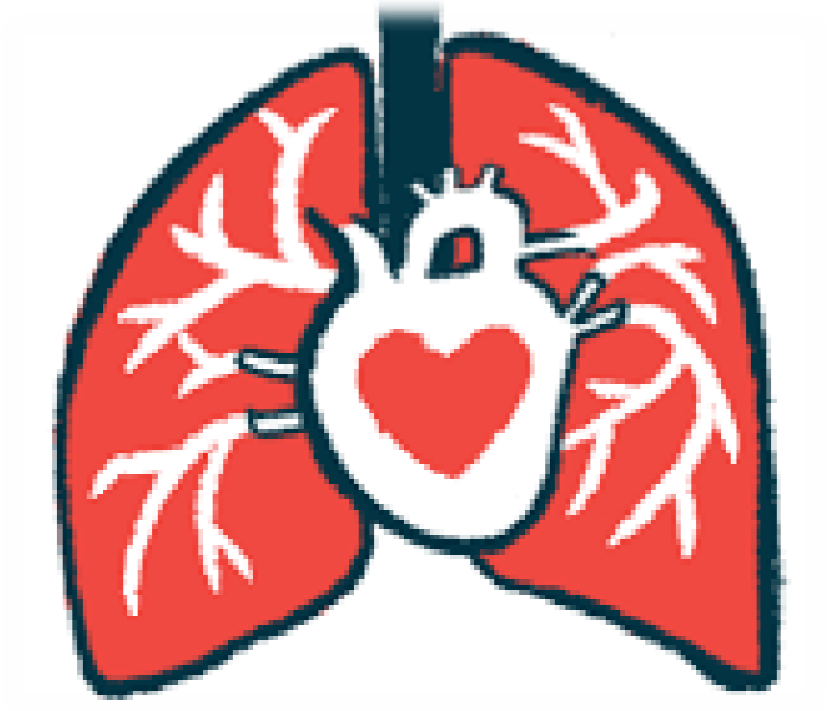
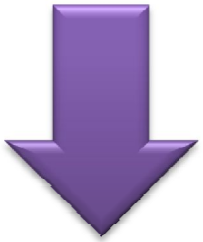
Pathogenesis of Pulmonary Hypertension



Dr. Anan Ismail

normal pulmonary artery pressure



mean pulmonary artery pressure ≤20 mmHg **at rest**

pulmonary **hypertension** (PH)

mean pulmonary artery pressure ≥20 mmHg **at rest**

pulmonary vascular resistance ≥3 Wood units

Pulmonary hypertension (PH) is classified into five groups based on the World Health Organization (WHO) classification system

1 PAH
1.1 **Idiopathic** PAH
1.2 **Heritable** PAH
1.3 **Drug** and **toxin-induced** PAH
1.4 PAH associated with:
1.4.1 **Connective tissue disease**
1.4.2 **HIV** infection
1.4.3 **Portal hypertension**
1.4.4 **Congenital heart disease**
1.4.5 **Schistosomiasis**
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome

Pulmonary hypertension (PH) is classified into five groups based on the World Health Organization (WHO) classification system

2 PH due to left heart disease
2.1 PH due to **heart failure** with **preserved LVEF**
2.2 PH due to **heart failure** with **reduced LVEF**
2.3 **Valvular** heart disease
2.4 **Congenital/acquired** cardiovascular conditions **leading to post-capillary PH**

Pulmonary hypertension (PH) is classified into five groups based on the World Health Organization (WHO) classification system

3 PH due to lung disease and/or hypoxia
3.1 **Obstructive lung disease**
3.2 **Restrictive lung disease**
3.3 Other lung disease with **mixed restrictive/obstructive pattern**
3.4 **Hypoxia without lung disease**
3.5 Developmental **lung disorders**

Pulmonary hypertension (PH) is classified into five groups based on the World Health Organization (WHO) classification system

4 PH due to pulmonary artery obstructions
4.1 **Chronic thromboembolic PH**
4.2 Other **pulmonary artery obstructions**

Pulmonary hypertension (PH) is classified into five groups based on the World Health Organization (WHO) classification system

5 PH with unclear and/or multifactorial mechanisms
5.1 **Hematologic disorders**
5.2 **Systemic and metabolic disorders**
5.3 **Others**
5.4 **Complex congenital heart disease**

Pulmonary hypertension (PH) is classified into five groups based on the World Health Organization (WHO) classification system

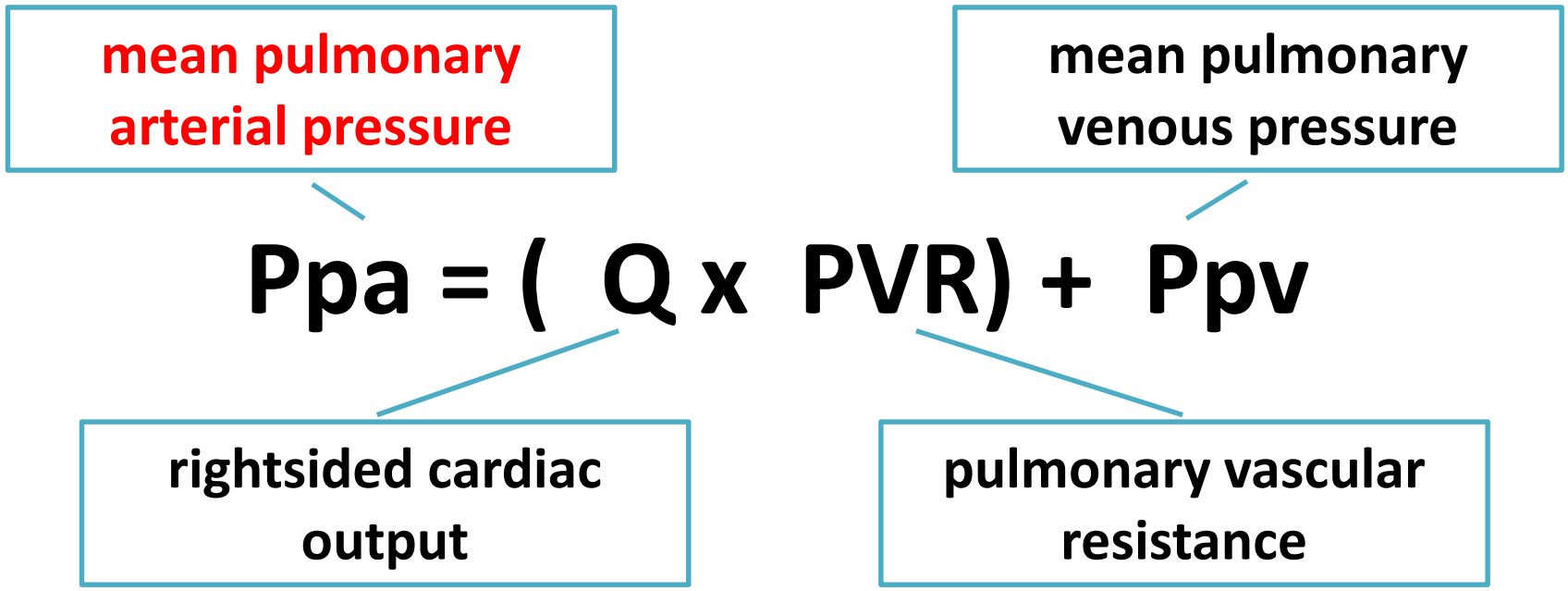
- **The term PAH is used to describe those included in WHO group 1**
- **The term PH is used when collectively describing all five groups**

General physiologic mechanisms

Ohms law

Change in pressure = flow x resistance

Ppa - Ppv = Q x PVR

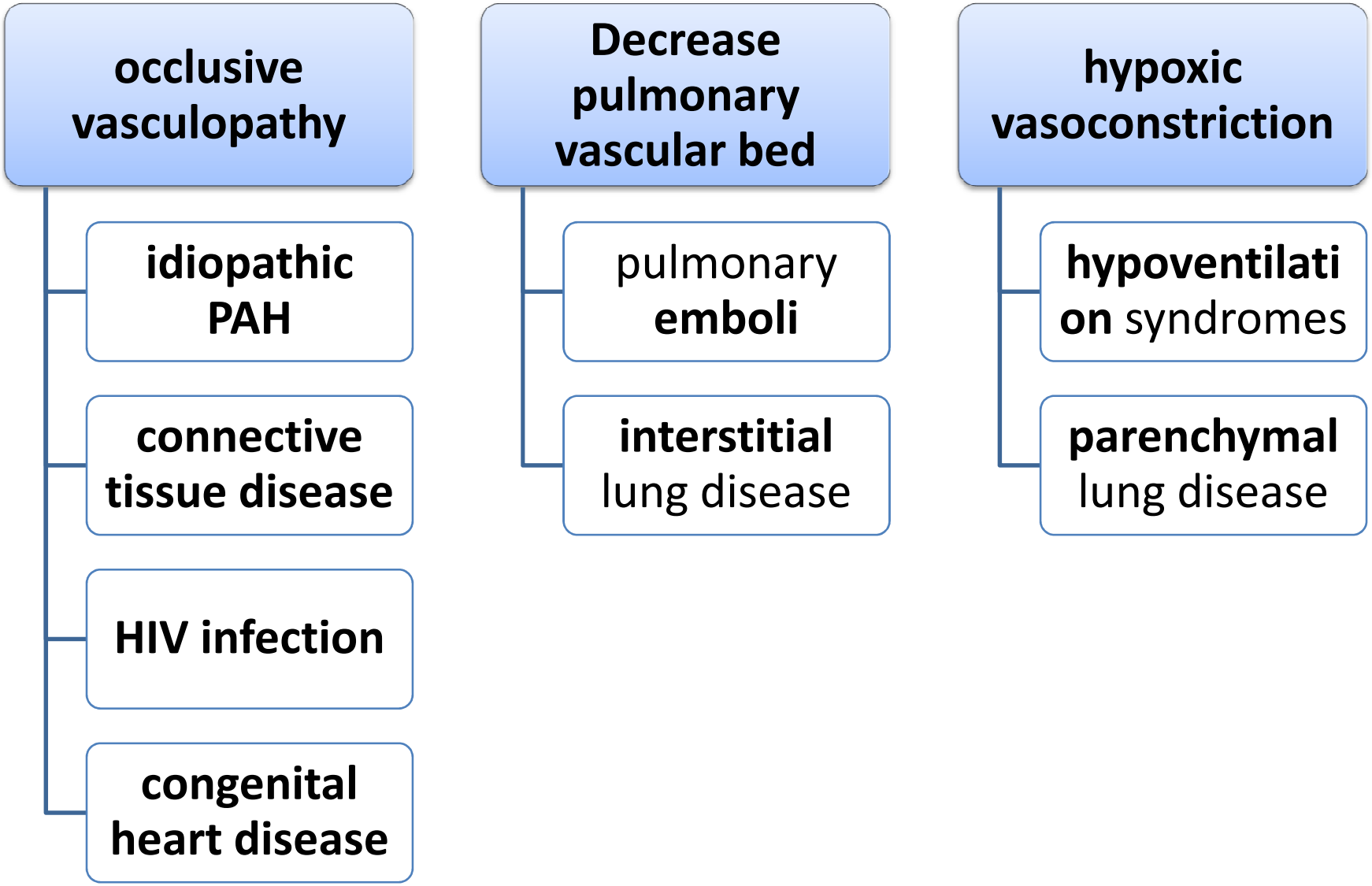


⇈⇈Ppa = (Q x ↑ PVR) + Ppv

The primary cause of significant PH is almost

increased pulmonary vascular resistance

Increased pulmonary vascular **resistance**



↑ Ppa = (↑Q x PVR) + Ppv

Increased flow alone

does not usually cause <u>significant</u> pulmonary hypertension

- pulmonary vascular bed **vasodilates**
- **recruits vessels** in response to increased flow

Increased **flow**

congenital heart defects with left to right shunt (ASD , VSD , PDA)

liver cirrhosis

Anemia

arteriovenous malformations

arteriovenous fistulas (dialysis)

↑ Ppa = (Q x PVR) + ↑Ppv

increased pulmonary venous pressure

alone

does not usually cause significant PH

Increased pulmonary **venous** pressure

mitral valve disease

left ventricular systolic or diastolic dysfunction

constrictive pericarditis

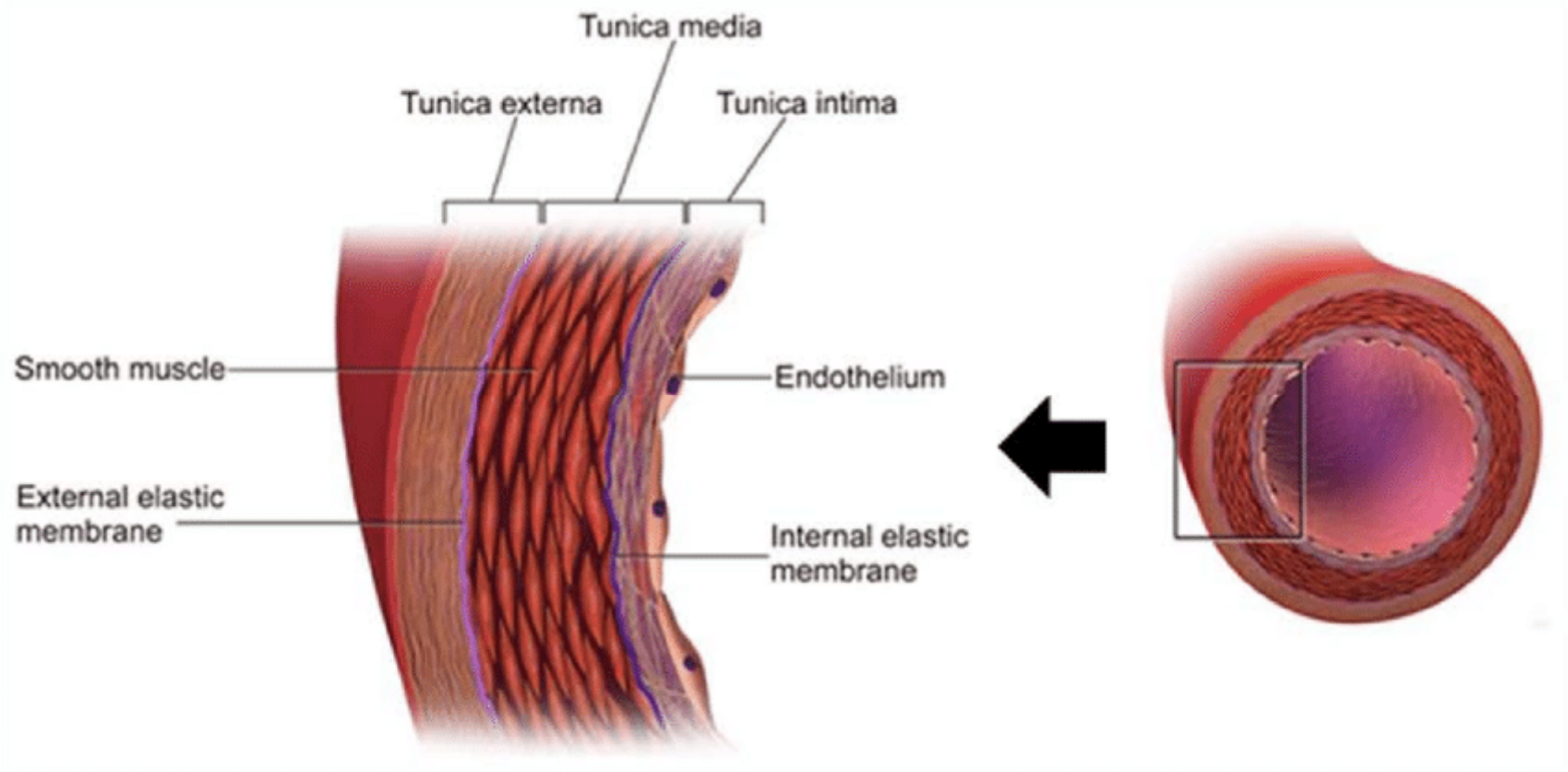
restrictive cardiomyopathy

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

chronic increase of either **flow** and/or pulmonary **venous pressure** can increase pulmonary vascular **resistance**

pathology

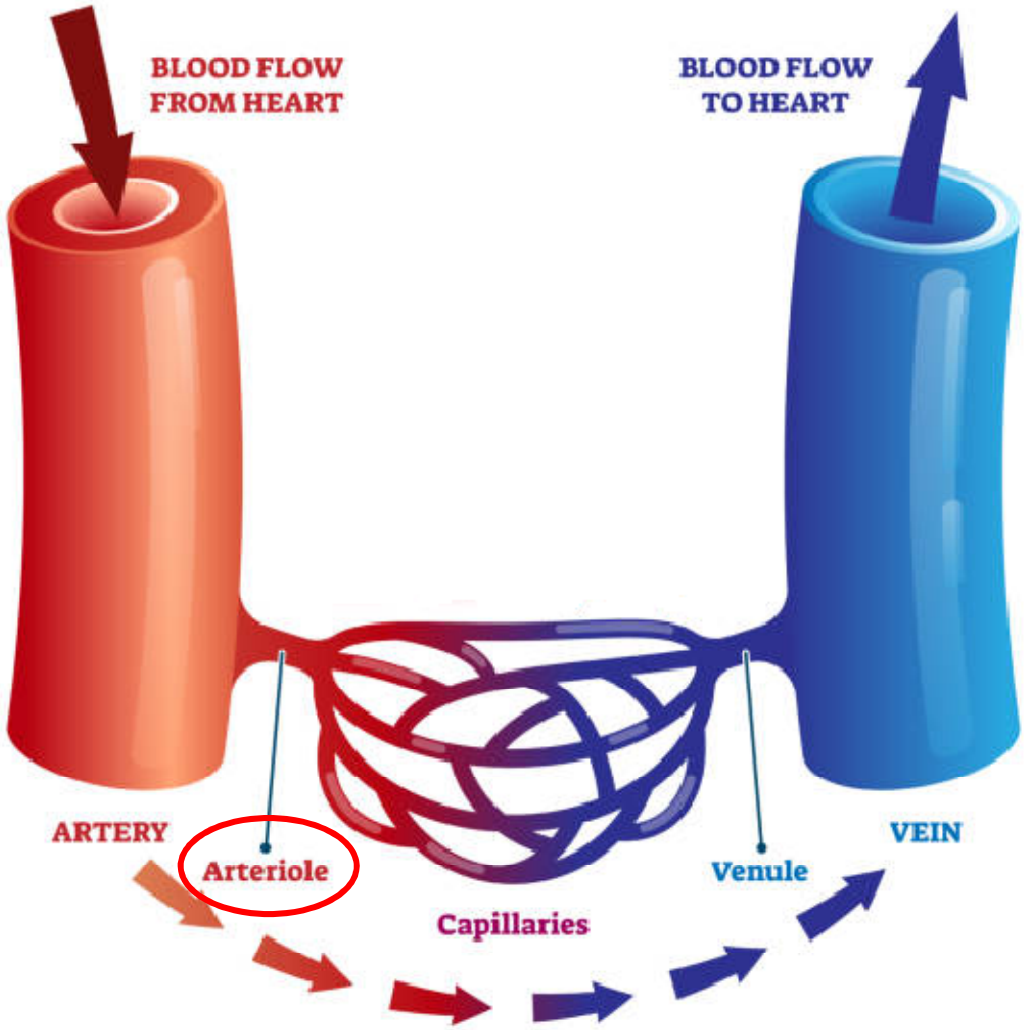
The pathologic appearance of the small pulmonary arteries and arterioles is qualitatively similar in all patients with group 1 PAH



In the normal lung

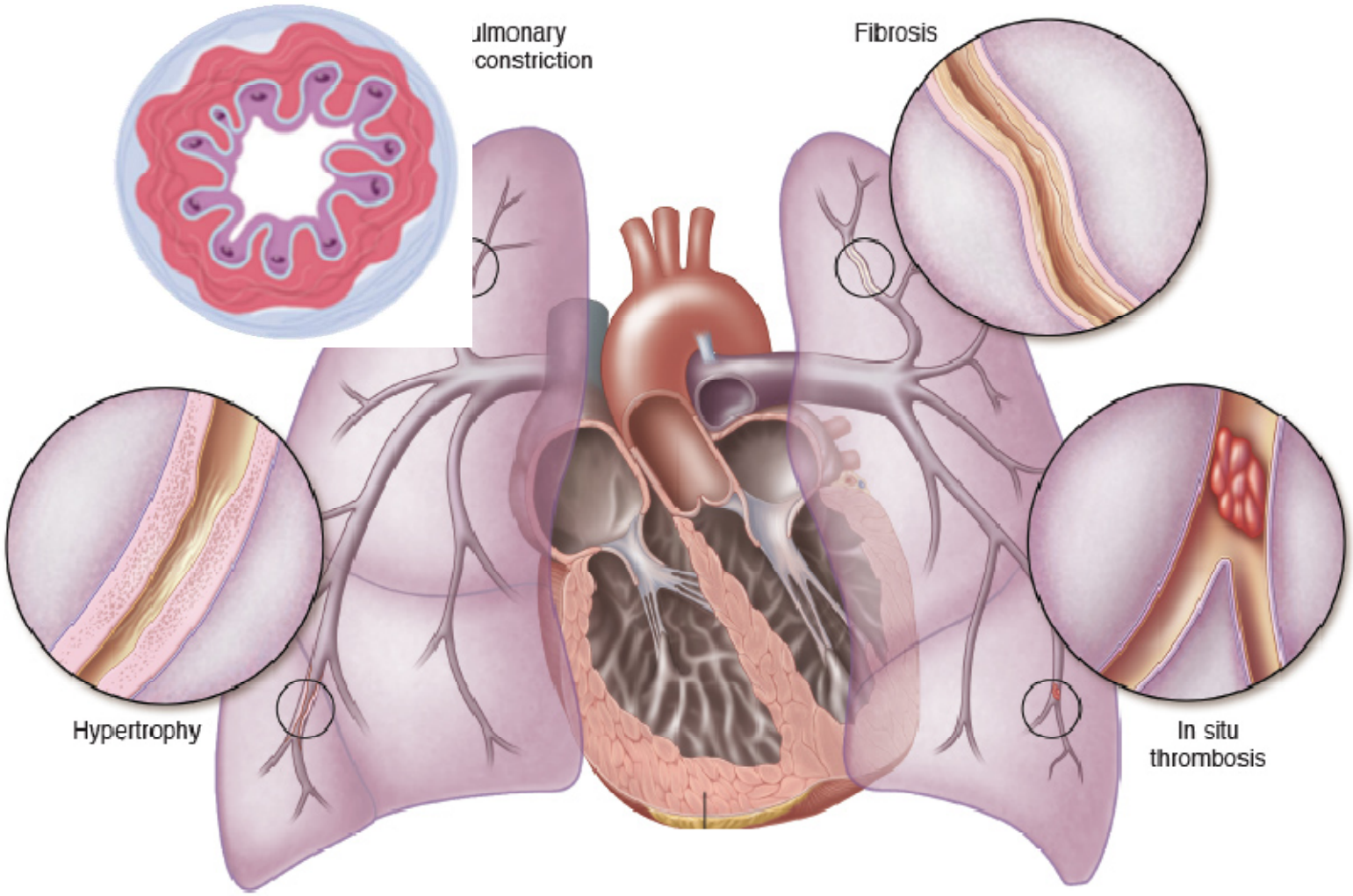
the muscle in the precapillary arteries thins progressively

as the capillary bed approached



PAH

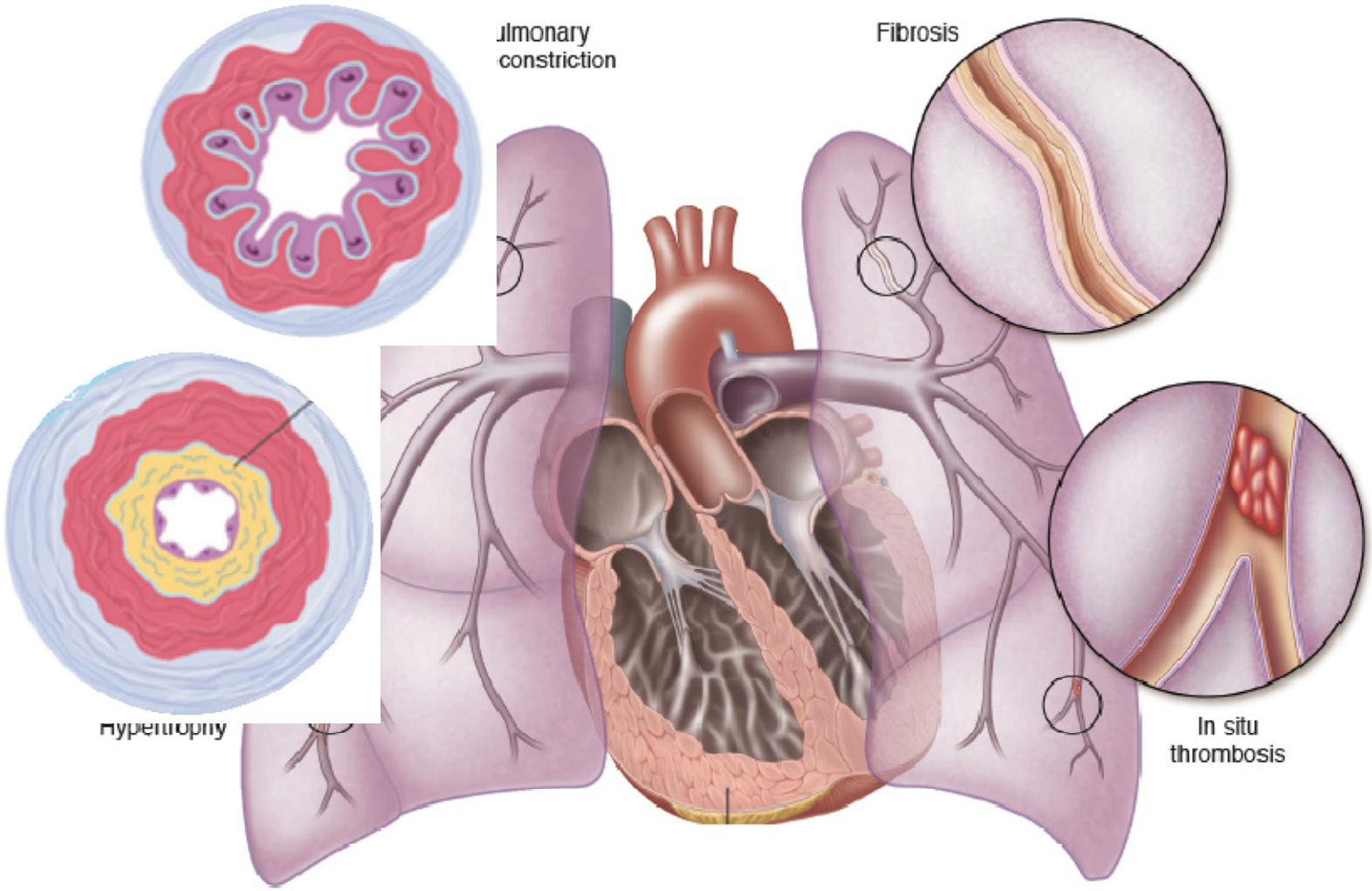
proliferative vasculopathy of the **small pulmonary muscular arterioles** (<50 microns)



It is characterized by

vasoconstriction, **hypertrophy**, **fibrosis**, and **thrombosis**

that involves **all three layers** of the vascular wall (intima, media, adventitia)

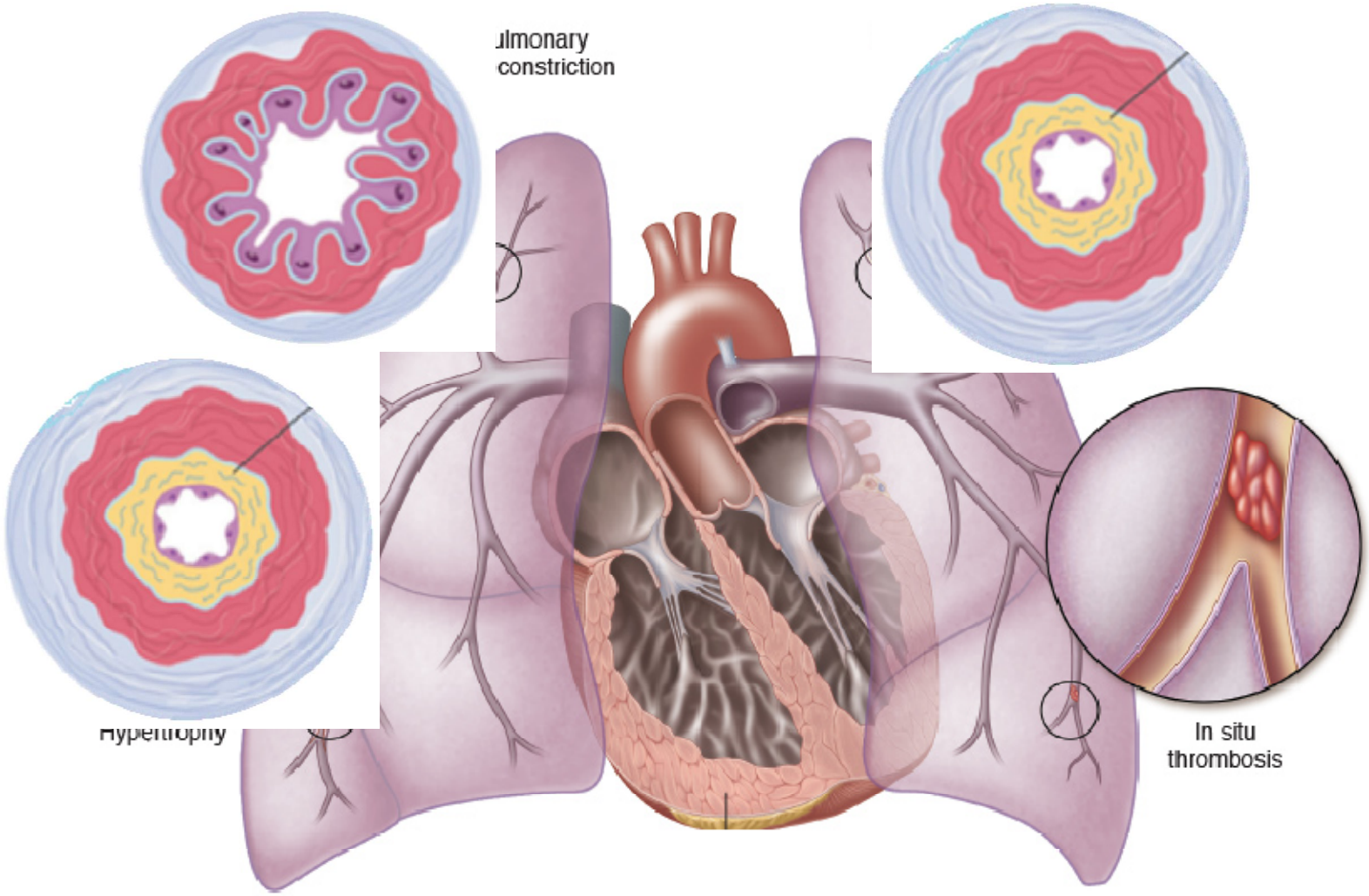


Grade I and II changes (medial hypertrophy and intimal hyperplasia)

Intimal proliferation

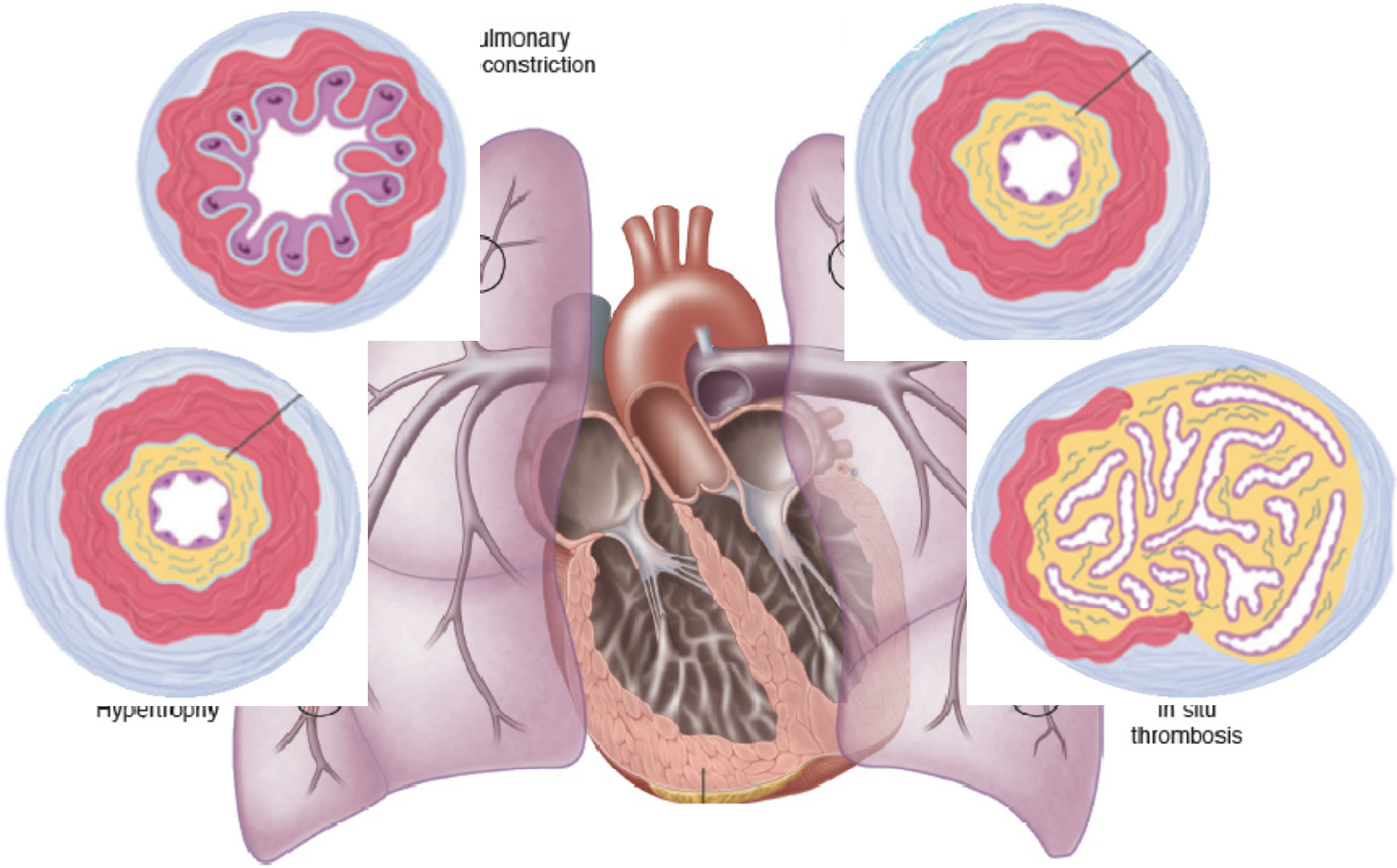
Increase in smooth muscle cell mass (number and size)

Extension of smooth muscle cells into vessels normally only partially muscularized



Grade III abnormalities

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

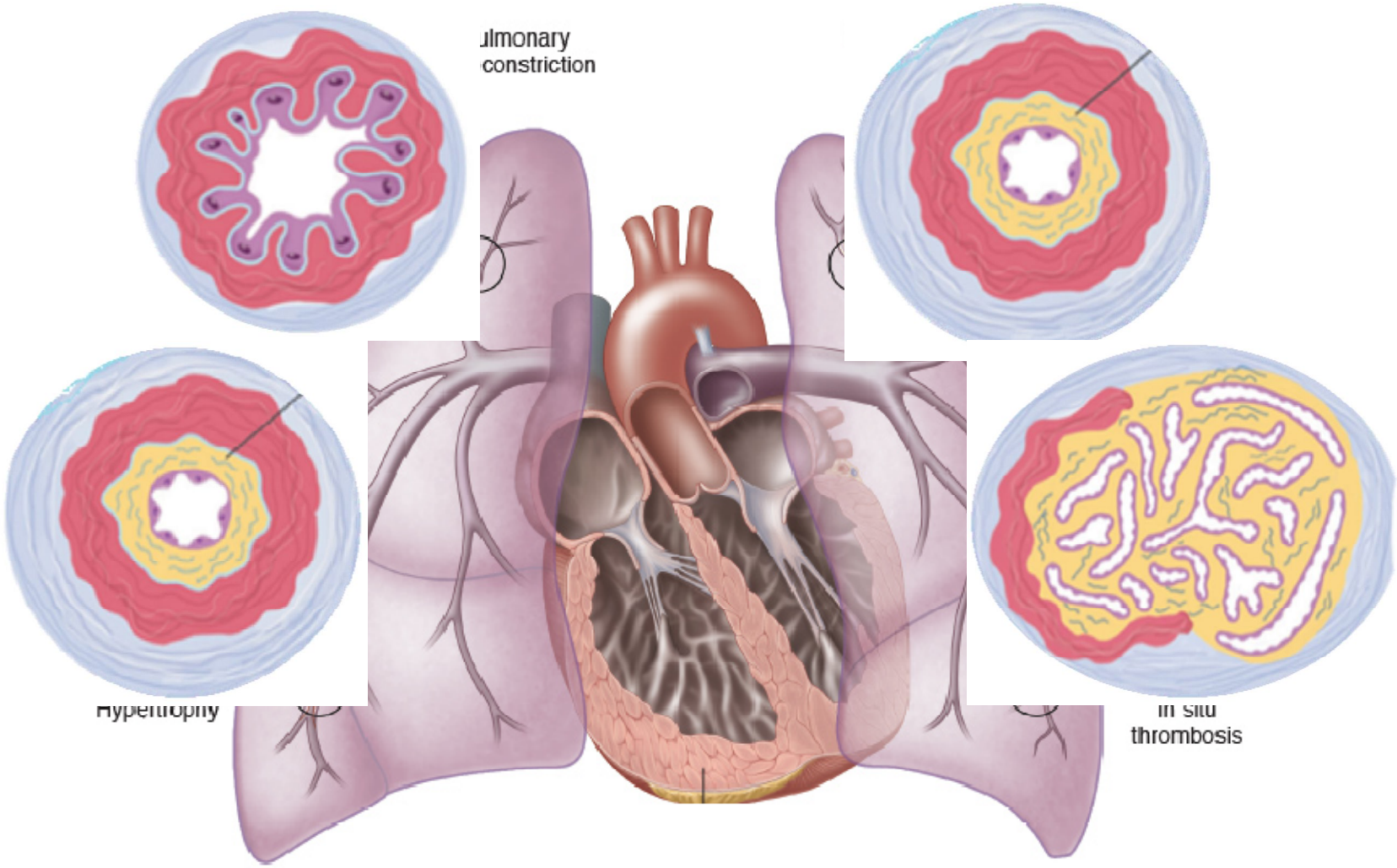


Grade IV through VI

in situ thrombi

plexiform lesions (collections of proliferating endothelial, smooth muscle cells, Myofibroblasts, matrix proteins)

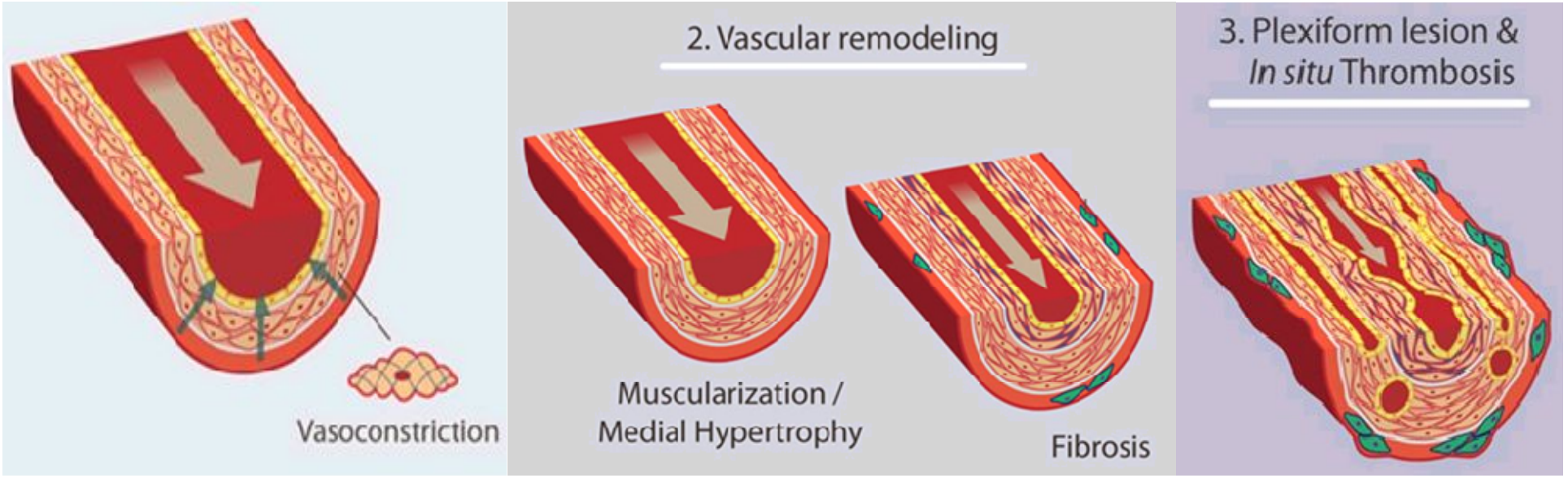
partially or completely occlude the vessel lumen

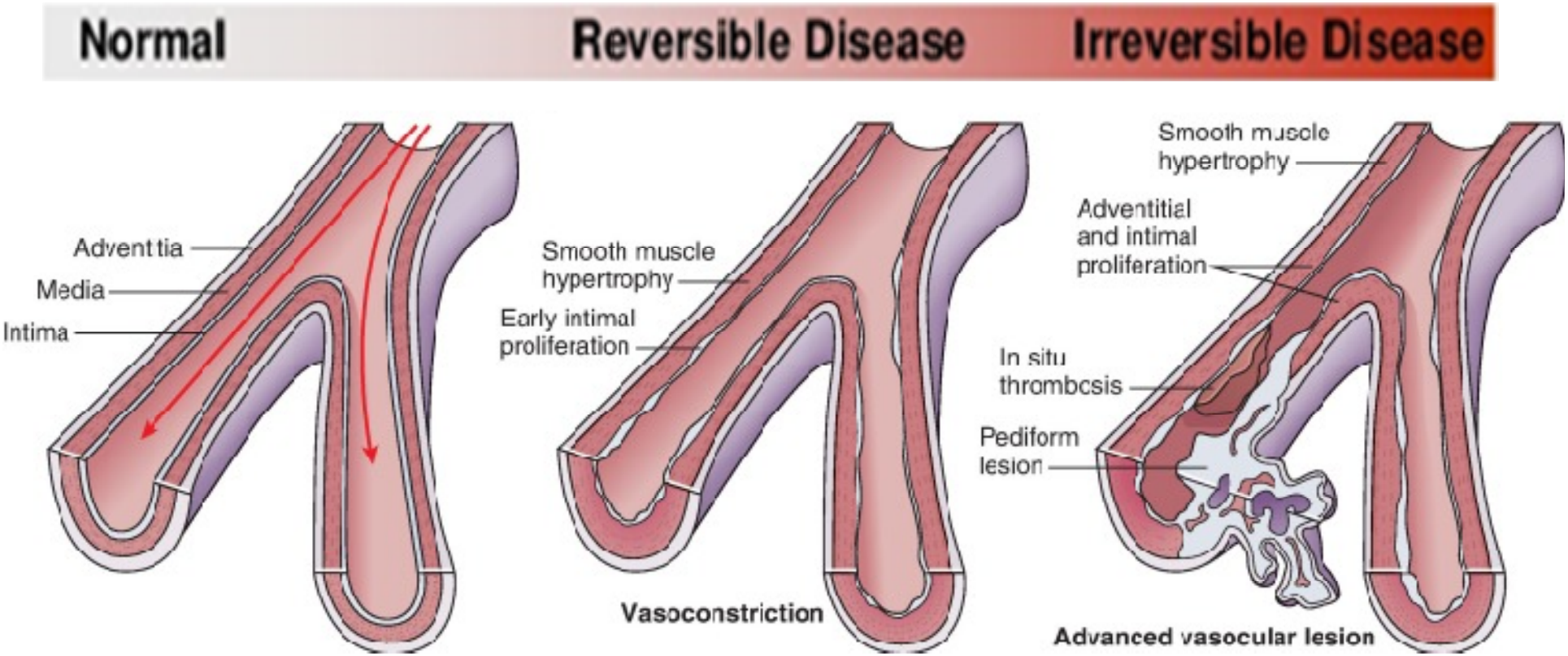


Grade I, II, and III lesions are reversible

While

Grade IV through VI lesions are not


Vasoconstriction
2. Vascular remodeling
Muscularization /
Medial Hypertrophy
Fibrosis
3. Plexiform lesion &
In situ Thrombosis


Normal
Reversible Disease
Irreversible Disease
Adventitia
Media
Intima
Smooth muscle
hypertrophy
Early intimal
proliferation
Vasoconstriction
Smooth muscle
hypertrophy
Adventitial
and intimal
proliferation
In situ
thrombosis
Pediform
lesion
Advanced vasocular lesion

Genetic mutations

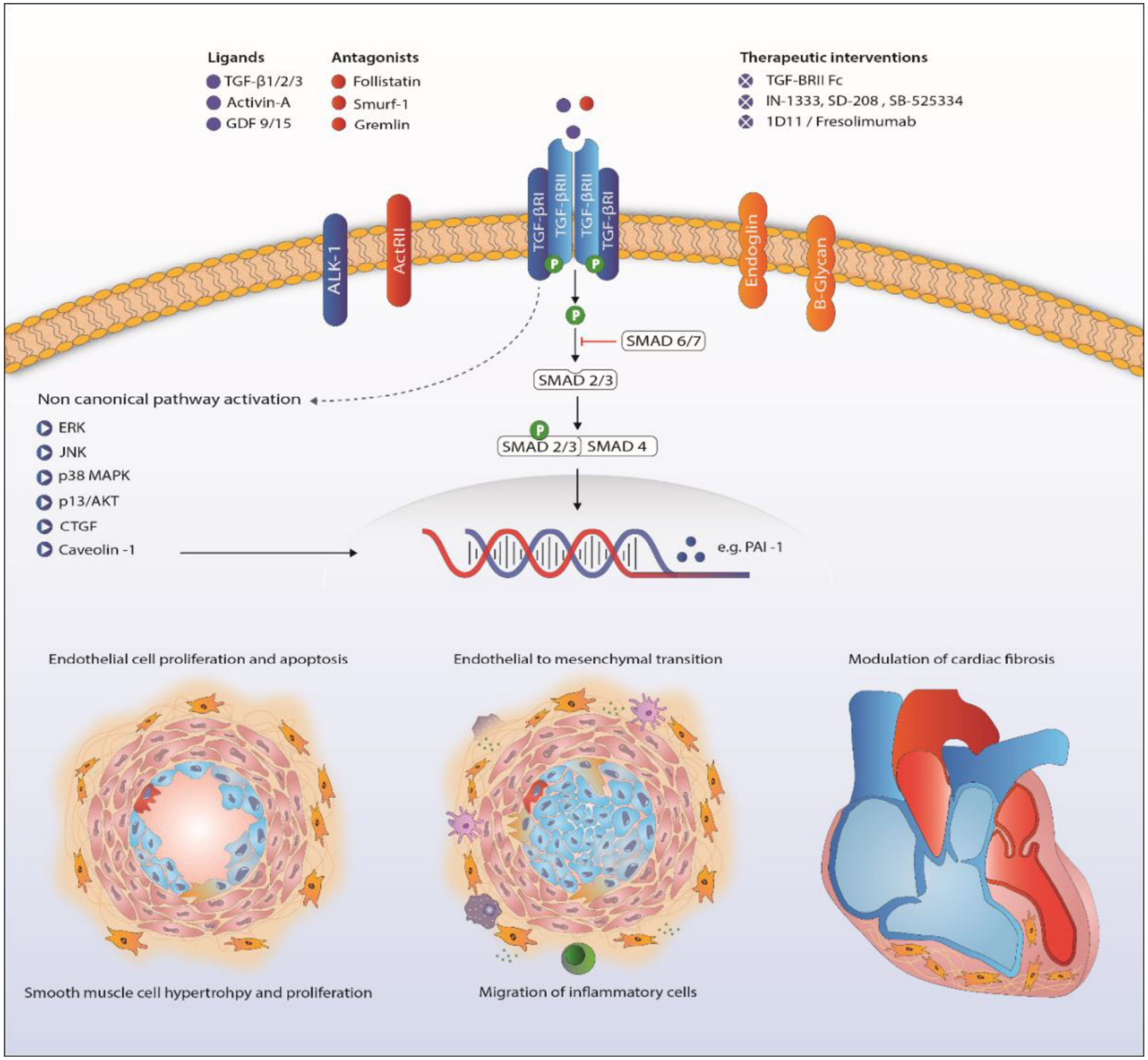
Mutations in the following genes have been variably associated with:

familial, **idiopathic**, or **hereditary hemorrhagic telangiectasia (HHT)**

Associated

PAH

Gene	Disease	Inheritance	Function
BMPR2	IPAH/HPAH	Autosomal dominant	**Type II receptor of TGF-beta** family of signaling molecules
ALK1	HHT	Autosomal dominant	Type I receptor of TGF-beta family
ENG	HHT	Autosomal dominant	Type II receptor of TGF-beta family
SMAD9	IPAH/HPAH	Autosomal dominant	Signal transduction molecule
KCNK3	IPAH/HPAH	Autosomal dominant	pH-sensitive potassium channel
CAV1	IPAH/HPAH	Autosomal dominant	Membrane protein required for formation of caveolae
EIF2AK4	PVOD/PCH	Autosomal recessive	Kinase involved in control of angiogenesis

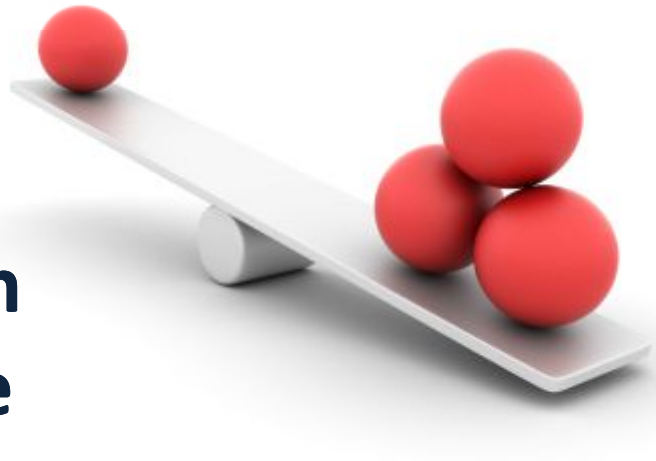

Ligands
TGF-β1/2/3
Activin-A
GDF 9/15
Antagonists
Follistatin
Smurf-1
Gremlin
Therapeutic interventions
TGF-BRII Fc
IN-1333, SD-208 , SB-525334
1D11 / Fresolimumab
ALK-1
ActRII
TGF-βRI
TGF-βRII
TGF-βRII
TGF-βRI
Endoglin
B-Glycan
P
SMAD 6/7
SMAD 2/3
SMAD 2/3
SMAD 4
Non canonical pathway activation
ERK
JNK
p38 MAPK
p13/AKT
CTGF
Caveolin -1
e.g. PAI -1
Endothelial cell proliferation and apoptosis
Endothelial to mesenchymal transition
Modulation of cardiac fibrosis
Smooth muscle cell hypertrohpy and proliferation
Migration of inflammatory cells

Vascular mediators

Vasodilator factors

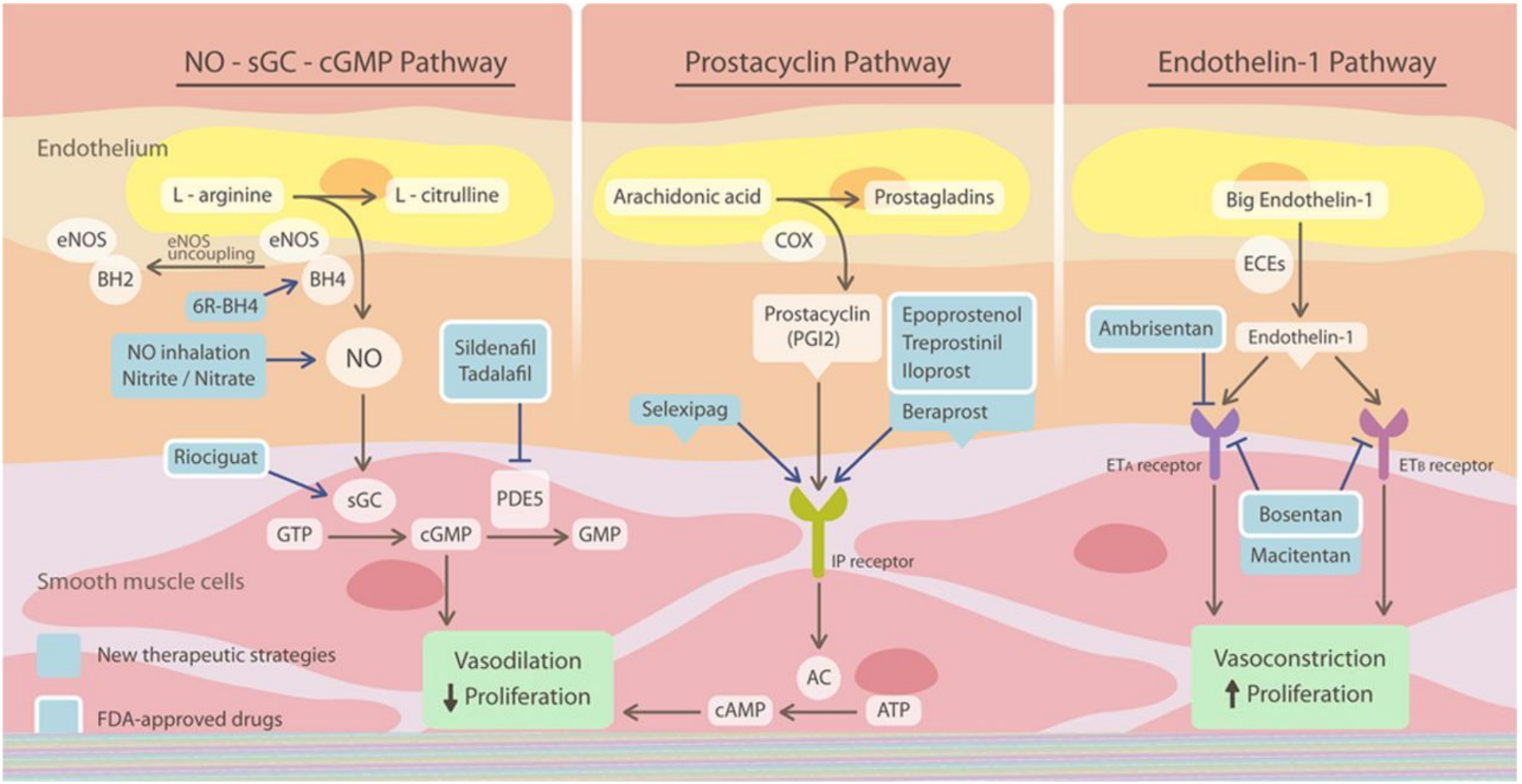
⇊Prostacyclin

⇊Nitric oxide



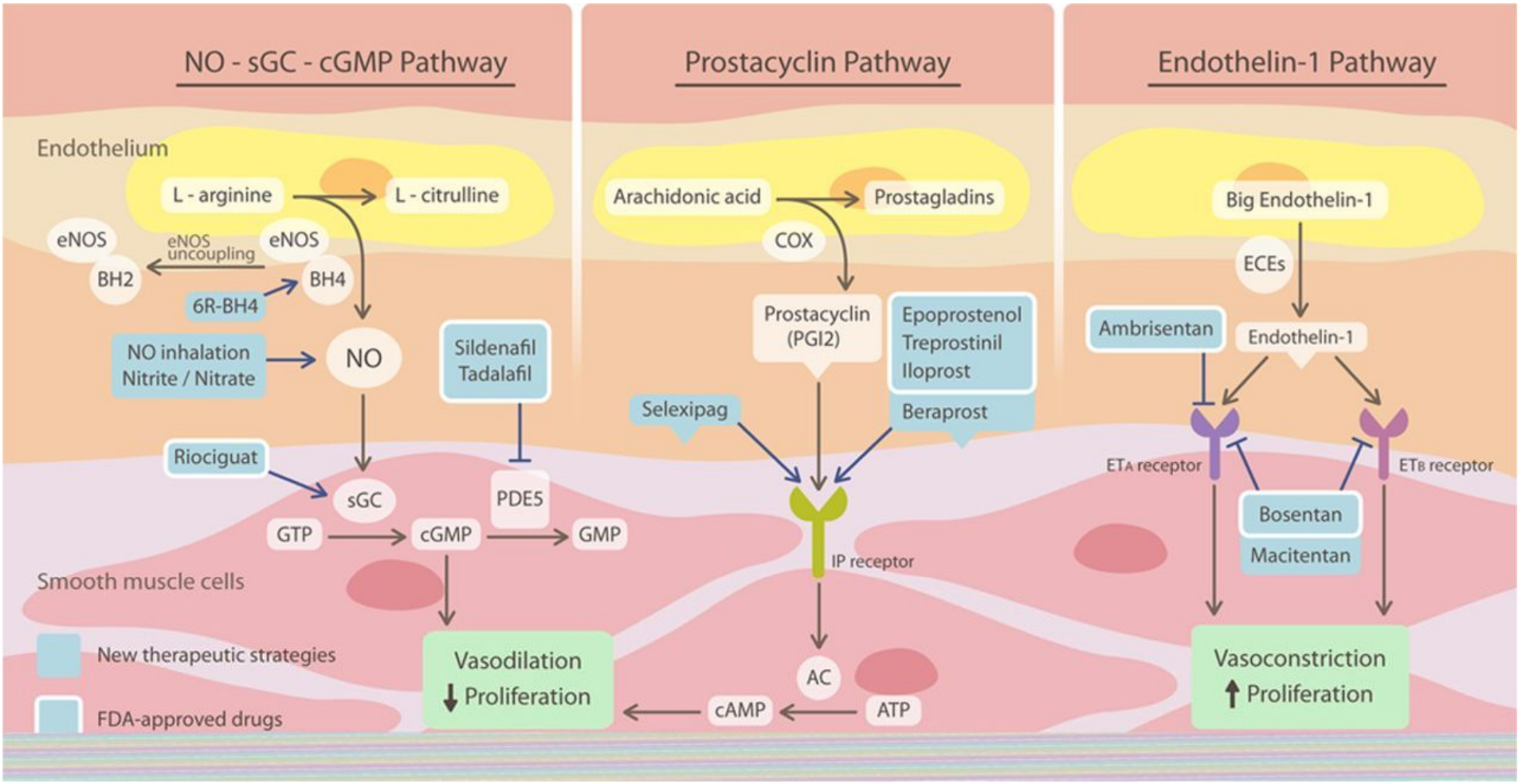
⇈ Endothelin 1

Vasoconstrictor factors



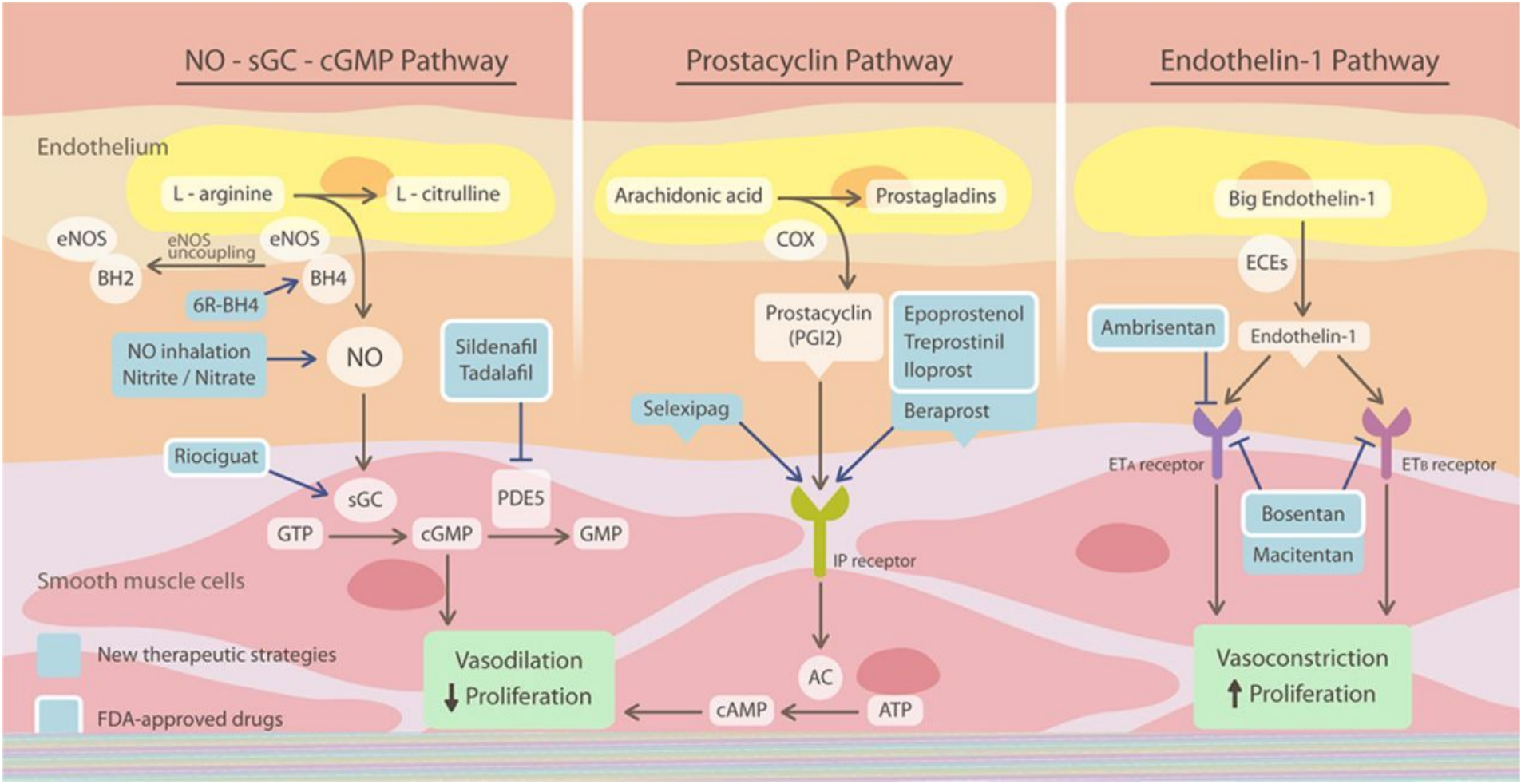
Increased endothelin levels

(endothelin is a **vasoconstrictor** and **mitogen**)



Decreased prostacyclin levels

(prostacyclin is a **vasodilator**, is **antiproliferative**, and **inhibits platelet function**)

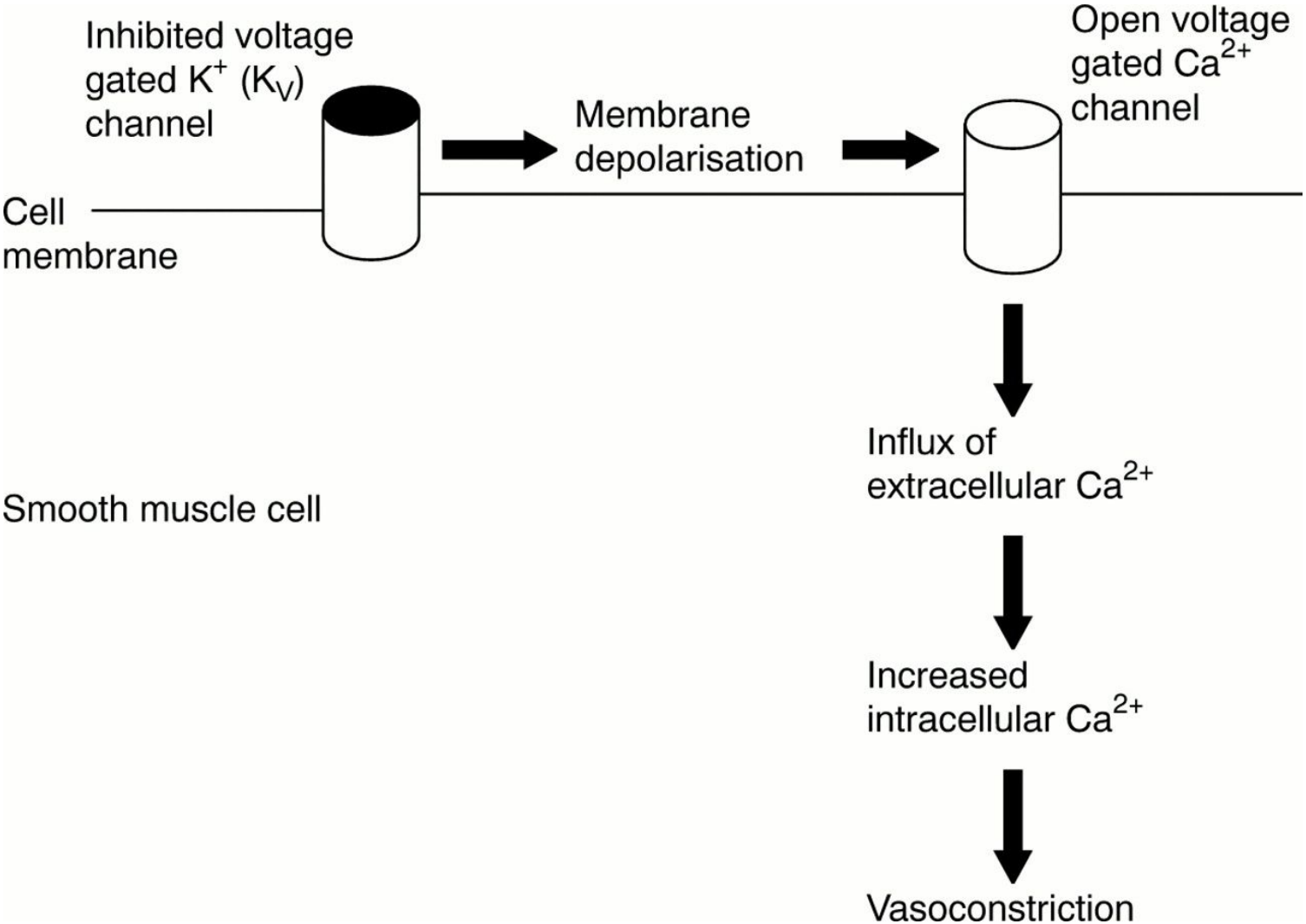


Decreased nitric oxide levels

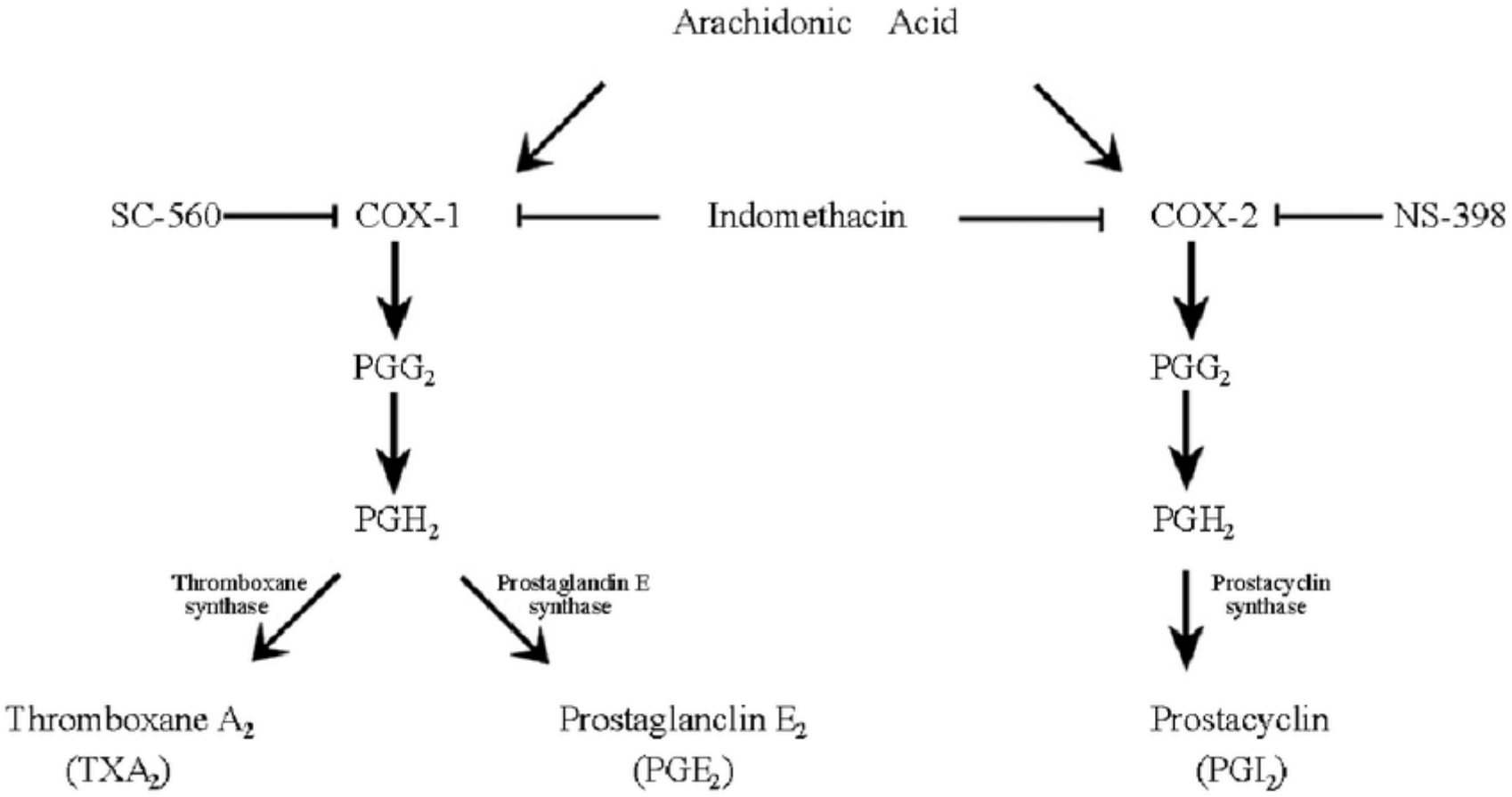
(nitric oxide is a **vasodilator** and is **antiproliferative**)

additional contributing mechanisms

potassium channel dysfunction



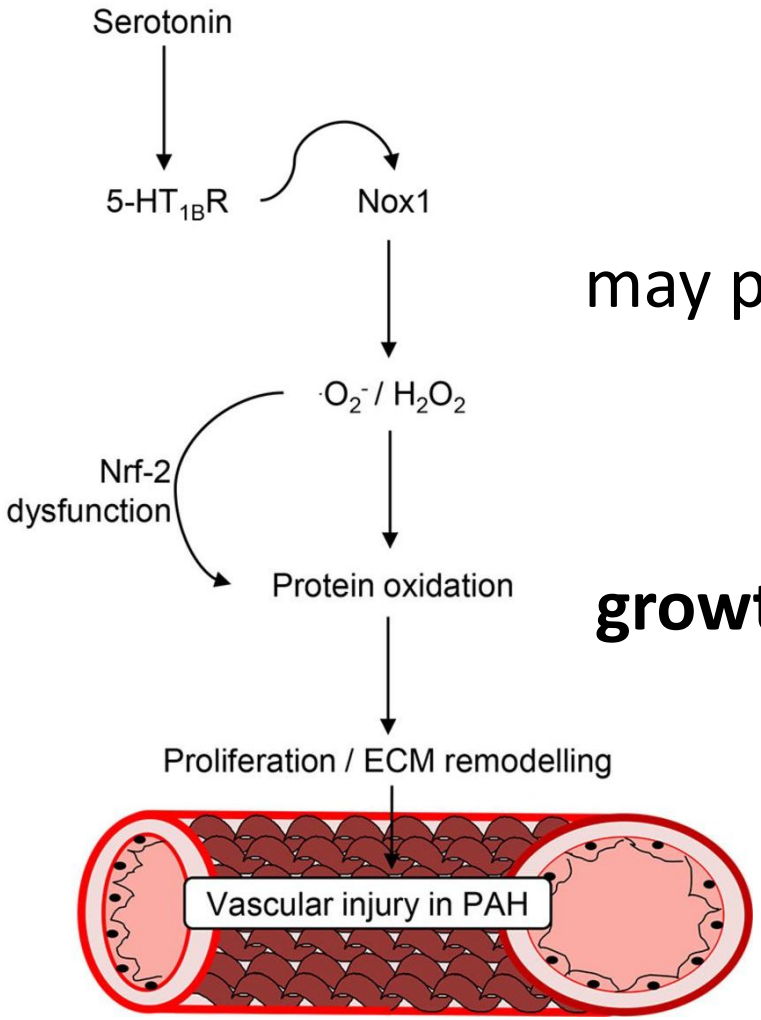
Increased thromboxane



vasoconstriction
smooth muscle mitogen

Vasodilator
antiproliferative

altered serotonin biology



may play a role in other forms of PAH

(drugs and toxins)

Induce

growth of pulmonary artery **smooth muscle cells**

abnormal response to estrogen

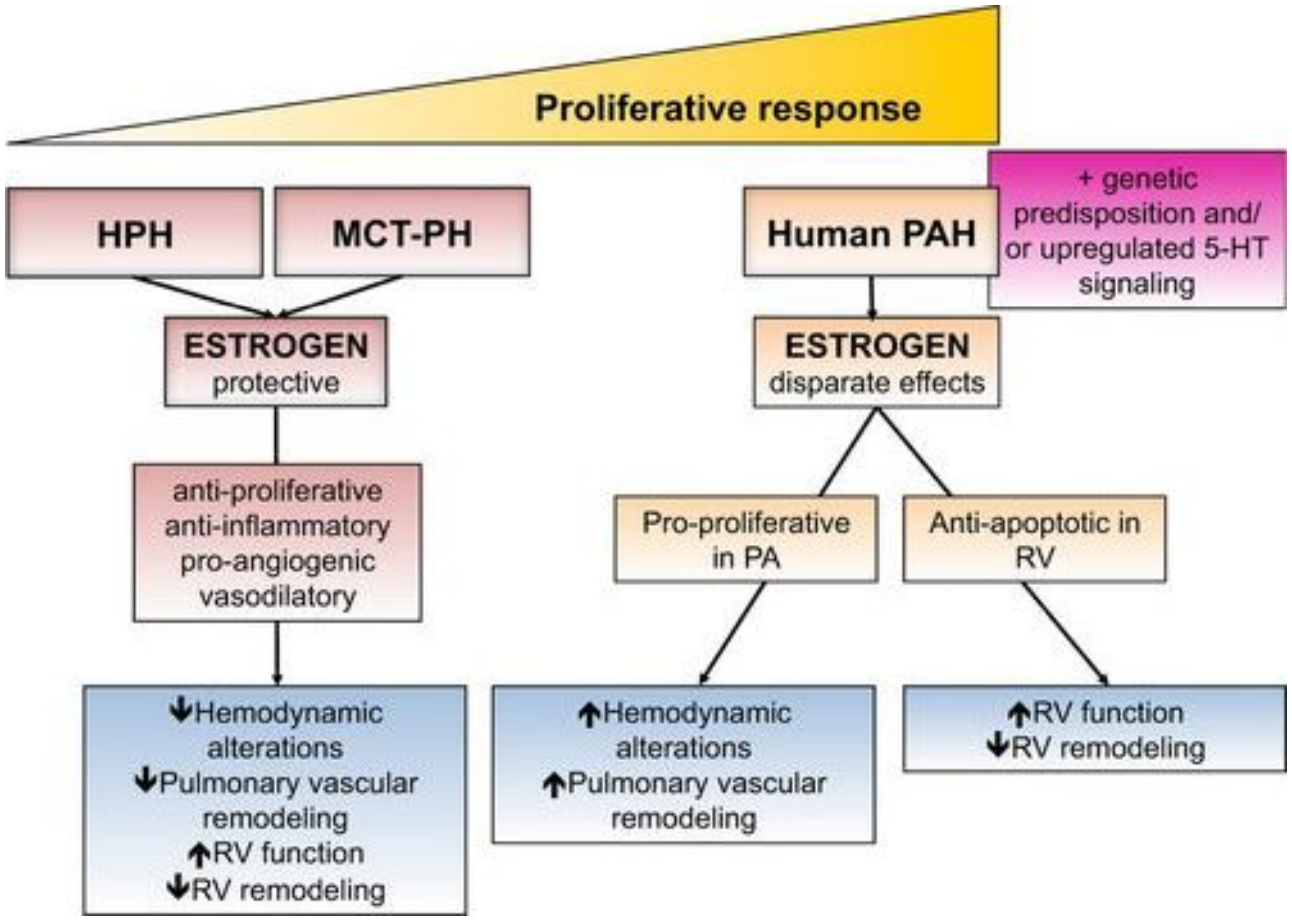
“estrogen paradox”

Hypoxia
Or
Monocrotaline

induced pulmonary hypertension

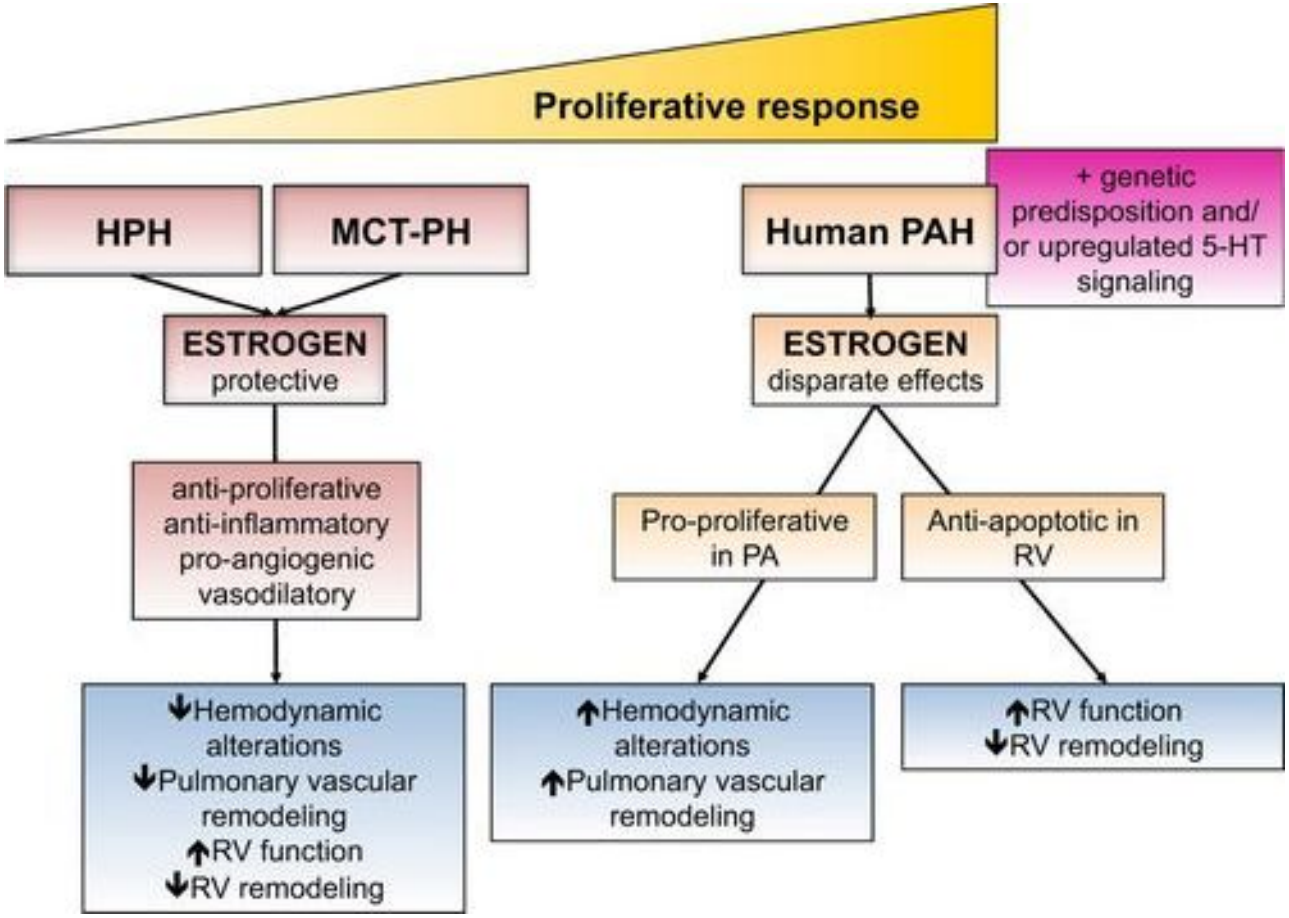
less proliferative state

protective effects of estrogens



abnormal response to estrogen

“estrogen paradox”



genetic alterations
in BMPR2
or
increased
serotonin (5-HT)
signaling

proproliferative estrogen effects predominate

The pathogenesis of

connective tissue disease

congenital heart disease

human immunodeficiency virus

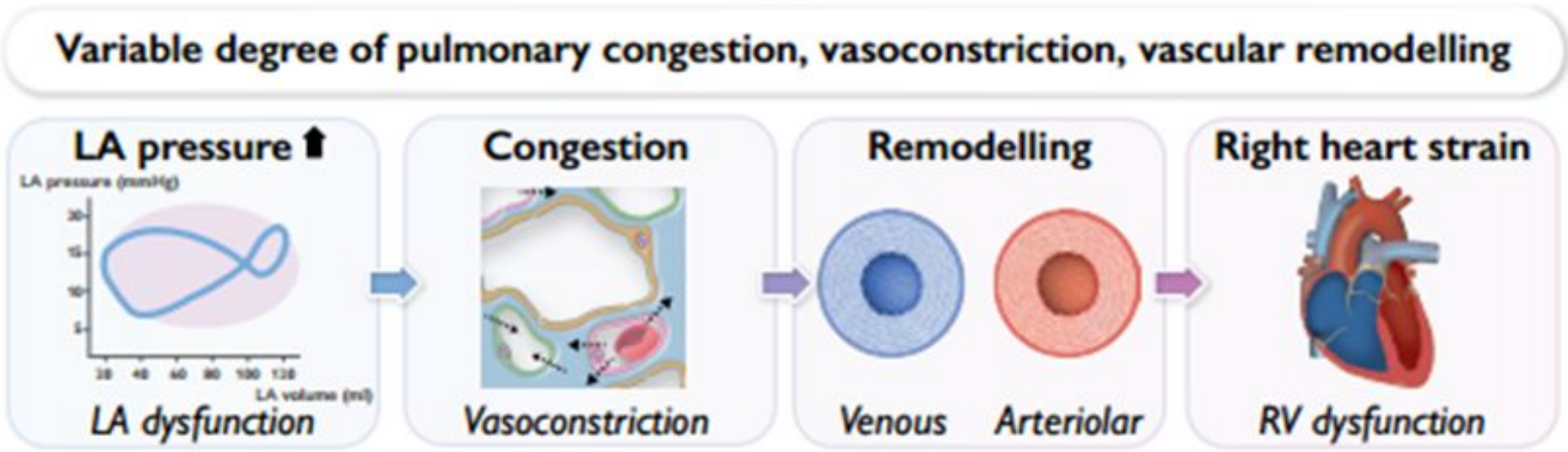
portopulmonary hypertension

Schistosomiasis

pulmonary venoocclusive disease

persistent pulmonary hypertension of the newborn

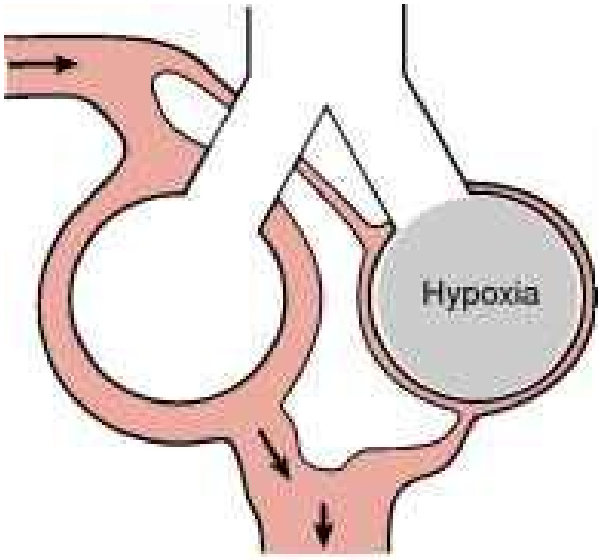
is poorly understood

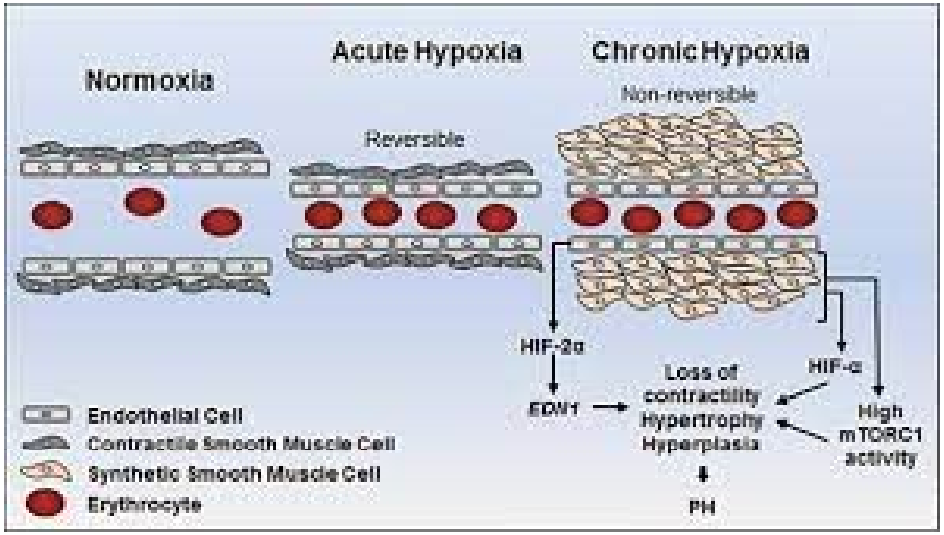


group 2 PH
due to left heart disease

medial hypertrophy
intimal fibrosis
insitu thrombosis
plexiform lesions are rarely seen

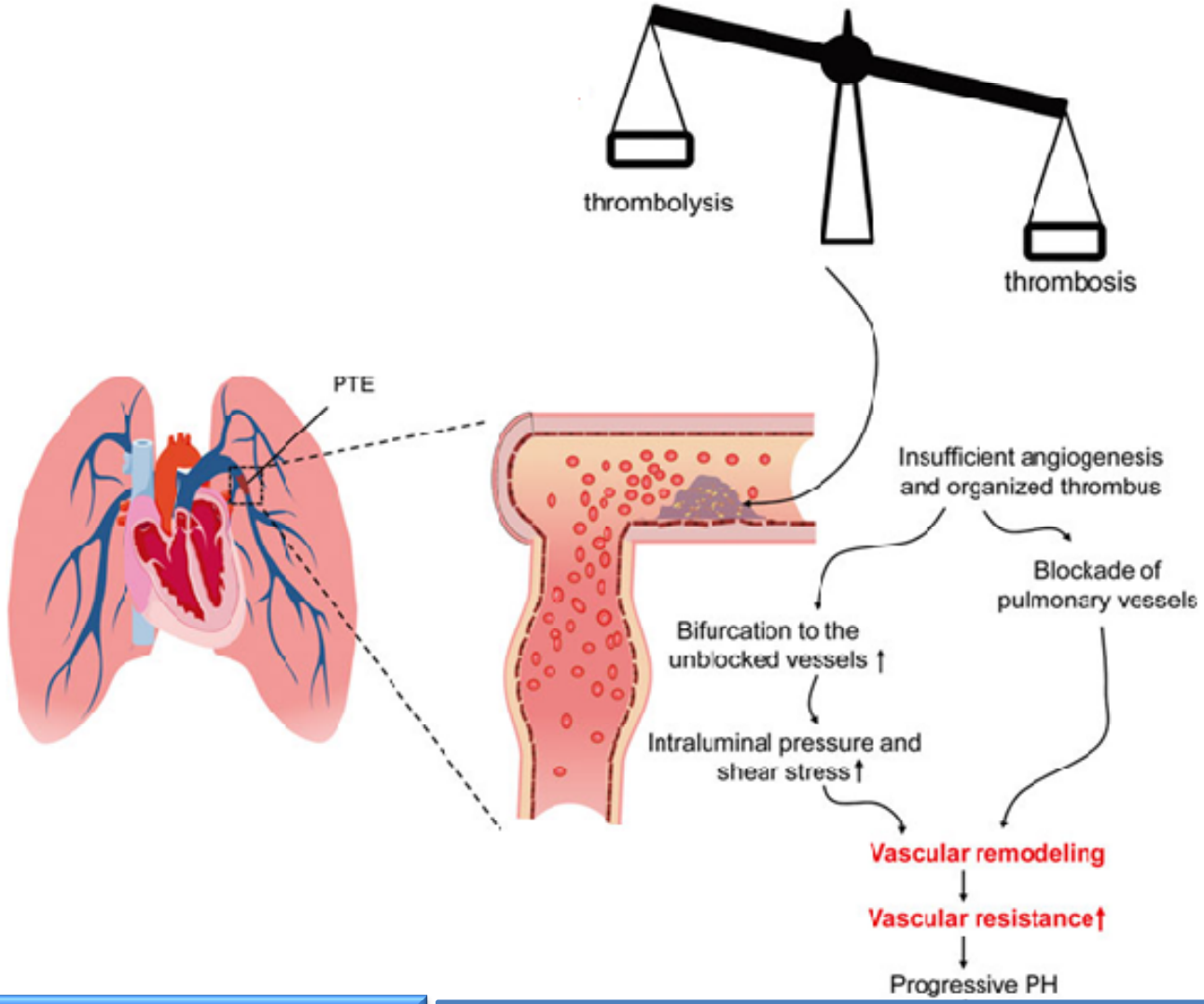
intimal thickening in **veins** was more prominent than in arteries





group 3 PH
due to lung disease and/or hypoxemia

hypoxic pulmonary vasoconstriction (HPVC)
preserve ventilation-perfusion matching
remodelling of the pulmonary vascular bed



group 4 PH
due to chronic thromboembolic

CTEPH
may be due to an underlying
hypercoagulable state

PH in patients with end-stage kidney disease

AV access flow

↓

Fluid overload

↓

increase in cardiac output

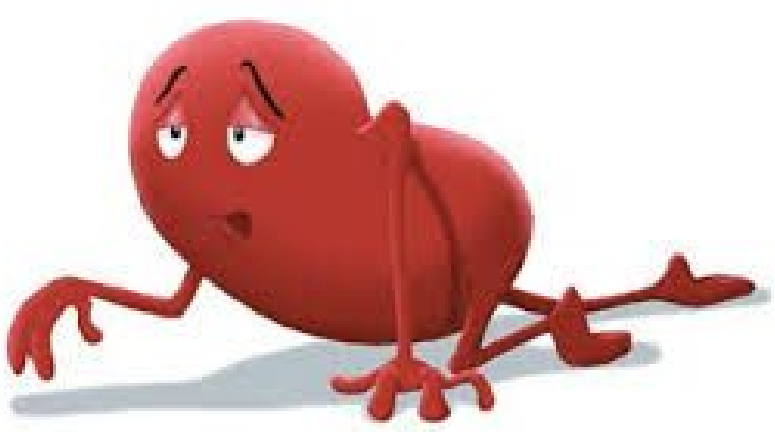
↓

increase in pulmonary arterial pressure

Endothelial dysfunction

↓

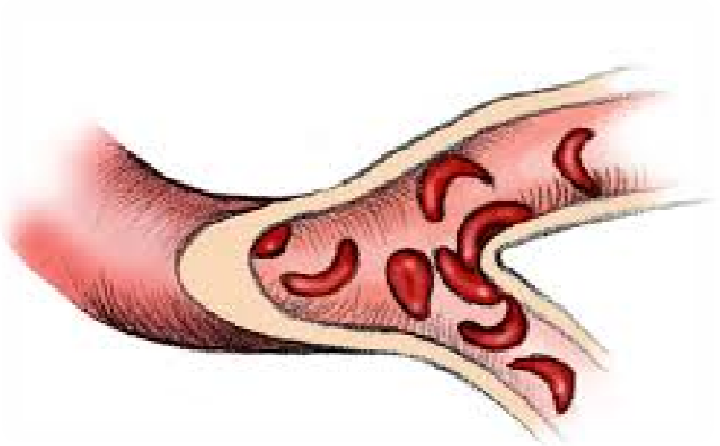
reduced levels of NO



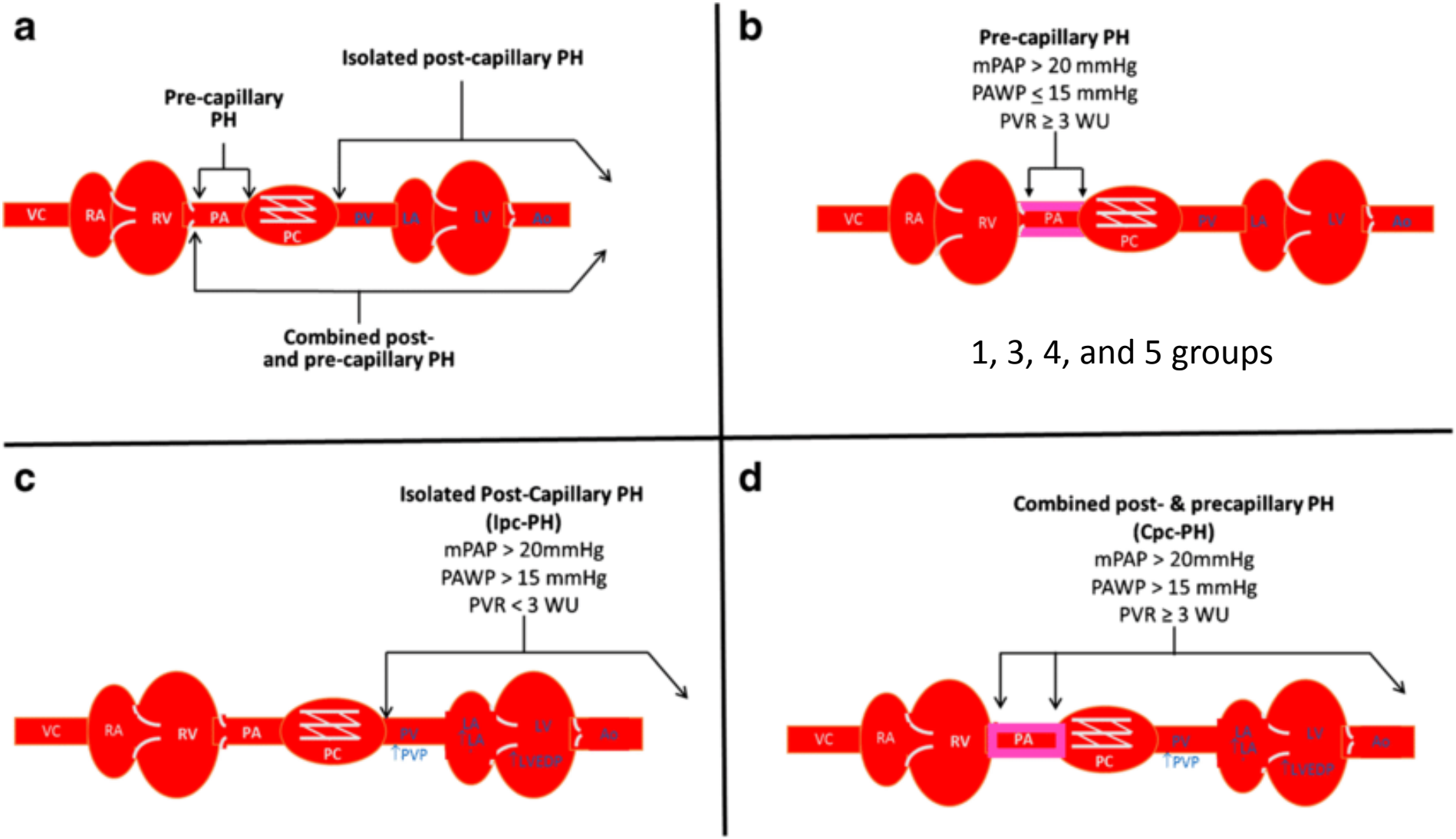
PH associated with sickle cell disease

The exact pathogenesis **not known**

- endothelial injury from recurrent sickling
- acute and chronic inflammation
- hypercoagulability and thrombosis
- chronic intravascular hemolysis
- altered bioavailability of vasodilator nitric oxide (NO)
- elevated left heart pressures from diastolic dysfunction may also contribute



Hemodynamic definitions of pre- and post-capillary pulmonary hypertension




thank you so much