Pulmonology

Volume - 2

MARROW
Super Speciality

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PULMONARY HTN : PATHOPHYSIOLOGY, TYPES AND EVALUATION

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Introduction

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Challenge :

- Diagnosis often missed : 2 year gap between disease onset and diagnosis.
- Non specific symptoms.
- Treatment cannot completely revert the disease.
- Expensive drugs used for treatment.
- Limited treatment options for pulmonary hypertension occurring secondary to lung diseases.

PAH vs PHTN :

- PAH : Pulmonary artery hypertension d/t abnormality of vessel.
- PHTN/PH : Pulmonary hypertension d/t heart disease/lung disease/chronic pulmonary embolism.

Determinants of pulmonary artery (PA) pressure :

- High flow, low resistance, low pressure system.
- 2 properties :

1. Distensibility : D/t compliance of pulmonary vasculature.
2. Recruitment : With increase in cardiac output, more vessels take part in pulmonary blood flow.

- Normal mean pulmonary artery (PA) pressure : 12 mm of Hg.
- PA pressure : Cardiac output x pulmonary vascular resistance (PVR).
- PVR : Resistance offered by pulmonary arteries, veins and capillaries.

Poiseuille's law : PVR is inversely proportional to $(Radius)^4$.

↑PVR → ↑Strain to right ventricle → Right ventricular hypertrophy → Right ventricular failure.

Hypoxic vasoconstriction : Pulmonary vessels vasoconstrict in response to hypoxia to maintain ventilation/perfusion ratio.

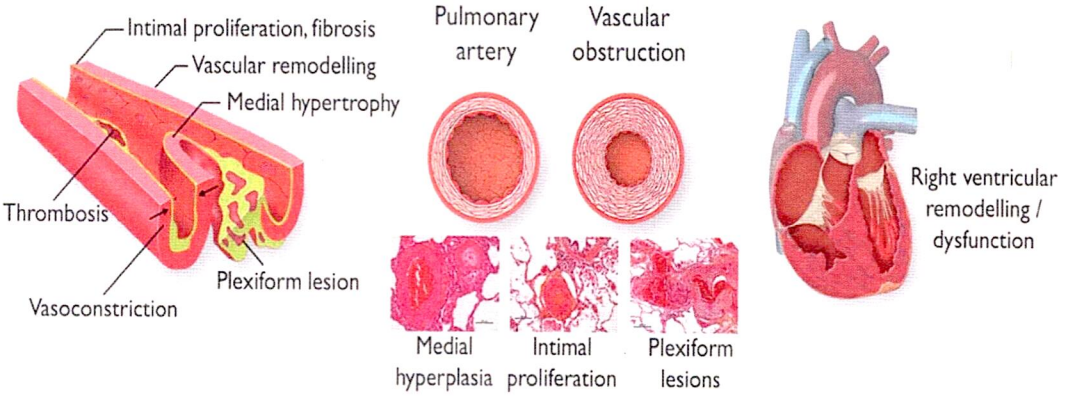
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Pathophysiology

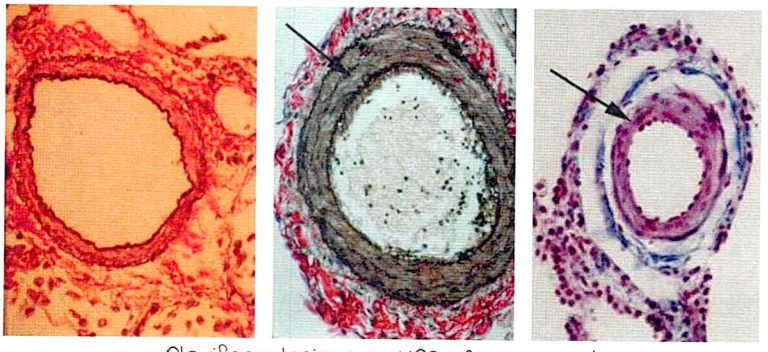
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Structural and functional changes in pulmonary vessels :

1. Sustained vasoconstriction : D/t Ca^{2+} imbalance.
2. Vascular remodelling : ↑ No. of fibroblasts.
   ↑ Smooth muscle mass (medial hypertrophy).
   Endothelial hyperplasia.
3. In situ thrombosis.
4. ↑ Arterial wall stiffness : D/t extracellular matrix proteins (Tenascin-C) leading to ↓ compliance.



Structural and functional changes in pulmonary vasculature.



Plexiform lesions on HPE : Aneurysmal dilatation of pulmonary vasculature.

Pathogenic mechanisms of pulmonary hypertension :

1. Vasoconstrictive : In response to chronic hypoxia in end stage lung diseases (Interstitial lung diseases, emphysema).
2. Obstructive : Chronic thromboembolic pulmonary hypertension (CTPH).
3. Obliterative : Destruction of capillary bed in emphysema.
4. Passive : Left ventricular failure.
5. Idiopathic.
6. Hyperkinetic : Left → right shunt.

Genetic, cellular and molecular mechanisms :

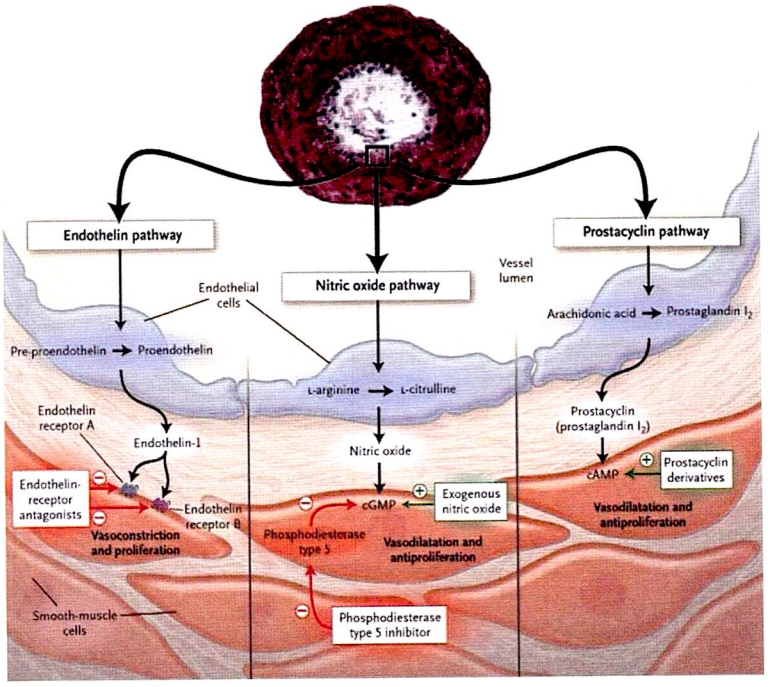
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3 pathways :

1. Endothelin pathway : Endothelin released by endothelium has 2 receptors.
   Endothelin A : Vasoconstriction and smooth muscle proliferation.
   Endothelin B : Vasodilation.

2. Nitric acid pathway : NO produced by L-arginine → cGMP → Vasodilation and anti proliferative effect.

3. Prostacyclin pathway : Produced from arachidonic acid → cAMP→Vasodilation and anti-proliferative effect.



Molecular pathways involved in pulmonary hypertension.

Pulmonary hypertension occurs due to :

Decrease in vasodilators :

- Nitric oxide.
- Prostacyclin.
- Vasactive intestinal peptide (VIP).

Increase in vasoconstrictors :

- Endothelin-1 (ET-1).
- Thromboxane.
- Serotonin (5-HT).

Increased expression of growth factors :

- Angiopoietin 1
- Vascular enothelial growth factor (VEGF).
- Platelet derived growth factor (PDGF).

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Changes in ion channels and membrane receptors :

- ↑ Ca^{2+} channels.
- ↓ K^{+} channels.
- ↑ Na^{2+}/Ca^{2+} exchanger.
- ↑ G protein coupled receptors.

Altered signalling pathways :

- Cyclic guanosine monophosphate.
- PDGF and Akt/MTOR signalling.
- RhoA/ROCK signalling.
- NOTCH signalling.

Genetic alterations related to idiopathic and heritable PAH :

- ↓ Bone morphogenetic protein receptor II (BMPR2) (m/c) : Regulates proliferation of smooth muscles and endothelium.
- ALKI, endoglin, Smad 8 mutation.

Note : ALKI and endoglin mutation : Also involved in AV malformation.

Clinical features

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Symptoms :

- Progressive dyspnea on exertion (m/c).
- Bendopnea : Dyspnea on bending forward d/t increase in RV filling pressure.
- Fatigue.
- Palpitations.
- Syncope/light headedness : RV, LV dysfunction in late stages.
- Pedal edema, abdominal distension, tender hepatomegaly : D/t RV failure.

WHO functional classification	
Class I	Patient with PH without limitation of physical activity.
Class II	Slight limitation of physical activity. Ordinary physical activity causes undue dyspnea, fatigue, chest pain, near syncope.
Class III	Marked limitation of physical activity but comfortable at rest. Less than ordinary activity causes symptoms.
Class IV	Symptoms even at rest.

Less common symptoms :

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- Chest pain/angina like pain : Dilated pulmonary artery can compress left main coronary artery.
- Hoarseness of voice : Compression of left recurrent laryngeal nerve (RLN) by dilated pulmonary artery K/a Ortner's syndrome.

Suspect PHTN when :

- Patient complains of progressive dyspnea without other symptoms.
- Poor response to management of common causes of dyspnea.
- Signs of underlying diseases that can cause PHTN (Such as scleroderma, obstructive sleep apnea, progressive emphysema.

Clinical examination :

General examination :

- Tachypnea.
- Tachycardia.
- Use of accessory muscles of respiration.
- Cyanosis +/-.
- Clubbing.
- Pedal edema.
- Dilated neck veins, raised JVP.

Systemic examination :

Respiratory system : Normal unless in presence of respiratory causes (Eg : Velcro crackles in interstitial lung disease).

Cardiovascular :

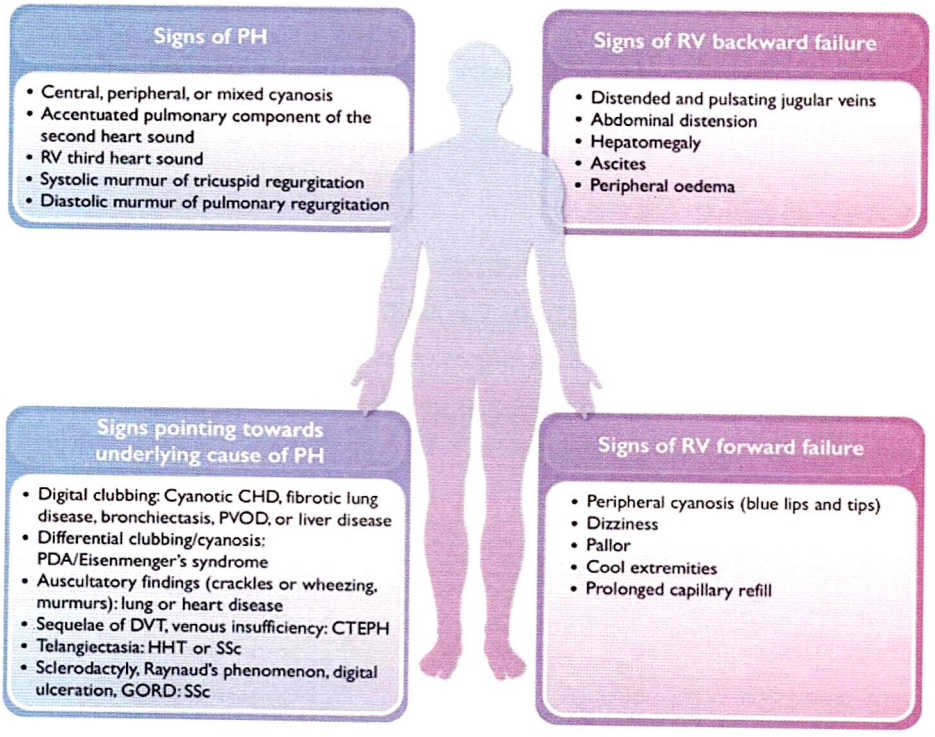
- Palpable P2 in left 2nd ICS (Intercostal space)
- Left parasternal heave. } Right ventricular hypertrophy.
- Epigastric impulse. }
- Dull note over left 2nd ICS.
- Loud P2.
- Right ventricular gallop rhythm RV S3).
- Pulmonary ejection click.
- Tricuspid regurgitation murmur : Systolic.
- Pulmonary regurgitation murmur : Diastolic.

Signs of right heart failure :

- Raised JVP.
- Ascites/abdominal distension.
- Tender hepatomegaly.
- Pedal edema.

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Joint examination, skin examination, GIT examination : To find the cause of pulmonary hypertension.



Signs of pulmonary hypertension.

Diagnosis

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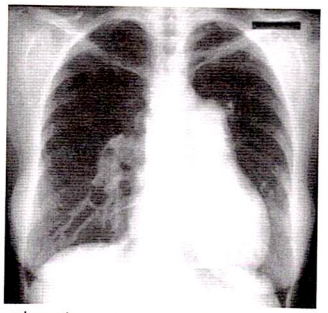
Aim of diagnostic studies :

- Confirm presence of pulmonary hypertension.
- Staging.
- Adjust treatment.
- Determine prognosis.
- Detect underlying etiology.

Diagnostic tests :

Chest x-ray :

- Dilated central pulmonary artery.
- Absence of peripheral vasculature (Pruning of peripheral vessels).
- Cardiomegaly.
- Underlying lung diseases such as interstitial lung disease, emphysema.



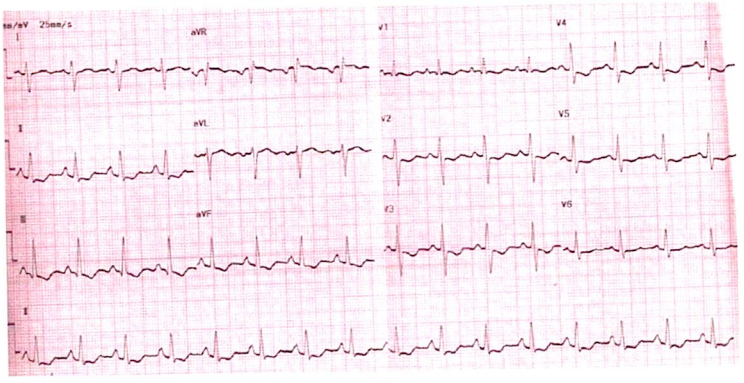
Chest x ray in pulmonary hypertension.

ECG :

- Right axis deviation (Lead I predominantly negative and lead avF predominantly positive).

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- P-pulmonale (RV dilatation) : Amplitude of P wave >0.25 mV (>2.5 small squares).
- Right ventricular hypertrophy : R/S in V1 > 1, R >0.5 mV.
- Right bundle branch block.
- RV strain pattern : T inversions, ST depression in V1-4 and inferior leads.
- Other features s/o cardiac abnormalities.



ECG

Echocardiogram :

Non invasive.

Peak tricuspid regurgitant velocity (TRV) :

- < 2.8 m/s : Low probability of pulmonary HTN.
- 2.9 to 3.4 m/s : Moderate probability of pulmonary HTN.
- >3.9 m/s : High probability of pulmonary HTN.

Other findings s/o bad prognosis :

- Dilatation of RV > LV.W
- D shaped inter ventricular septum.
- Pericardial effusion.

To find etiology of pulmonary HTN :

- LV ejection fraction.
- Check for valvular heart disease /congenital heart disease.

Other tests :

Pulmonary function tests (PFT) :

- Normal PFT with reduced DLCO (Diffusing capacity of lung for carbon monoxide).
- Abnormal in presence of lung pathologies (Interstitial lung disease, COPD).

6 minute walk test : To assess exercise capacity of the patient.

Cardiopulmonary exercise testing.

Polysomnography : Sleep apnea.

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Arterial blood gas : To assess need for long term oxygen therapy.

CT pulmonary angiography :

In case of chronic pulmonary embolism leading to pulmonary HTN.

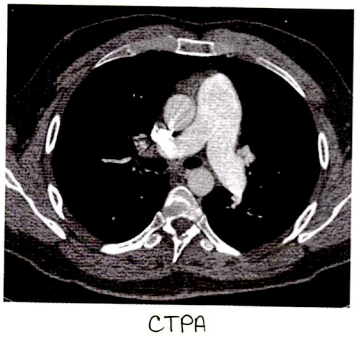
Features s/o pulmonary HTN :

- Main pulmonary artery (MPA) diameter >29 mm.
- MPA/ascending aorta diameter >0.9
- RV dilatation >LV dilatation.
- Pericardial effusion.

Can detect lung pathologies.

Lung window :

- Mosaic pattern classically see in chronic thromboembolic pulmonary hypertension.
- D/t block of pulmonary artery d/t thrombus, some areas receive lesser blood supply than other areas.



CTPA



Lung window : mosaic pattern

Laboratory tests :

Complete hemogram.

Liver function tests :

- Cirrhosis/chronic liver disease leading to portopulmonary hypertension.
- Congestive hepatomegaly d/t RV dysfunction.
- Baseline LFT levels done before starting patient on bosentan (S/e : Transaminitis).

Renal function tests, serum electrolytes.

HIV : Cause of pulmonary hypertension.

ANA (Antinuclear antibodies) : Connective tissue diseases.

N terminal pro BNP :

- Released by straining right/left ventricle.
- Levels of NT pro BNP correlate with degree of RV strain indicating prognosis.

Cardiac catheterisation :

Confirmatory test.

mPA pressure >20 mm of Hg s/o pulmonary hypertension.

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Vasoreactivity testing :

- Positive test : Pulmonary artery pressure reduced by ≥10 mm of Hg and to <40 mm of Hg in response to inhaled nitric oxide/iloprost (or) i/v epoprostenol without any change in cardiac output.
- A patient showing positive vasoreactivity test will respond to treatment with calcium channel blocker.

Definition of pulmonary hyertension (ESC guidelines 2022) :
Mean pumonary arterial pressure (mPAP) > 20 mm of Hg at rest.

Pulmonary artery hypertension/pre capillary PH :

- mPAP >20 mm Hg.
- Pulmonary artery wedge pressure (PAWP) ≤15 mm Hg : Normal LV function.
- PVR >2 Wood units (WU).

Isolated post capillary PH : D/t LV dysfunction with normal PVR.

Hemodynamic definitions of pulmonary hypertension (ESCC 2022 guidelines)	
Pulmonary hypertension	mPAP >20 mm Hg
Precapillary PH/PAH	mPAP >20 mm Hg PAWP ≤15 mm Hg PVR >2 WU
Isolated post capillary PH (IpcPH).	mPAP >20 mm Hg PAWP >15 mm Hg PVR ≤2 WU
Combined precapillary and post capillary PH.	mPAP >20 mm Hg PAWP >15 mm Hg PVR >2 WU
Unclassified PH.	mPAP >20 mm Hg PAWP ≤15 mm Hg PVR ≤2 WU

Classification

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Updated classification of pulmonary hypertension (WSPH 6th 2018) :
mPAP cut off changed from 25 mm of Hg to 20 mm of Hg.
SVR cutoff changed from 3 WU to 2 WU.

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Clinical classification of PH (ESC guidelines)		
Group 1	Pulmonary artery hypertension (PAH).	Idiopathic : • Non responders at vasoreactivity testing. • Responders at vasoreactivity testing. Heritable. Associated with drugs and toxins. Associated with : • Connective tissue disorders. • HIV infection. • Portal hypertension. • Congenital heart disease. • Schistosomiasis. PAH with features of venous/capillary involvement. Persistent PH of the newborn.
Group 2	PH associated with left heart disease.	Heart failure : • With preserved ejection fraction. • With reduced or mildly reduced ejection fraction. Valvular heart disease. Congenital/acquired cardiovascular conditions leading to post capillary PH.
Group 3	PH associated with lung diseases.	Obstructive lung disease or emphysema. Restrictive lung disease. Lung disease with mixed restrictive/obstructive pattern. Hypoventilation syndromes. Hypoxia without lung diseases (Eg : High altitude). Developmental lung disorders (Lymphangioleiomyomatosis/LAM).
Group 4	PH associated with PA obstructions.	Chronic thromboembolic PH. Other pulmonary artery obstructions.
Group 5	miscellaneous.	Hematological disorders : Thalassemia, sickle cell anemia. Systemic disorders : Sarcoidosis. metabolic disorders : Glycogen storage disorders, Gaucher's Chronic renal failure with/without hemoptysis. Pulmonary tumour causing thrombotic microangiopathy. Fibrosing mediastinitis.

Heritable pulmonary arterial hypertension :

- Group 1 PH.
- Genetic mutations : BMP R II, ALK 1, endoglin.

PAH associated with connective tissue diseases :

- Pulmonary artery involved : Group 1.
- Interstitial lung disease : Group 3.
- Involvement of heart (LV failure) : Group 2.

- Chronic pulmonary embolism (In SLE) : Group 4.
- Different groups of PH can coexist in a patient.
- m/c CTD involving PH : Limited scleroderma (CREST).
- Diffuse systemic sclerosis → Interstitial lung disease.
- SLE, Sjogren syndrome, mixed CTD commonly a/w PH.
- Rheumatoid arthritis is not commonly associated with PH.

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Drugs and toxins associated with PH (Dietary pulmonary hypertension) :

- Anorectic agents (Aminorex, fenfluramine derivative) → ↑ Levels of serotonin → Pulmonary constriction.
- Toxic oil syndrome : Rapeseed oil contaminated with aniline dye (Food adulteration).
- Hence these are banned.

PH due to hemoglobinopathies :

Group 5.

- Hemolysis → Heme released → Scavanges nitric oxide → Reduced vasodilation.
- Recurrent infections in sickle cell anemic patient → Lung abnormalities, hypoxia.
- Free radical injury d/t hemolysis.
- Increased platelet aggregation.
- LV involvement.
- Thrombosis.

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PULMONARY HTN : MANAGEMENT

Introduction

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Risk groups :

According to Fishman :

Determinants of Prognosis[3] (Estimated 1-Year Mortality)	Low Risk <5%	Intermediate Risk 5%–10%	High Risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[13]	Repeated syncope
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak$\dot{V}O_2$ >15 mL/min/kg (>65% pred.) VE/VCO, slope <36	Peak$\dot{V}O_2$ 11–15 mL/min/kg (35%–65% pred.) VE/VCO, slope 36–44.9	Peak$\dot{V}O_2$ <11 mL/min/kg (<35% pred.) VE/VCO, slope >45
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–300 ng/L NT-proBNP 300–1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mm Hg CI >2.5 L/min/m^2 SvO >65%	RAP 8–14 mm Hg CI 2.0–2.4 L/min/m^2 SvO 60%–65%	RAP >14 mm Hg Ci <2.0 L/min/m^2 SvO <60%

Important factors :

- WHO class.
- 6 min walk distance.
- NT proBND.

Pharmacological treatment

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Group I :

- Different trials have been conducted for treatment of group I.
- But whatever treatment is given complete reversal of pulmonary artery HTN cannot be done.

Targeted pharmacotherapy :

- Both vasodilator & anti-proliferative property present.
- No trials regarding the efficacy of targeted pharmacotherapy present.

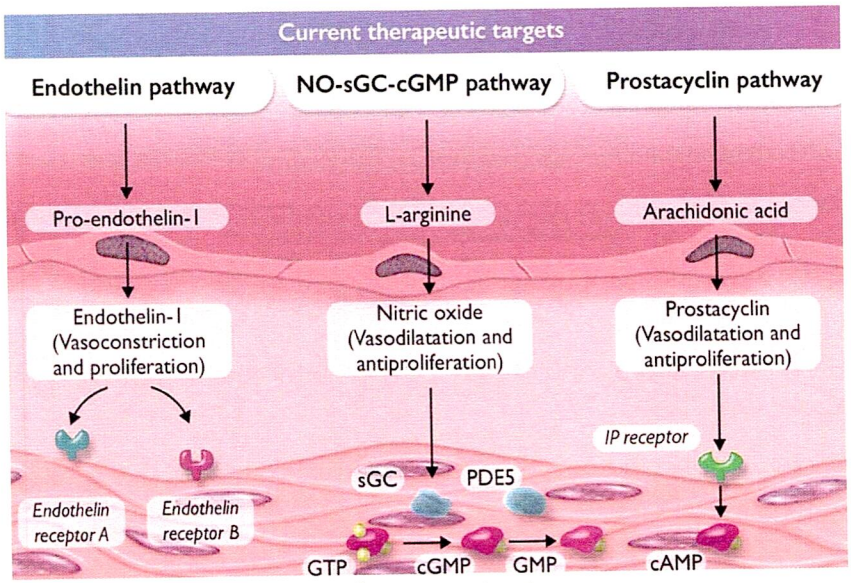
Calcium channel blockers :

- Increased cytosolic Ca^{2+} causes sustained vasoconstriction.
- CCB's are given to prevent the sustained vasoconstriction.
- Positive vasoreactive response in cardiac catheterization → Treated with CCB's.

- CCB's not given for negative vasoreactive response → Causes only side effects.
- High doses are given in case of pulmonary HTN → monitor for side effects (pedal edema, hypo-tension).
- Sustained response should be monitored → Only few people show positive response to treatment.

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Current therapeutic drugs :



MOA of therapeutic drugs

Endothelin receptor antagonists :

- Dual ETA/ETB antagonist : Bosentan, macitentan.
- Selective ETA antagonist : Ambrisentan.
- Dosage :
  i. Bosentan 62.5 mg → 125 mg BD.
  ii. Ambrisentan 10mg OD.
- Adverse effects of Bosentan : Transamiitis.
- Teratogenic → C/I in reproductive age group.
- Other S/E :
  i. Pedal edema.
  ii. Headache.
  iii. Nasal congestion.
  iv. Epistaxis.
  v. Anemia.

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Nitric oxide therapies :

Phosphodiesterase 5 inhibitors :

- Drugs : Sildenafil, tadalafil.
- Dosage :
  - i. Sildenafil : 20 mg TID.
  - ii. Tadalafil : 40 mg OD.
- Adverse effects :
  - i. Diarrhea.
  - ii. Pedal edema.
  - iii. Headache.
  - iv. Nasal congestion.

Soluble guanylate cyclase inhibitor :

- MOA : Augments cGMP without the help of nitric oxide.
- Riociguat : 1.5 mg TID → 2.5 mg TDS.
- Additional to Group I it is also used in chronic thromboembolic pulmonary HTN (group IV).

Note :

- PDE-5 inhibitors and guanylate cyclase inhibitor should not be given together.
- PDE-5 inhibitors should not be given along with nitrites → S/E like syncope can occur.

Prostacyclin pathway therapies :

Drugs : Epoprostenol, Treprostinil, Iloprost, Beroprost.

Epoprostenol :

- Shorter half life.
- Route of administration : I/V infusion.
- Dose should be titrated from lower dose to higher dose.
- Increased risk of sepsis with catheter → Bacteremia.

Treprostinil :

- Route of administration : Subcutaneous.
- A/e : Pain at the site of injection.
- Cannot be used for immediate relief as it takes time to titrate the dose.
- Inhalational route of drug is under trial.

Iloprost : Route of administration → Inhalational.

Beroprost :

- Route of administration : Oral.
- Not used nowadays.