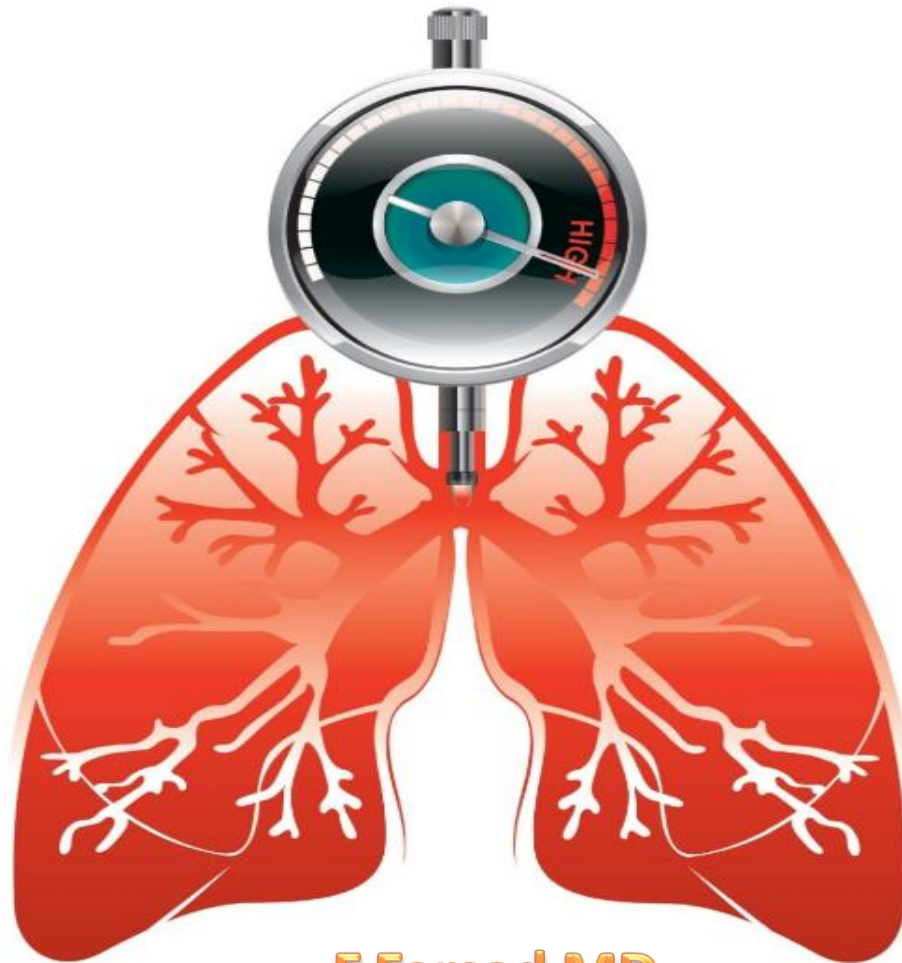


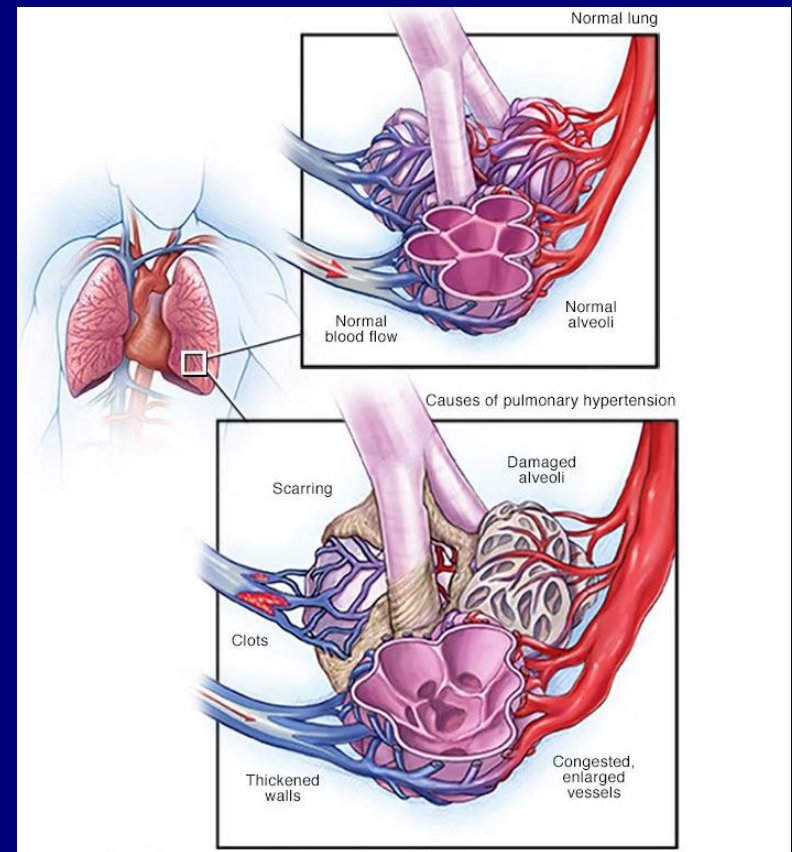
Pulmonary Hypertension in systemic sclerosis



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Definitions

- **Pulmonary hypertension (PH):**
mean pulmonary artery pressure (mPAP) ≥ 25 mmHg measured by right heart catheterization
- **Pulmonary arterial hypertension (PAH):**
primary elevation of pressure in the pulmonary arterial system alone with a mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg and aPVR > 3 wood units, without other causes of pre-capillary PH



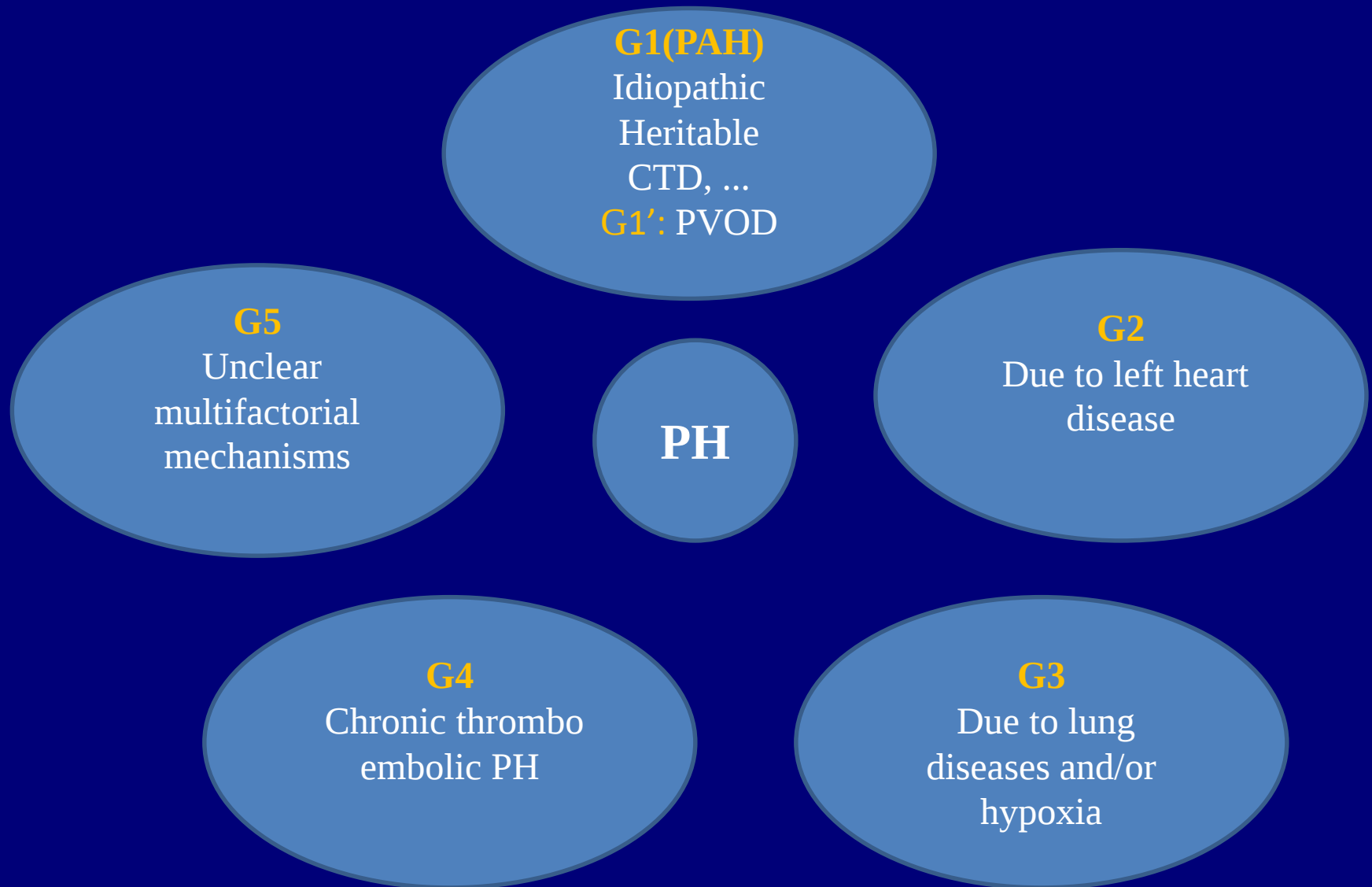
Epidemiology

- The prevalence of SSc-PH has been between 5-12%, occur at any stage of the disease.
- PH is a major cause of morbidity and mortality in SSc, Mortality rate of SSc- PAH is higher than PAH with other causes
- Most of patients in diagnosis are in advanced stages of PH (FCIII and IV)
- The prevalence of PAH was the same in both the lcSSc and the dcSSc subsets.

Morrisroe K, et al. Risk factors for development of pulmonary arterial hypertension in Australian systemic sclerosis patients: results from a large multicenter cohort study. BMC Pulm Med. 2016;16(1):134.

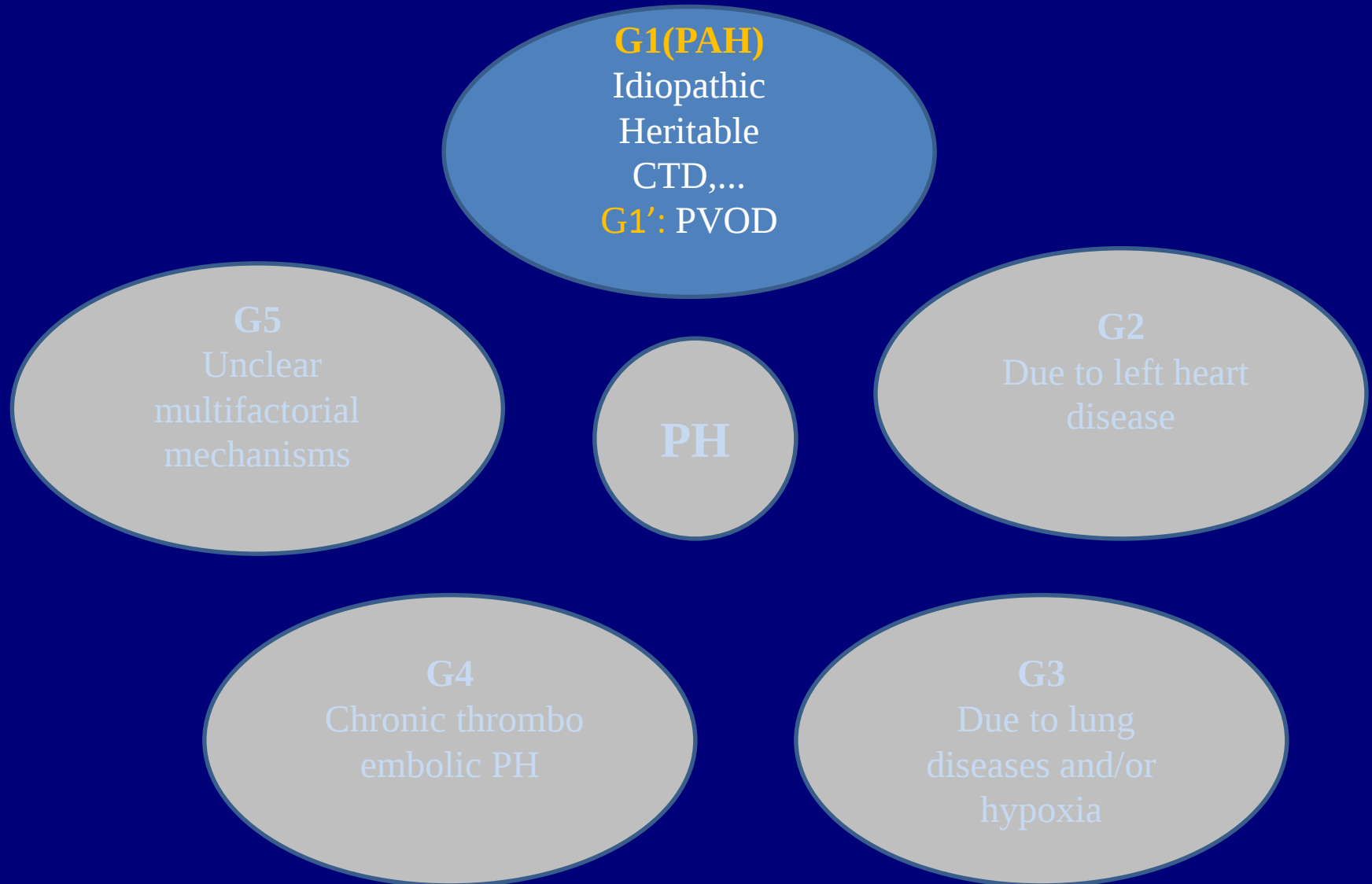
Morrisroe K, et al. Epidemiology and disease characteristics of systemic sclerosis related pulmonary arterial hypertension: results from a real-life screening program. Arthritis Res Ther. 2017;19(1):42.

WHO PH classification (latest revision 2013)



**Careful phenotyping of PH in SSc
is important as the therapy required
for each of these underlying
conditions is very different**

WHO PH classification (latest revision 2013)



G1:Isolated SSc-PAH

- This type is more frequent in the limited cutaneous form of SSc
- Clinical presentation is similar idiopathic PAH (insidious onset of fatigue and breathlessness progressing to symptoms of right heart failure, a prominent P2, Clubbing), only **pericardial effusion** occurs threefold more in SSc-PAH than in iPAH
- Management of this type is similar iPAH

G1': Pulmonary Veno-Occlusive Disease (PVOD)

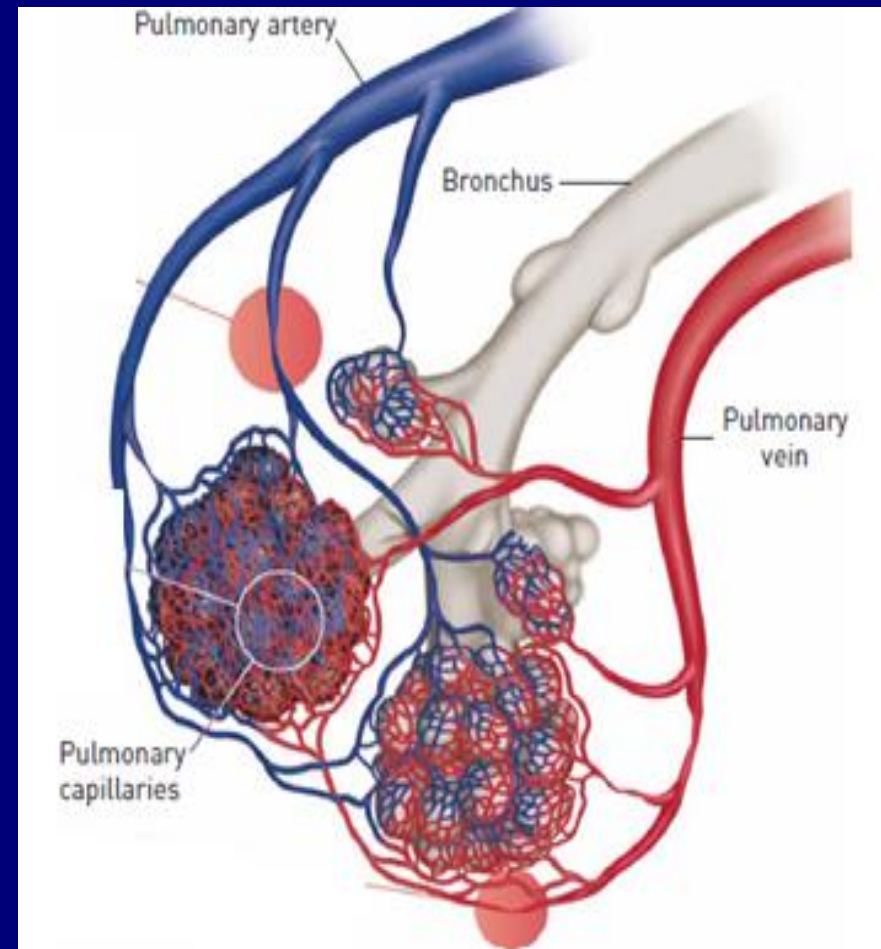
- PVOD is characterized by a diffuse obstruction of the small pulmonary veins

How to distinguish PVOD from isolated SSc-PAH ?

- Clinical presentation is similar, Only bi-basal crackles is more frequent

How do we recognize PVOD?

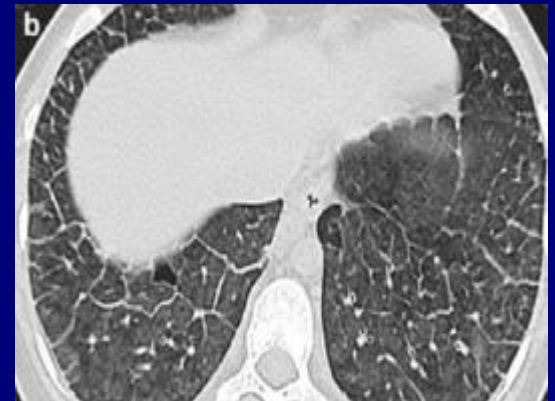
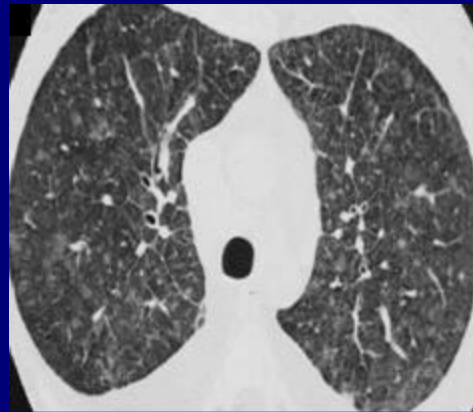
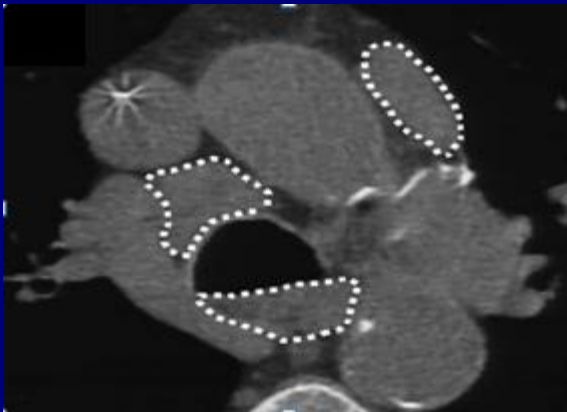
- Echocardiography and RHC findings are same of isolated SSc-PAH
- **DLCO and ABG** are ancillary diagnostic tools. (DLCO < 50% is common in PVOD, major resting hypoxemia in ABG)
- **HRCT** the mainstay imaging modality



Pulmonary veno-occlusive disease (PVOD)

A triad of characteristic HRCT include:

1. Mediastinal lymph node enlargement
2. Ill-defined centrilobular ground-glass opacities (most frequent)
3. Smooth thickening of the interlobular septa



**Thickening of interlobular septa in HRCT is the
most specific radiological feature of PVOD**

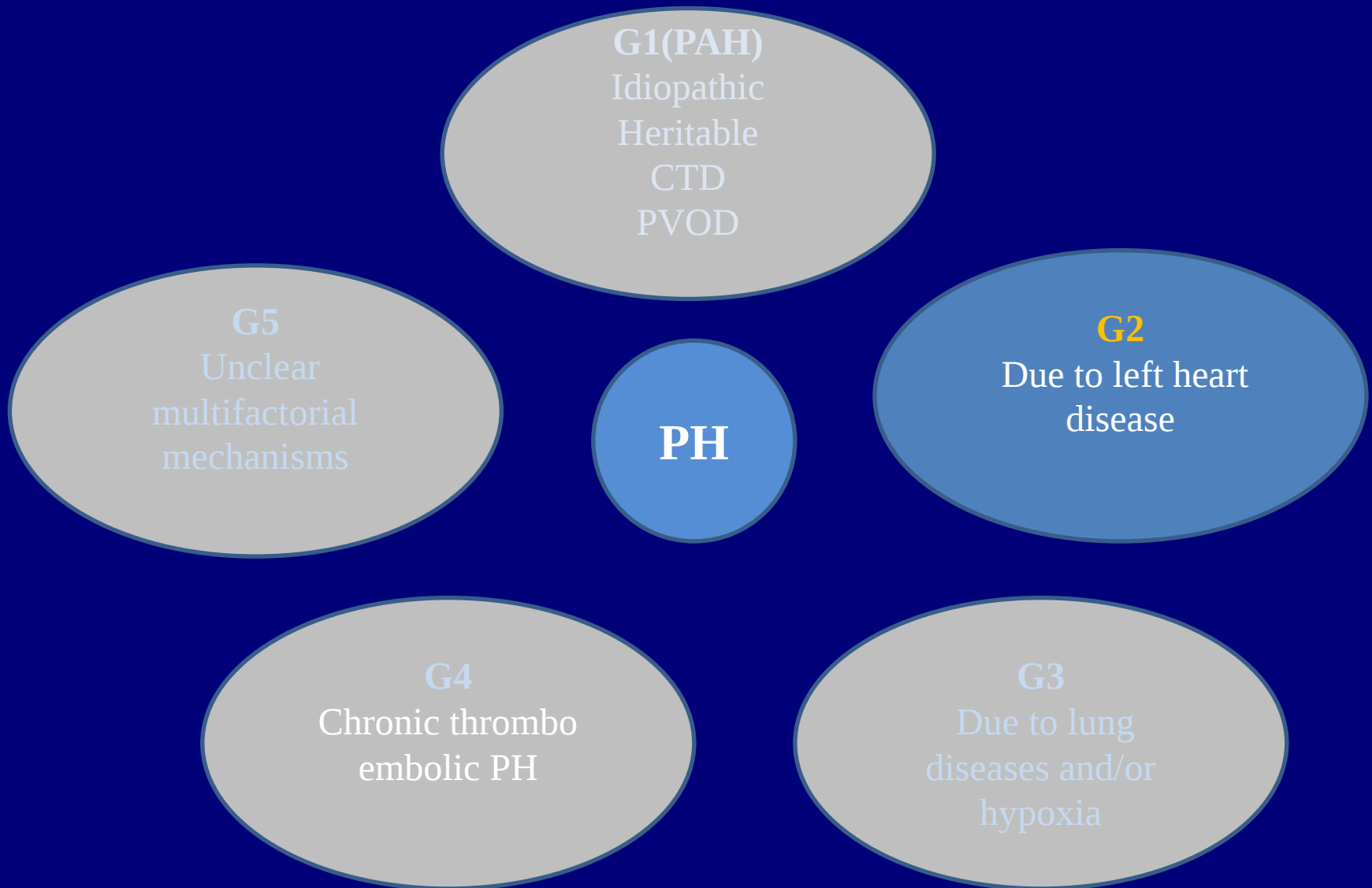


Important Clinical Points in PVOD

- PVOD affects both types of SSc, but is more common in L-SSc
- The development of **pulmonary edema following vasodilator therapy** strongly supports the diagnosis of PVOD
- The presence of alveolar hemorrhage on histological examination and significantly increased of **hemosiderin-laden macrophages** in BAL fluid and occult alveolar hemorrhage can result in normalization of DLCO
- Lung specimen is the gold standard for a definitive diagnosis, but **TBLB and lung biopsy** are contraindicated
- Bilateral **lung transplantation** is therapy of choice

PVOD should be looked at carefully in a patient who experiences an intriguing worsening after the initiation of the treatment or becomes refractory to therapy

WHO PH classification (latest revision 2013)



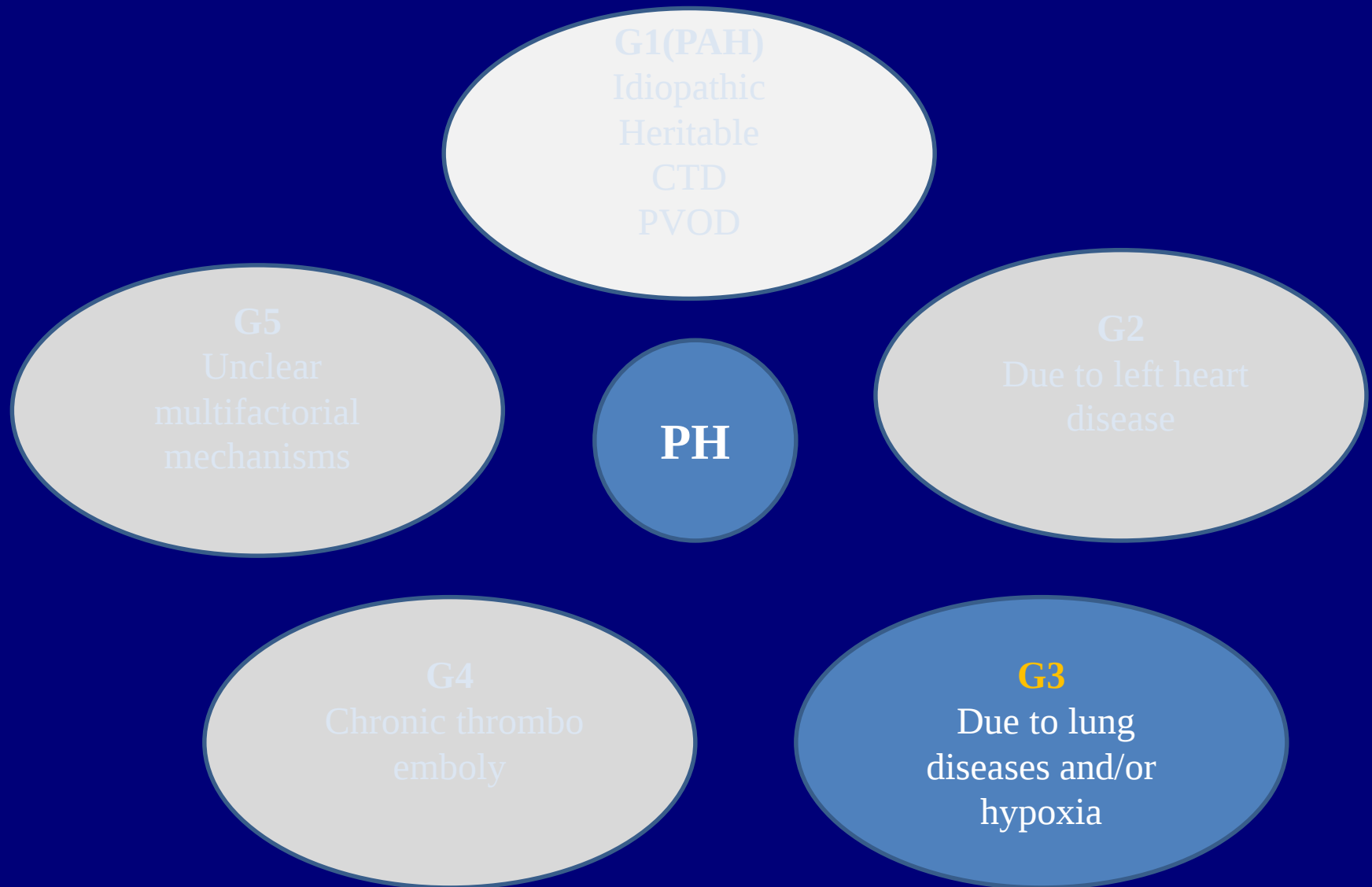
G2: PH due to left heart disease

- Diastolic dysfunction (heart failure with preserved ejection fraction) is the most common cardiac manifestation in SSc perhaps reflecting primary myocardial fibrosis and cause post-capillary PH
- Cardiac MRI and post mortem studies show that the 50-80% of patients have some cardiac involvement; thus, exclusion of any left heart abnormality is a prerequisite for diagnosis

G2: PH due to left heart disease

- Differentiated PH from iPAH with: old age, the presence of hypertension and coronary artery disease, left atrial enlargement , absence of right atrial enlargement , mPAP ≥ 25 mm Hg and PAWP > 15 mm Hg in RHC
- There is no validated treatment for Group 2, the major goal is treat the underlying heart disease

WHO PH classification (latest revision 2013)



G3: PH due to Interstitial Lung Disease

- SSc-PH-ILD appears to be associated with an older age at diagnosis, severe restriction (FVC<50%) and a lower arterial oxygen tension compared to SSc-PAH
- Patients in group have $\text{mPAP} \geq 25 \text{ mmHg}$, $\text{PAWP} \leq 15 \text{ mmHg}$ and **extensive ILD** (HRCT $\geq 30\%$ or HRCT 10-30% with FVC < 70%)
- Mortality in SSc-PH-ILD is 5-fold increase when compared to SSc-PAH
- The main treatment is treat of underline ILD, PAH-targeted therapies have no benefits on dyspnea and survival and might present an increased risk of hypoxia in SSc-PH and ILD

Combined Pulmonary Fibrosis and Emphysema syndrome (CPFE)

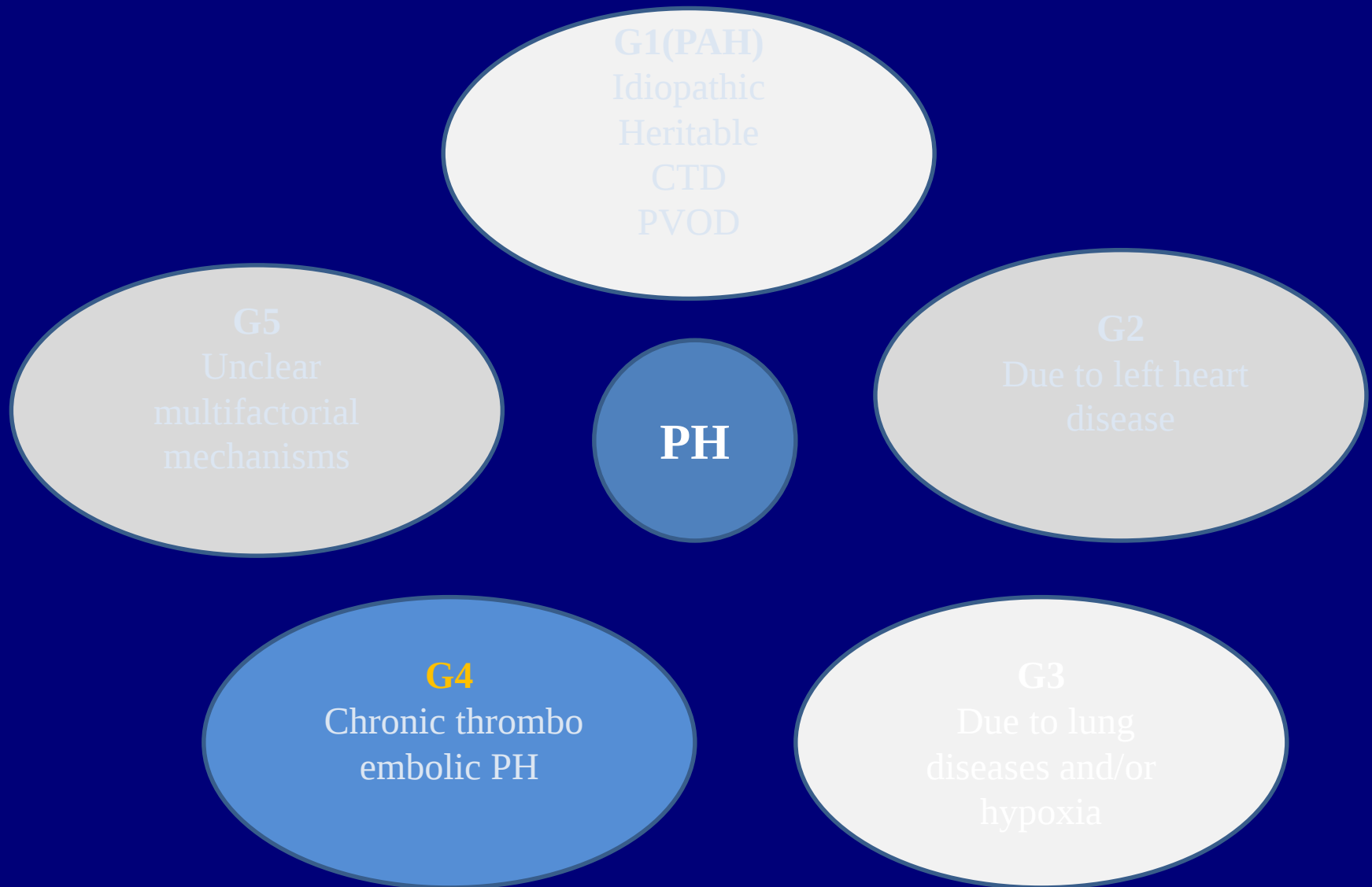
- CPFE syndrome was described in patients with CTDs, mainly among smokers with rheumatoid arthritis and systemic sclerosis
- It characterized by severe dyspnea and **sputum** many years before dyspnea, in contrast usual ILD that characterized by dry cough and dyspnea
- Spirometry is usually **normal**, very severely impaired DLCO and hypoxaemia
- CPFE is frequently complicated by PH & **lung cancer** and prognosis is poor

Combined Pulmonary Fibrosis and Emphysema syndrome (CPFE)

- The diagnosis is based on the presence of both emphysema predominating in the upper lobes and frequently pulmonary fibrosis in the lower lung zones
- This syndrome is under diagnosed in SSc because Patients with SSc had a less severely impaired DLCO



WHO PH classification (latest revision 2013)



G4: Chronic Thromboembolic PH (CTEPH)

- CTEPH is PH that caused by clots in the blood vessels that last after at least 3 months on blood thinners.
- SSc patients are at an increased risk of VTE, especially within the first year
- Underlying pulmonary arteriopathy, in situ thrombosis and APS antibodies likely contributes to CTEPH development.
- Contrary to the approach taken to diagnose acute PE, a V/Q scan is recommended over a CTPA in diagnosing CTEPH(97.4% vs 51%)
- Treatment is surgical intervention with pulmonary thromboendarterectomy

**The major issue is that there is not one
single PH group and one single
mechanism at play in SSc**

Risk Factors

Clinical finding	Older age, Post-menopausal status Longer disease duration, Late onset of disease, digital ulcer, Calcinosis, telangiectasia (Pseudo tumoral telangiectasia)
Laboratory	Anticentromere Ab, absence of anti-RNA polymerase III Ab, Nucleolar pattern ANA, Anti cardiolipin Ab, B2 Glycoproteien, Anti Endothelial Ab, Anti Endothelin receptor type A Ab, Anti Angiotensin receptor type 1 Ab
Transthoracic echocardiogram	Increase in RVSP > 2 mmHg/year
Pulmonary Function Test	DLCO < 50%, DLCO <70% and FVC/ DLCO > 1.6
RHC	Mean PAP 21-24mmHg Trans pulmonary gradient(TPG)>11 mmHg

Current Screening Recommendations

**PFTs, TTE, NT-proBNP: in baseline and at the
time of development of any new signs or symptoms.**

PFTs and TTE should be repeated annually

Diagnosis

- Right heart catheterization (RHC) is the gold standard for diagnosing PAH

Clues to diagnosis

- Elevated tricuspid regurgitation velocity (**TRV**) **jet** above 2.8 m/s in echo
- Decreasing carbon monoxide diffusing capacity (**DLCO**) is a marker of PH
- **Cardiopulmonary exercise testing** (CPET) and **Cardiac MRI** may also be helpful in the assessment of PAH.

In a study Ventricular mass index in MRI had strong positive correlations with mPAP and PVR, and a moderate negative correlation with cardiac index.

Treatment

- Basic Measures

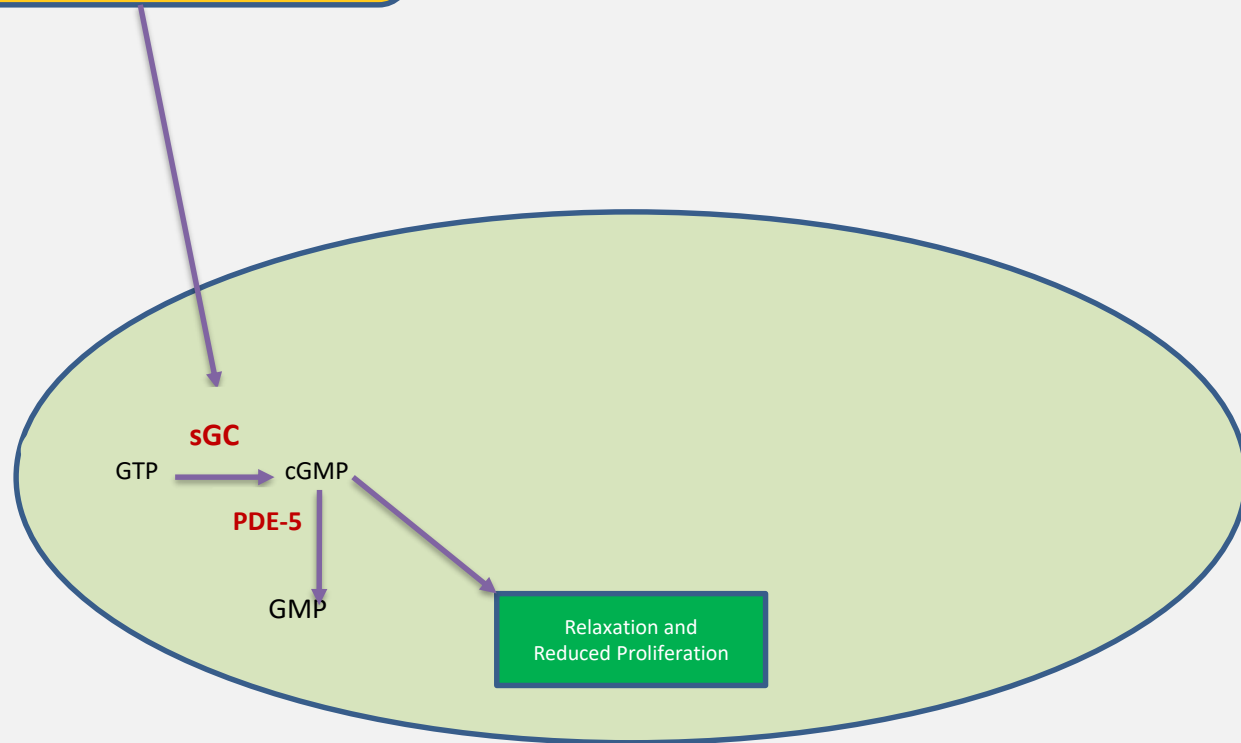
- Target Therapy



Target Therapy

Endothelial cell

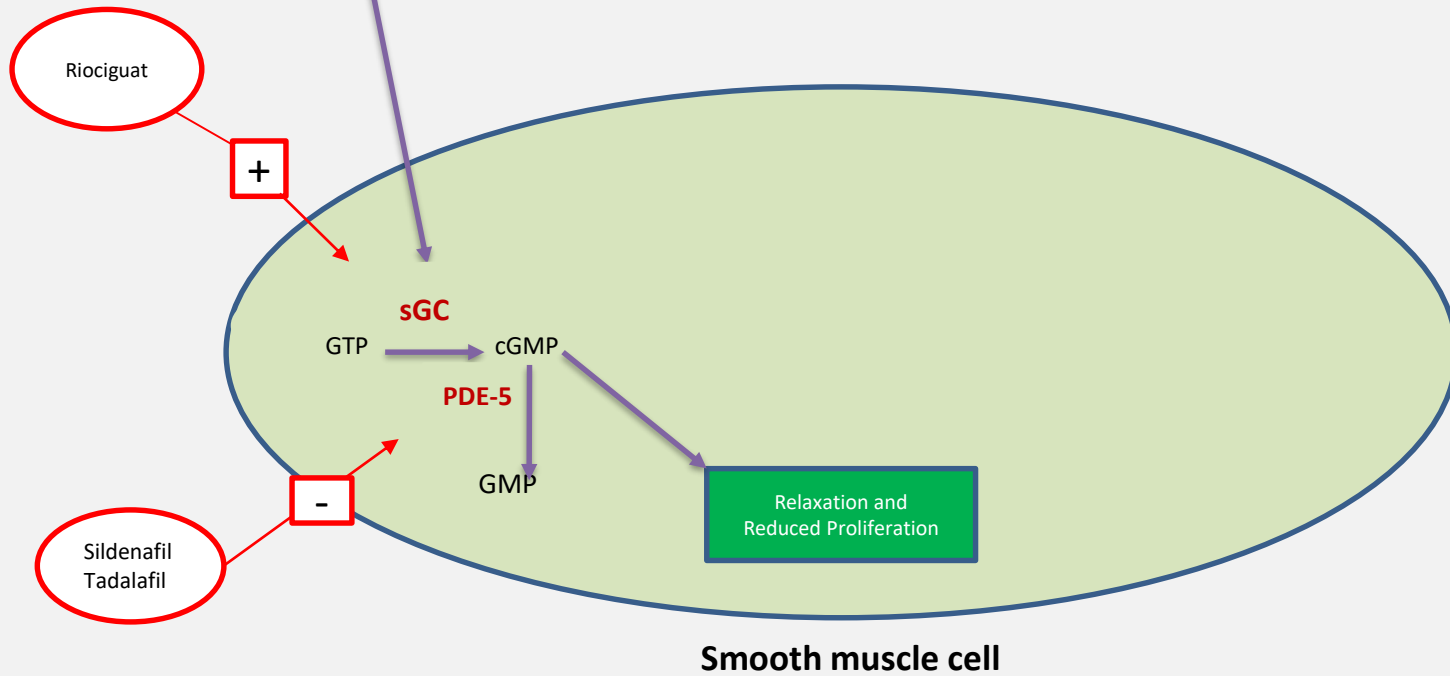
NO Pathway



Smooth muscle cell

Endothelial cell

NO Pathway



Endothelial cell

NO Pathway

PG Pathway

Riociguat

+

Sildenafil
Tadalafil

-

IP

AC

cAMP

ATP

sGC

GTP

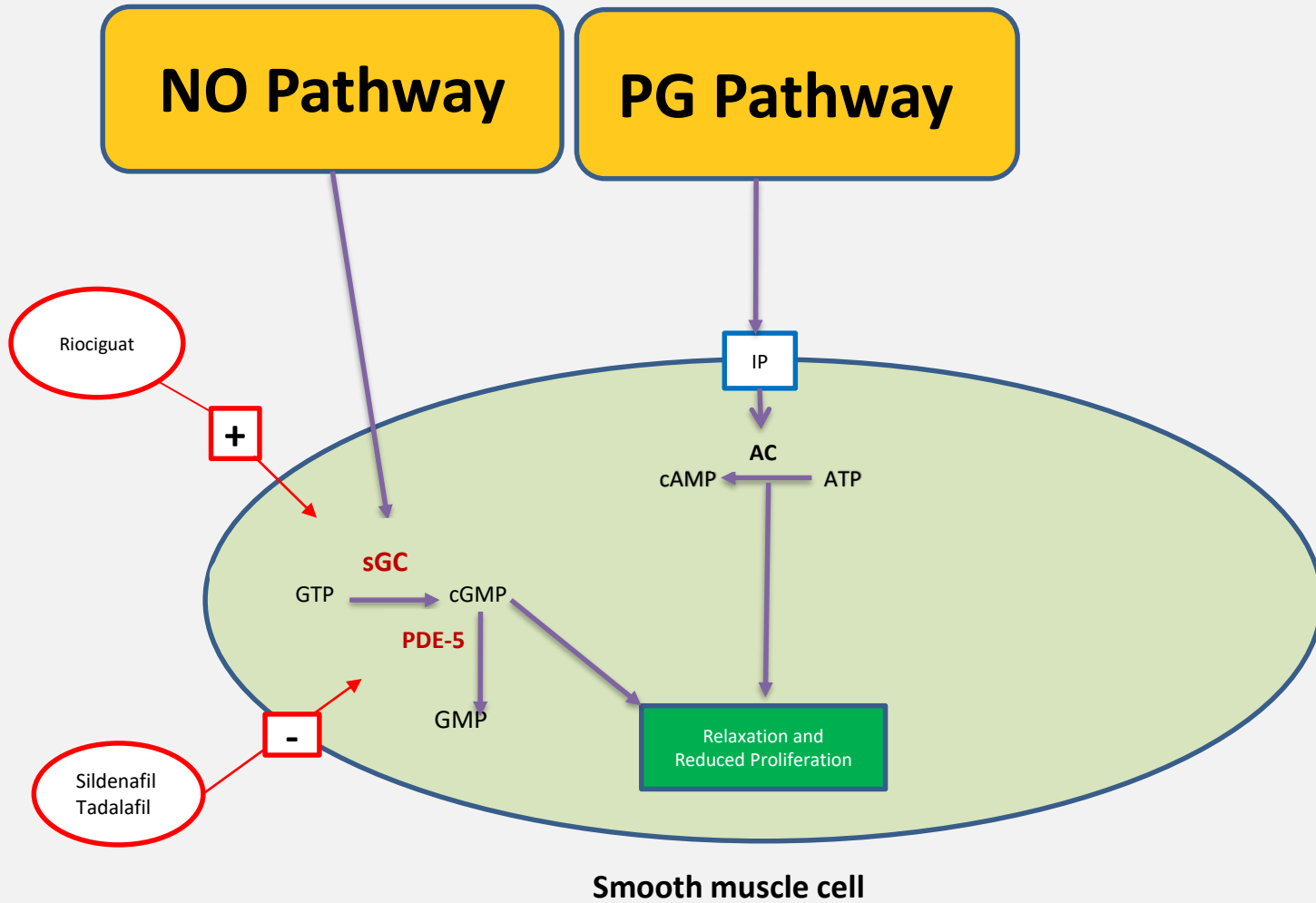
cGMP

PDE-5

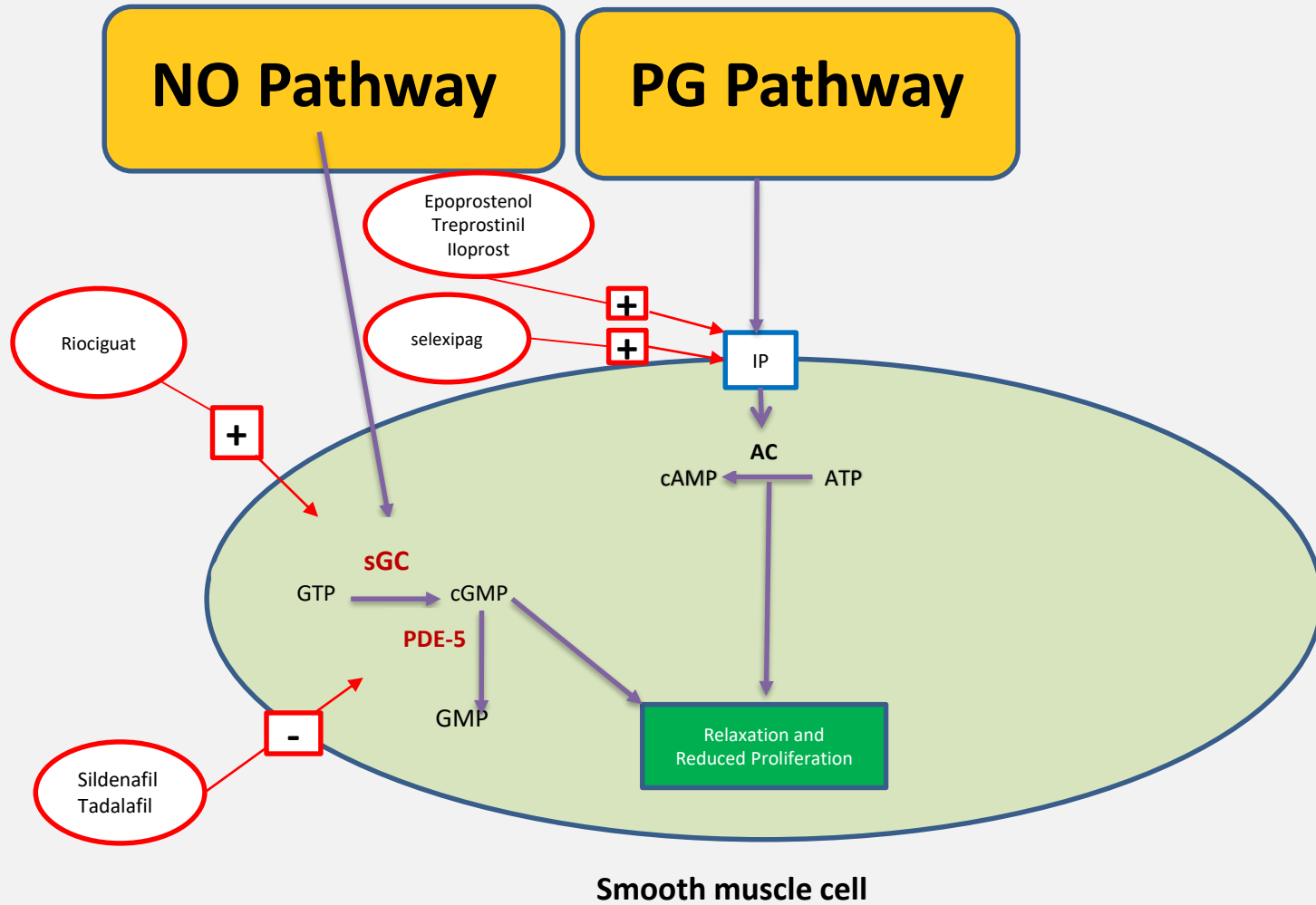
GMP

Relaxation and
Reduced Proliferation

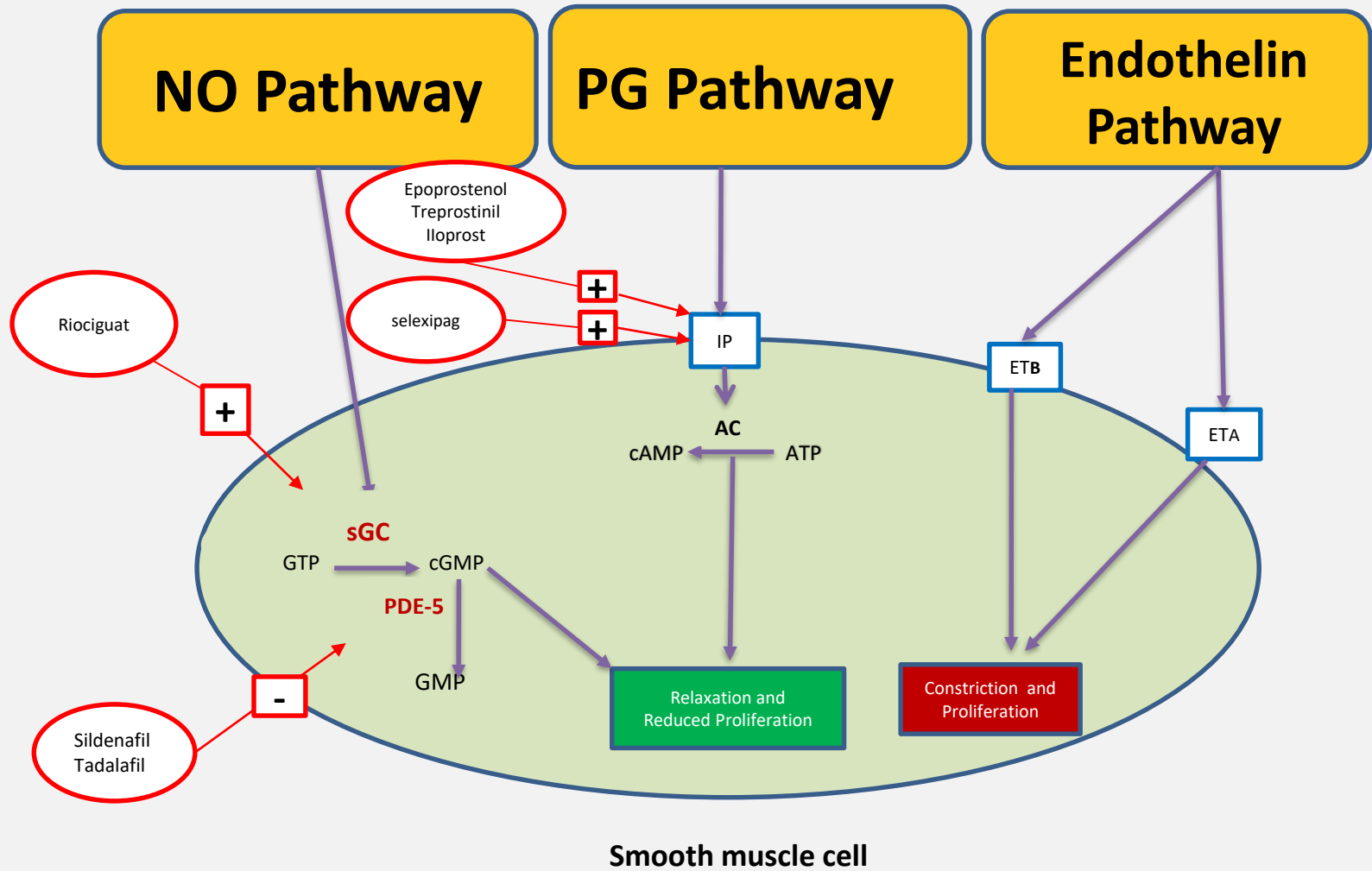
Smooth muscle cell



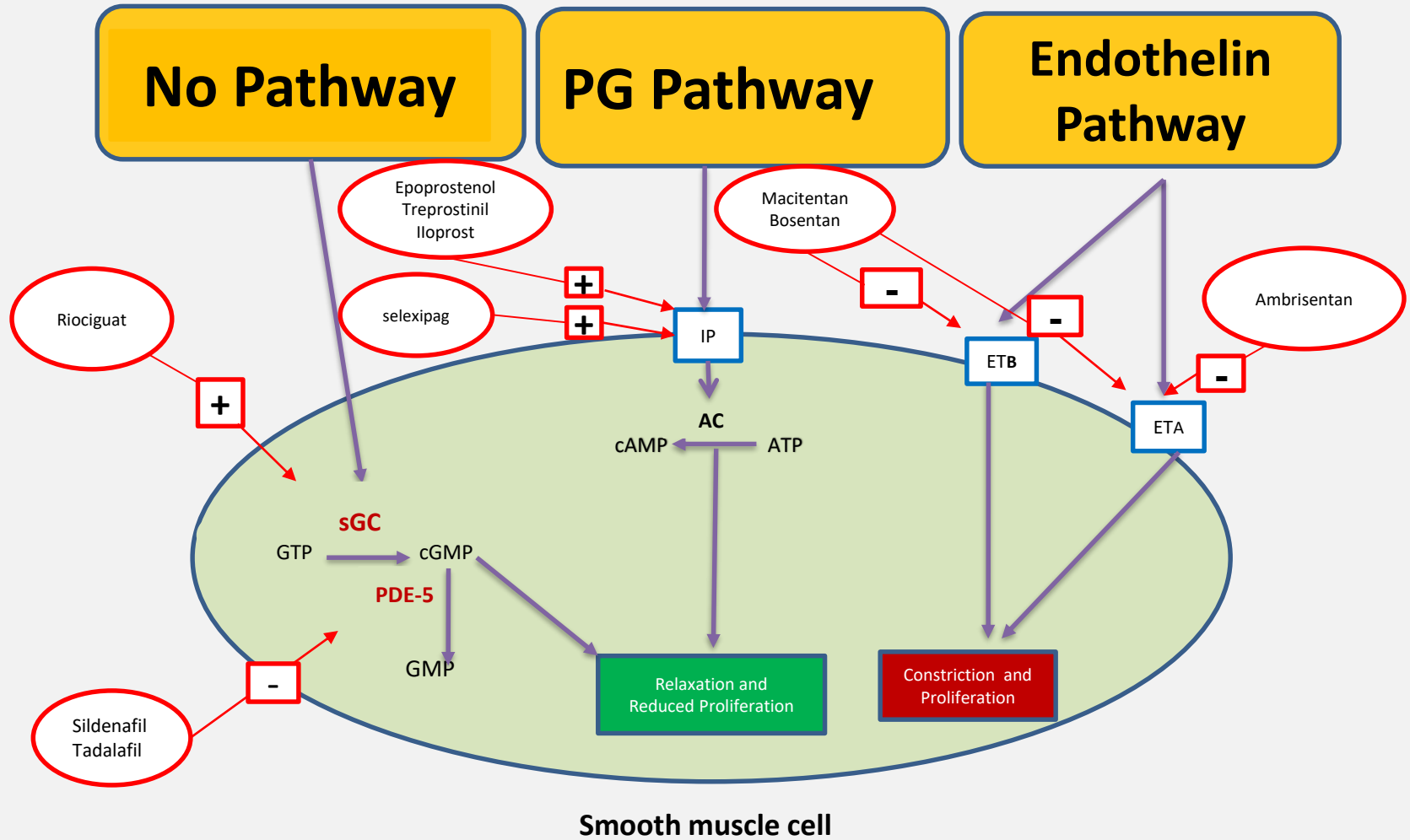
Endothelial cell



Endothelial cell



Endothelial cell



Treatment

- Treatment goals is reaching and maintaining FC I or II
- Patients are classified as low, intermediate and high risk (2015 ESC/ERS guidelines)
- At **low or intermediate risk** patients , initial monotherapy is an option
- ERA and PD-5-inh have similar efficacy*
- Three large study recommended (AMBITION, SERAPHIN, GRIPHON)
combination therapy in these patients
- The evidence show the combination of ERA and PD-5-inh is superior
- At **high-risk** patients, initial double or triple combination therapy
- Patients with end stage lung disease may be considered for lung transplantation

Novel therapy

- Tyrosine Kinase Inhibitor (Imatinib)
- Serotonin receptor antagonist: (Terguride)
- Rho-kinase inhibitor: (Fasudil)
- Endogenous peptide: (Apelin)
- Anti-inflammatory therapies: (Rituximab)
- Progenitor Cell Therapies(Endothelial, mesenchymal)



Thank You

- **Serotonin** vasoconstriction and PASMC proliferation. In IPAH, platelet storage of serotonin is depleted, peripheral blood serotonin levels are elevated
- **Vasoactive intestinal peptide** smooth muscle relaxation **cAMP**
- **Rho signaling** pathway is activated SMC hypercontractility by suppressing controls Ca^{2+} sensitivity of myofilaments
- the effect of serotonin on PASMC proliferation is mediated through increased Rho activity
- Fasudil 17% reduction in PVR in a small observation study
- The cholesterol activation of Rho and Ras small GTPases,

- Apelin regulation of endothelial NOS level, downstream target of BMPR-II signaling. Early-phase trials of apelin are underway
- Macrophage migration inhibitory factor is a cytokine that simulates the release of proinflammatory interleukin-6

- Tacrolimus interacts with type-1 BMP receptors and blocks its activation

- Manipulation of Ca^{2+} signaling pathways Progenitor. A human study of autologous transplantation of ex
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