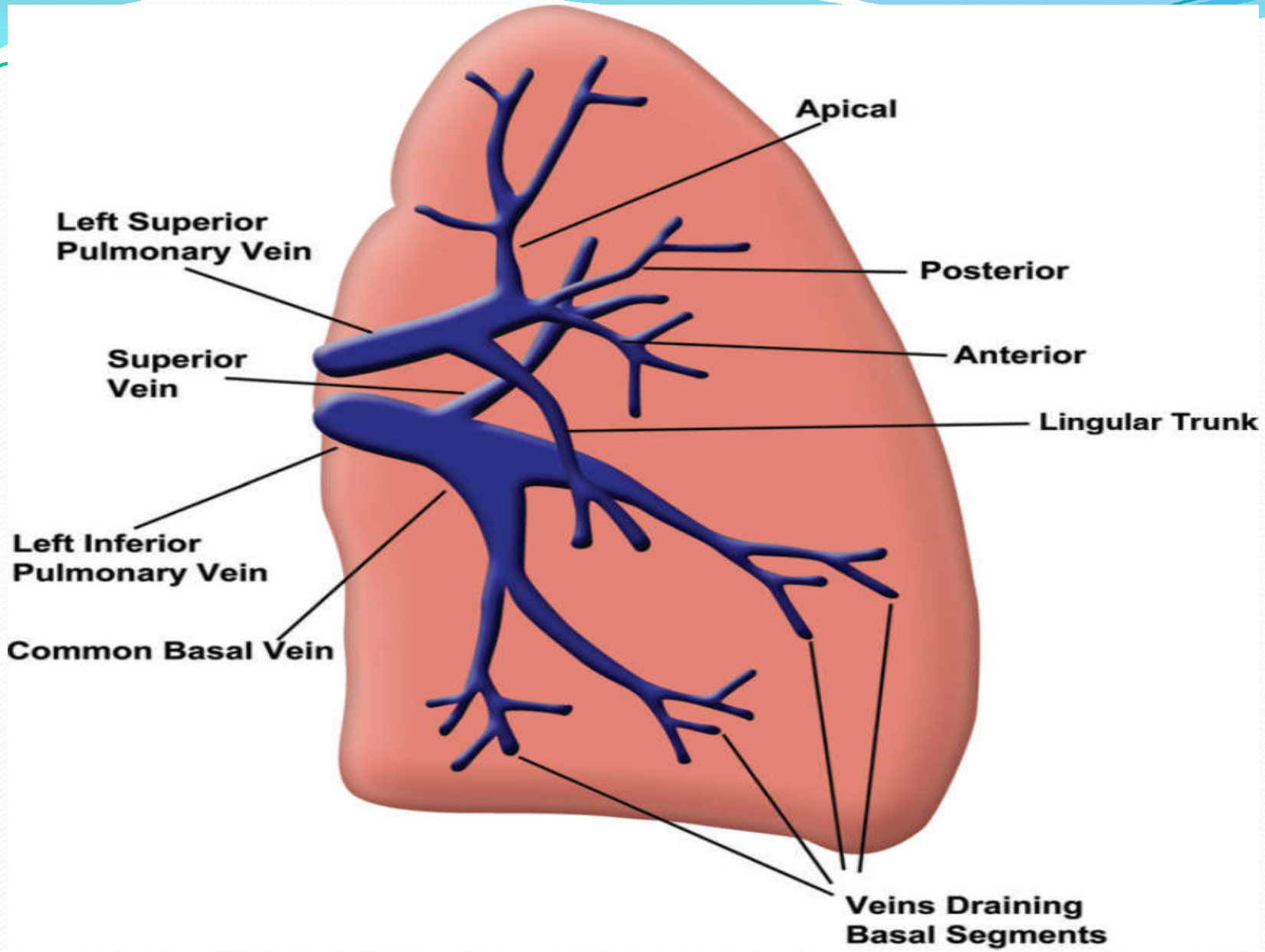

Apical
Ascending Artery
(to Posterior Segment)
Anterior
Right Middle
Lobe
Superior Trunk
Medial Segment
Right Middle Lobe
Right Pulmonary
Artery
Lateral Segment
Middle Lobe
Interlobar Pulmonary
Artery
Anterior Basal
Superior Segment
Lateral Basal
Medial Basal
Posterior Basal


Apicoposterior Trunk
(divides to Apical and
Posterior Segments)
Ascending Subsegment
Branch
(of the Posterior Segment)
Anterior
Left Pulmonary Artery
Superior Segment
Anteromedial
Posterior Basal
Superior Lingular
Inferior Lingular
Lateral Basal

Pulmonary Veins

- The veins are found in the periphery of the lung from the level of the secondary pulmonary lobule to the levels of the sub segments, segments, and lobes.
- Right superior and inferior pulmonary veins and left superior and inferior pulmonary veins drain directly into the left atrium.
- The right superior pulmonary vein drains the right upper lobe and right middle lobe.
- The right inferior pulmonary vein drains the right lower lobe
- The left superior pulmonary vein drains the left upper lobe and lingula.
- The left inferior pulmonary vein drains the left lower lobe.


Apical
Right Superior
Pulmonary Vein
Posterior
Anterior
Middle
Lobe Trunk
Superior Vein
Right Inferior
Pulmonary Vein
Common Basal Vein
Veins Draining
Basal Segments


Apical
Left Superior
Pulmonary Vein
Posterior
Superior
Vein
Anterior
Lingular Trunk
Left Inferior
Pulmonary Vein
Common Basal Vein
Veins Draining
Basal Segments

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

-Thinner than systemic arteries

-Have proportionately more elastic tissue in their walls.

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

-Low pressure system

-Low incidence of atherosclerosis

-Low vascular resistance

-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).

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

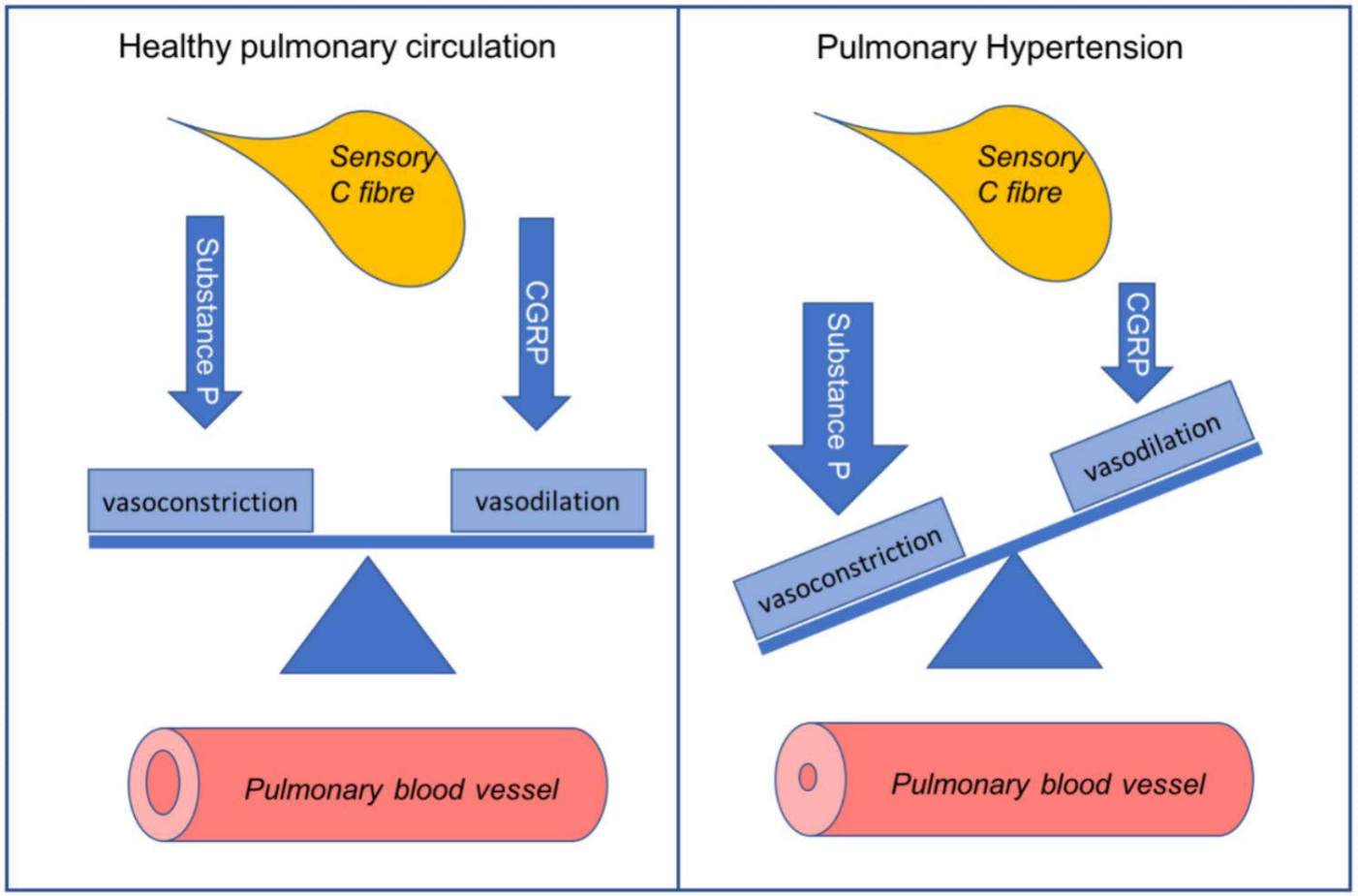
Pulmonary hypertension can occur due to pulmonary arterial hypertension alone or occur due to pulmonary venous hypertension.

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

-Pulmonary hypertension can affect patients of all ages and ethnicities but occurs more commonly in African-Americans.

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

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

TABLE 72-1 Updated Classification of Pulmonary Hypertension[a]

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, SMADS, CAV1, KCNK3
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

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

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 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 lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

TABLE 72-2 Pathogenetic Mechanisms of Pulmonary Hypertension

	Mechanism	Examples
Passive	Pulmonary venous hypertension	Mitral stenosis, left atrial myxoma, fibrosing mediastinitis, pulmonary venoocclusive disease
Hyperkinetic	Increased pulmonary blood flow[a]	Left-to-right intracardiac shunts
Obstructive	Thromboembolic pulmonary vascular disease	High grade obstruction of large pulmonary arteries by organized thromboemboli, multiple pulmonary emboli
Obliterative	Inflammatory and/or proliferative pulmonary vascular disease	Interstitial lung disease, pulmonary arterial hypertension, schistosomiasis
Venoconstrictive	Hypoxia	High altitude, chronic bronchitis and emphysema (COPD)
Idiopathic	Unknown	Drug-associated pulmonary hypertension, portopulmonary hypertension, HIV infection

[a]Most categories overlap to some extent. For example, increased pulmonary blood flow is usually coupled with anatomic changes in the resistance vessels to produce pulmonary hypertension.

TABLE 7 Updated risk level of drugs and toxins known to induce pulmonary arterial hypertension

Definite	Likely	Possible
• Aminorex • Fenfluramine • Dexfenfluramine • Toxic rapeseed oil • Benfluorex • Selective serotonin reuptake inhibitors[a]	• Amphetamines • Dasatinib • L-tryptophan • Methamphetamines	• Cocaine • Phenylpropanolamine • St John's Wort • Amphetamine-like drugs • Interferon α and β • Some chemotherapeutic agents such as alkylating agents (mitomycine C, cyclophosphamide)[b]

[a]Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors; [b]Alkylating agents are possible causes of pulmonary veno-occlusive disease.

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

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

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

-Patients who have underlying cardiac or pulmonary disease and present with increasing breathlessness 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 oedema, tricuspid regurgitation, and Hepatomegaly).

TABLE 72-4 World Health Organization Functional Classification of Patients with Pulmonary Hypertension

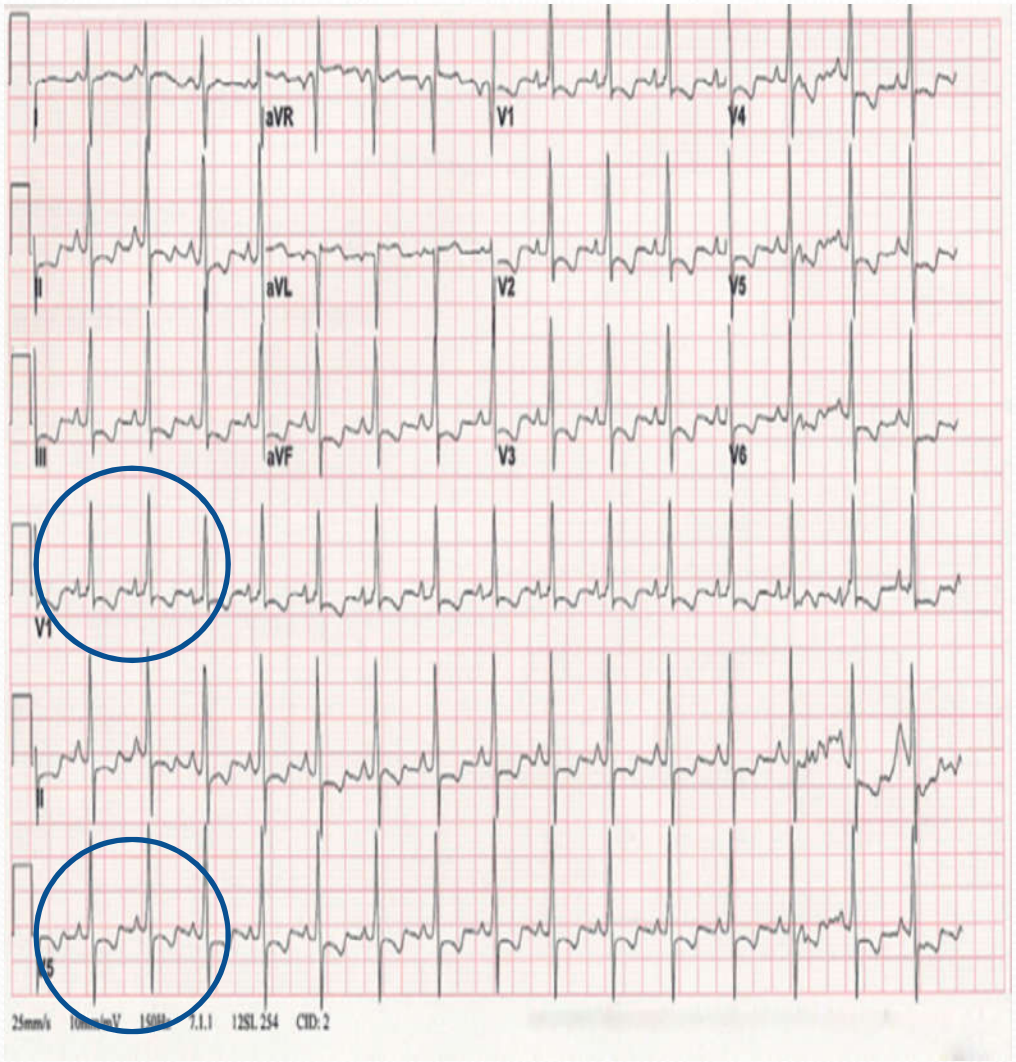
Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II: Patients with PH 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 PH 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 PH 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.

ELECTROCARDIOGRAM

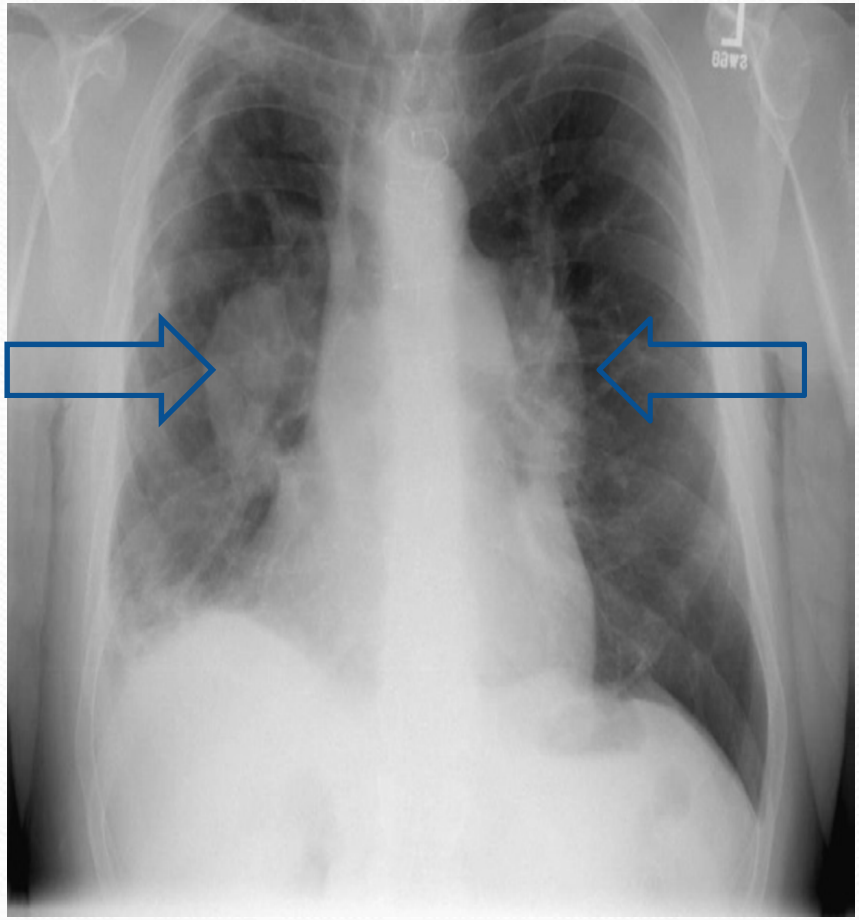


(1) a tall R wave and small S wave with R/S ratio greater than 1 in lead V1,

(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



enlarged hilar pulmonary arterial shadows (right descending greater than 1.6 cm, left greater than 1.8 cm)

concomitant attenuation of peripheral pulmonary vascular markings (“pruning”)

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-Doppler ultrasound estimates PA systolic pressure

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

Right-sided heart catheterization is required to confirm the presence of PH and to determine the severity and prognosis of PH. In particular, an elevated right atrial pressure and a depressed cardiac output are associated with worse prognosis and decreased survival.

Right-sided heart catheterization also can be used to evaluate for 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 when treated with calcium channel blockers

Treatment

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

.General care

.PAH-specific therapy.

GENERAL THERAPY

-Supplemental oxygen to maintain oxygen saturation above 90%

-Careful diuresis is indicated in patients with evidence of right ventricular failure.

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

-Oral anticoagulation in patients with idiopathic PAH.

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.(e.g. sildenafil, tadalafil)

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:

.Continuous intravenous epoprostenol therapy

.Inhaled, subcutaneous, intravenous treprostinil therapy

.Inhaled iloprost

Thank You