PULMONARY HYPERTENSION

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CASE REPORT

A 35 year old female, general worker. Married with 2 children with the youngest aged 12 years.

Presenting complaints :

- Progressive dyspnea for 5 months,
- Leg swelling for 2 months,
- Abdominal distension for 1 month
- Reduced urine output

Past medical history

- No similar illness in the past.
- No history of Hypertension, DM

Lifestyle and habits:

- She is a non-smoker and a teetotaler.
- No h/o substance abuse.

Clinical examination

The patient was fully conscious and well orientated.

Afebrile, well hydrated

Muddy conjunctiva +

No pallor/cyanosis/lymphadenopathy
JVP elevated – CV waves prominent
Bilateral pitting pedal edema

Pulse rate - 80/min regular
BP- 110/70 mm hg

CVS - Apical impulse left 5th ICS 2.5cm lateral to MCL, normal character
Prominent parasternal heave
Palpable P2
Loud P2 with an ESM graded 2/6
PSM graded 3/6 in the tricuspid area

Respiratory system – Normal findings

Abdomen – Non-tender, pulsatile hepatomegaly and ascites

CNS – Grossly intact.

IMPRESSION

PULMONARY HYPERTENSION
? CAUSE

RV FAILURE

Pulmonary hypertension (PH) is an abnormal elevation in pulmonary artery pressure, as a result of left heart failure, pulmonary parenchymal or vascular disease, thromboembolism, or a combination of these factors.

Definition of PAH by WHO

Increase in blood pressure in pulmonary circulation (either in the arteries, or both in arteries and veins)

Normal pressure is 14-18mmHg at rest.

20-25mmHg on exercise.

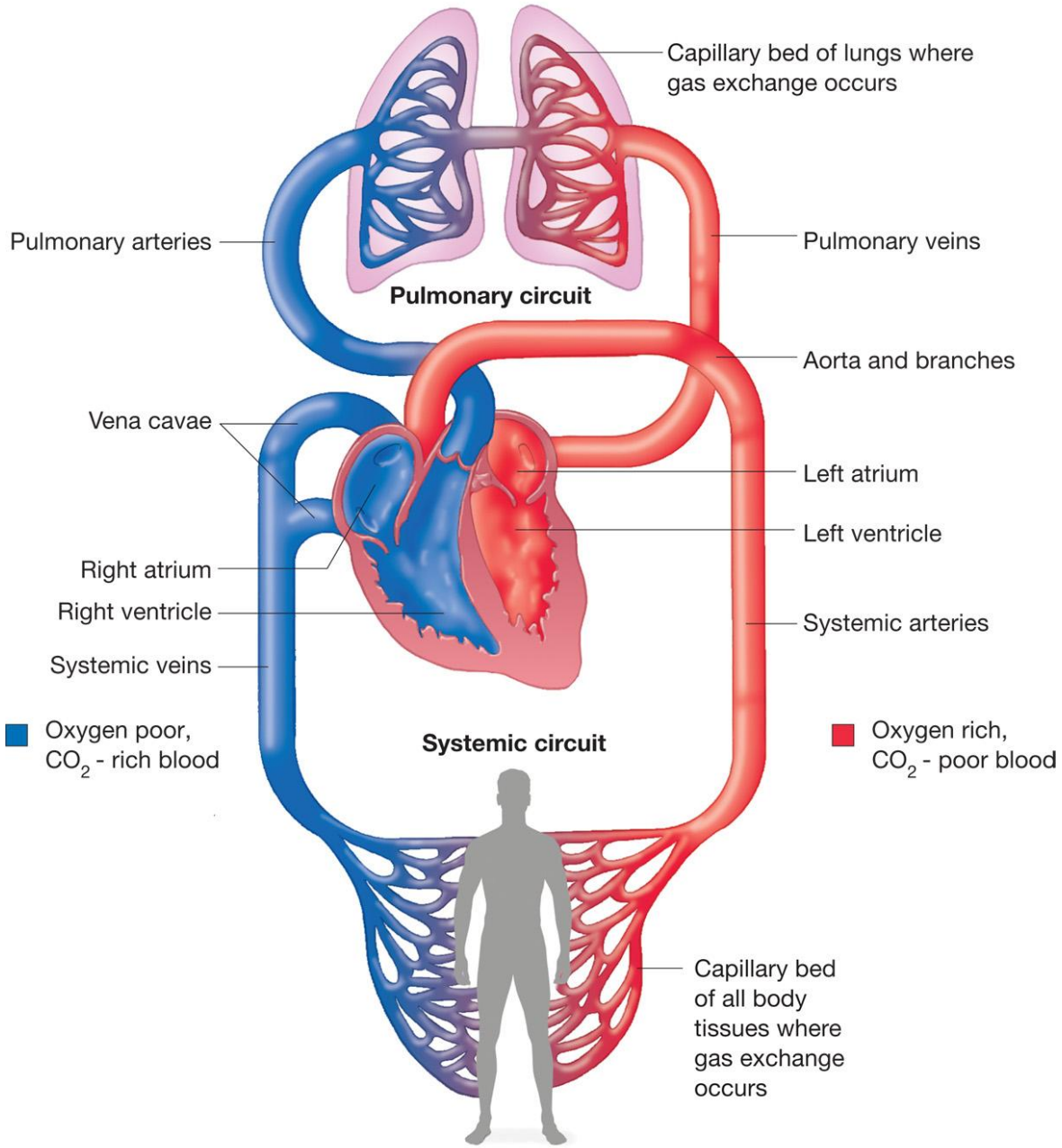
Hemodynamically it is defined as an increase in mean pulmonary arterial pressure to >-25mmHg at rest.

Can be measured by right heart catheterization.

WHO Classifications of Pulmonary Hypertension

1. Pulmonary Arterial Hypertension
2. Pulmonary Hypertension owing to left heart disease
3. PH Secondary to Chronic Hypoxemia
4. Chronic Thrombo-Embolic Pulmonary Hypertension (CTEPH)
5. Miscellaneous (usually extrinsic compression of pulmonary arteries)

WHO Venice 2003 – Later updated in 2008 (Dana point)


Capillary bed of lungs where gas exchange occurs
Pulmonary arteries
Pulmonary veins
Pulmonary circuit
Aorta and branches
Vena cavae
Left atrium
Left ventricle
Right atrium
Right ventricle
Systemic arteries
Systemic veins
Oxygen poor, CO_2 - rich blood
Systemic circuit
Oxygen rich, CO_2 - poor blood
Capillary bed of all body tissues where gas exchange occurs

Group 1 - PAH

IPAH

Familial – BMPR2, ALK 1,Unknown

Associated with PAH

- Connective Tissue Disease (Scleroderma, SLE, MCTD, RA)
- Congenital Heart Disease
- Portal hypertension (5-7% of patients)
- HIV (0.5% of patients)
- Drugs/toxins (aminorex-, dexfenfluramine-, or fenfluramine-containing products, cocaine, methamphetamine)
- Other:

Associated with venous/capillary involvement

- Pulmonary veno-occlusive disease (evidence of pulmonary vascular congestion)
- Pulmonary capillary hemangiomatosis

Persistent PH of newborn.

Group 2: Pulmonary hypertension due to left heart disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

Group 3: Pulmonary hypertension associated with lung disease and/or hypoxemia

- Chronic obstructive lung disease
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Group 4: Pulmonary hypertension due to chronic thrombotic and/or embolic disease

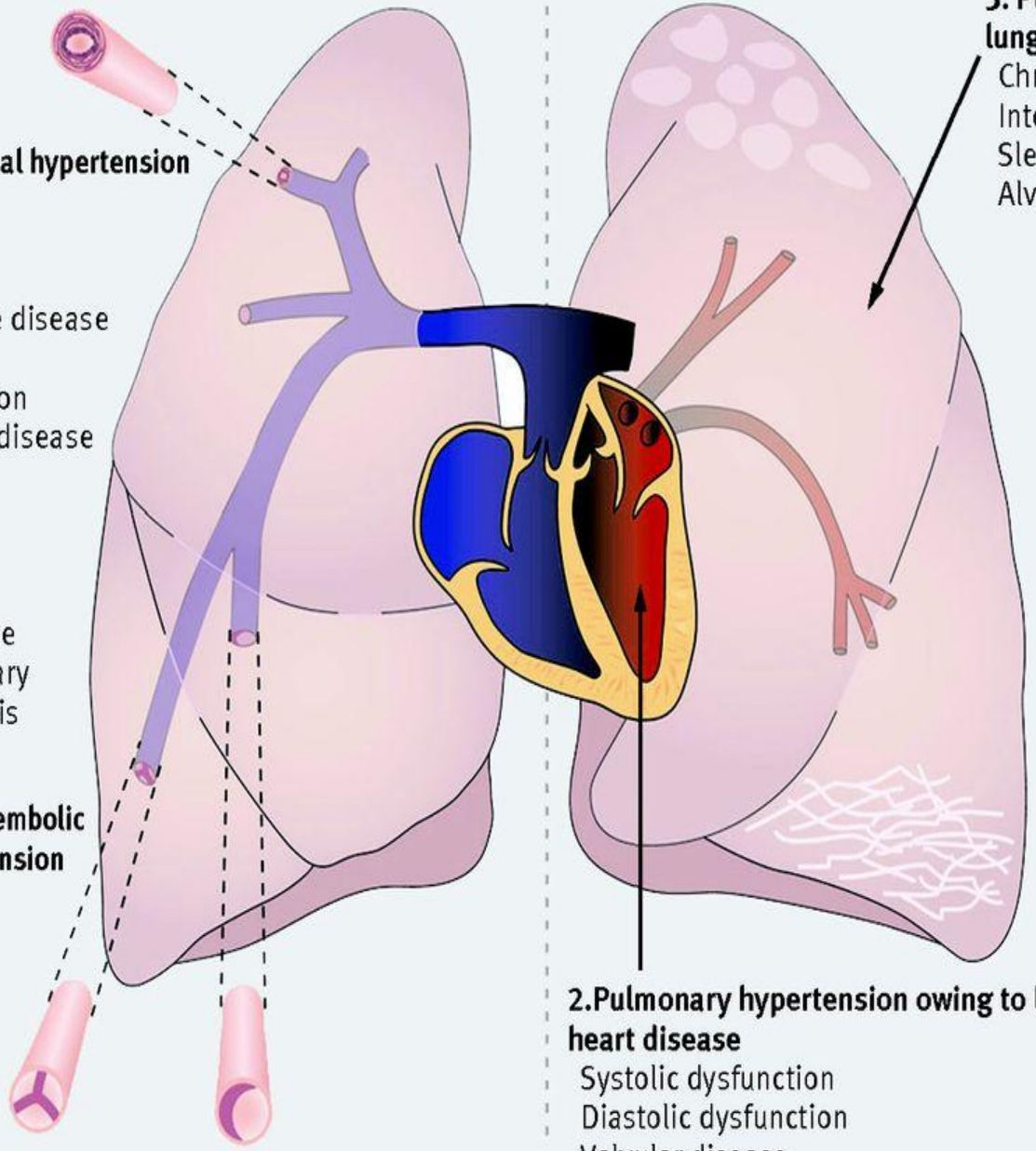
- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries

Group 5: Miscellaneous

- Sarcoidosis, histiocytosis X, lymphangiomyomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis, thyroid disorders, glycogen storage disease, Gaucher's disease,

Defined treatments

Optimal treatment not clear



1. Pulmonary arterial hypertension
- Idiopathic
- Heritable
- Drugs
- Connective tissue disease
- HIV
- Portal hypertension
- Congenital heart disease
- Schistosomiasis

1'
- Pulmonary veno-occlusive disease
- Pulmonary capillary haemaglomatosis

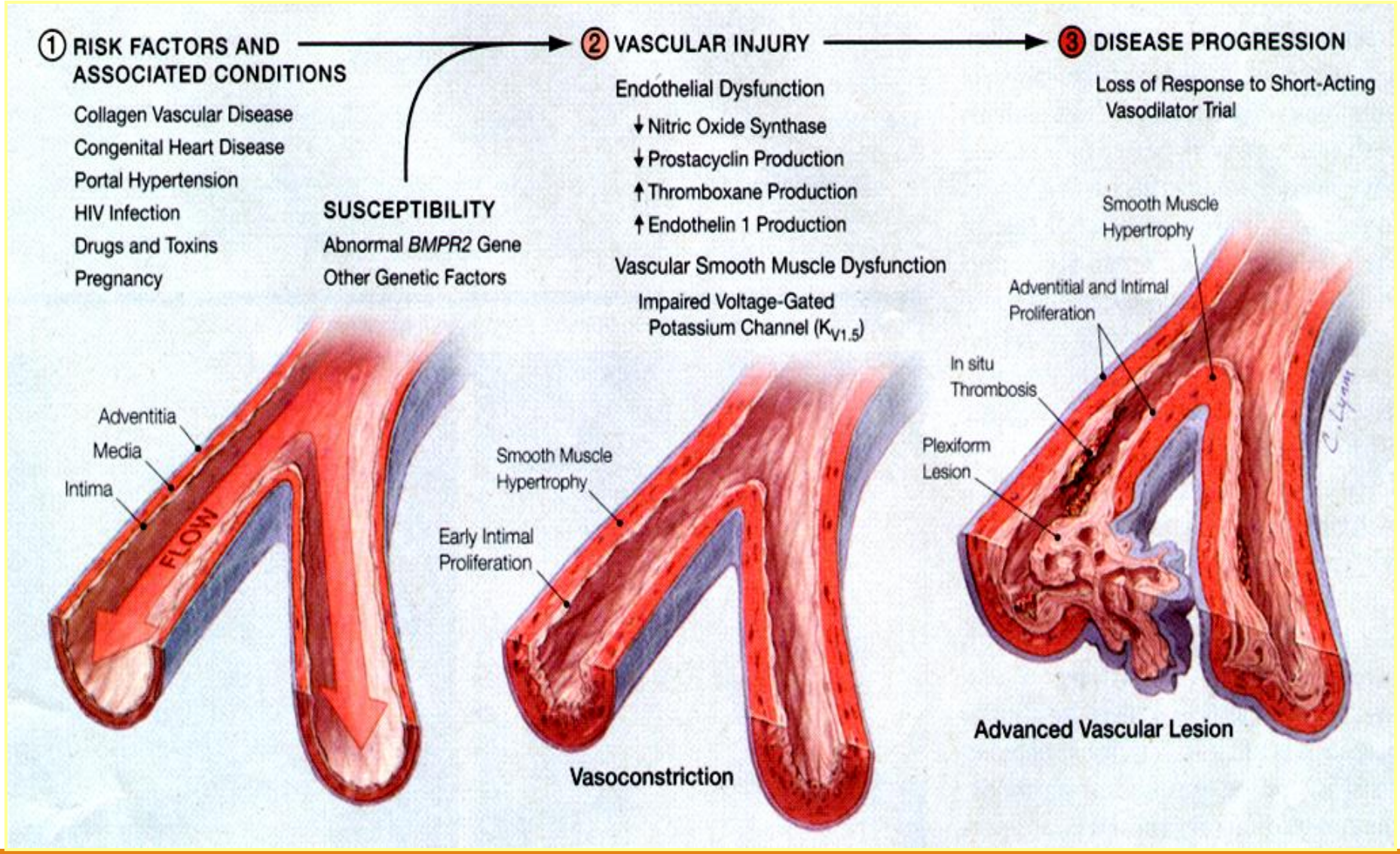
4. Chronic thromboembolic pulmonary hypertension
- Operable
- Inoperable

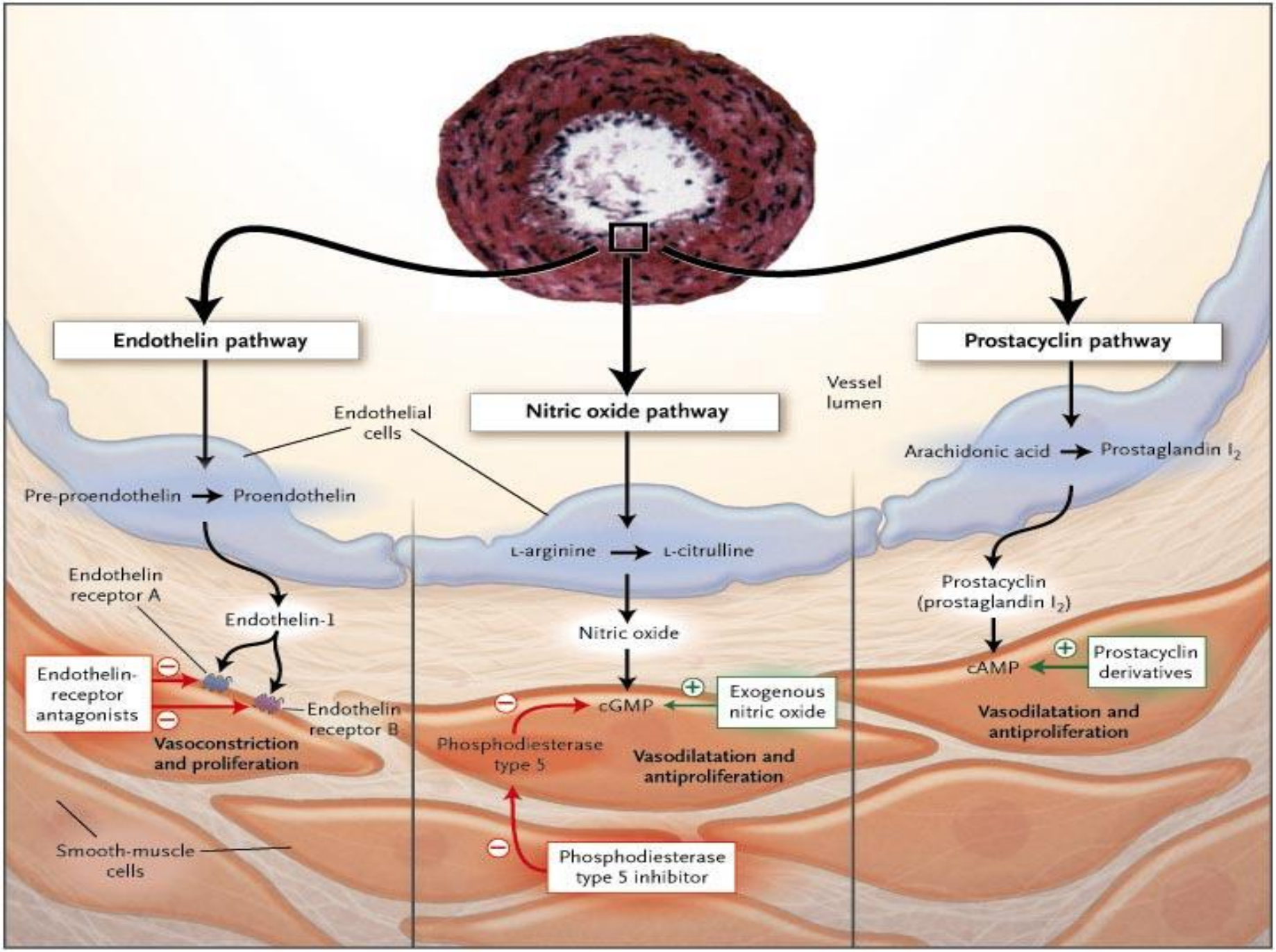
3. Pulmonary hypertension owing to lung disease/hypoxia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep disorder
- Alveolar hypoventilation

5. Multifactorial/unclear mechanisms
- Haematological
  - Chronic haematolytic anaemia
  - Myeloproliferative disease
  - Splenectomy
- Systemic disorders
  - Sarcoidosis
  - Langerhans cell histiocytosis
  - Lymphangioleiomyomatosis
  - Neurofibromatosis
  - Vasculitis
- Metabolic disorders
  - Glycogen storage disease
  - Gaucher's disease
  - Thyroid disorder
- Others
  - Tumour obstruction
  - Fibrosing mediastinitis
  - Chronic renal failure

2.Pulmonary hypertension owing to left heart disease
- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

Pathogenesis of Pulmonary Arterial Hypertension




Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Pre-proendothelin
Proendothelin
L-arginine
L-citrulline
Arachidonic acid
Prostaglandin I_2
Endothelin receptor A
Endothelin-1
Nitric oxide
Prostacyclin (prostaglandin I_2)
Endothelin-receptor antagonists
Endothelin receptor B
Vasoconstriction and proliferation
cGMP
Exogenous nitric oxide
cAMP
Prostacyclin derivatives
Vasodilatation and antiproliferation
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor

Pathophysiology & Pathology – Group 1

Exact mechanism – unknown.

Multifactorial.

1)Excessive vasoconstriction -abnormal function or expression of potassium channels in the smooth muscle cells .

2) Endothelial dysfunction leads to chronically impaired production of vasodilator and Vasoconstrictors

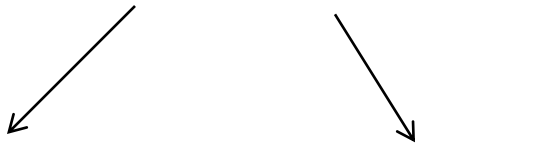
(NO, prostacyclin, thromboxane A2 and endothelin-1)

3) Reduced plasma levels of other vasodilator and antiproliferative substances such as vasoactive intestinal peptide

4) In the adventitia there is increased production of extracellular matrix including collagen, elastin, fibronectin. Inflammatory cells and platelets (through the serotonin pathway)

5) Prothrombotic abnormalities have been demonstrated in PAH patients, and thrombi are present in both the small distal pulmonary arteries and the proximal elastic pulmonary arteries

1. Tunica media hypertrophy
2. Tunica intima proliferation
3. Fibrotic changes of tunica intima



4.Tunica adventitial thickening with moderate perivascular infiltrates

5. Complex lesions

6. Thrombotic lesions.

Pathophysiology & Pathology – Group 2

Due to left heart diseases:

Pulmonary venous hypertension-most common cause

Usually due to left-sided heart disease (valvular, coronary or myocardial), →obstruction to blood flow downstream from the pulmonary veins.

Reversibility is variable, dependent on lesion.

Pathophysiology & Pathology – Group 3

due to lung diseases and/or hypoxia:

Multiple

1) hypoxic vasoconstriction,
2) mechanical stress of hyperinflated lungs,
3) loss of capillaries – emphysema, fibrosis
4) inflammation, and toxic effects of cigarette smoke.
5) endothelium-derived vasoconstrictor–vasodilator imbalance.

Hypoxia induced pulmonary vasoconstriction and anatomical destruction of the vascular bed due to high pulmonary resistance and ultimately RV failure.

Pathophysiology & Pathology – Group 4

CTEPH: non-resolution of acute embolic masses which later undergo fibrosis leading to mechanical obstruction of pulmonary arteries is the most important process.

Pathophysiology & Pathology – Group 5

PH with unclear and/or multifactorial mechanisms.

Drugs and toxins known to induce PAH

Definite
- Aminorex
- Fenfluramine
- Dexfenfluramine
- Toxic rapeseed oil
- Benfluorex

Possible
- Cocaine
- Phenylpropanolamine
- St John's Wort
- Chemotherapeutic agents
- Selective serotonin reuptake inhibitors
- Pergolide

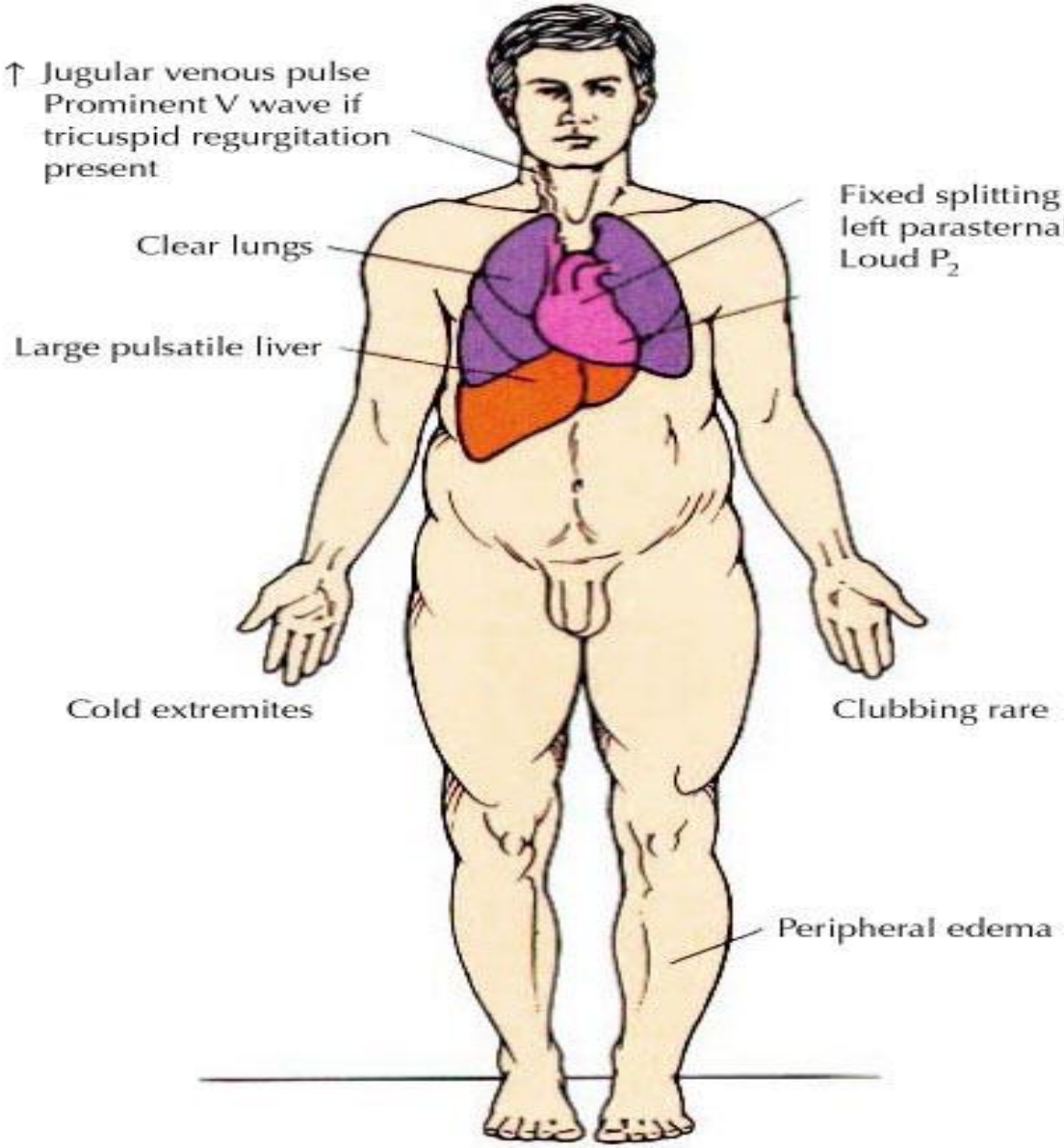
Likely
- Amphetamines
- L-tryptophan
- Methamphetamines

Unlikely
- Oral contraceptives
- Oestrogen
- Cigarette smoking

Symptoms of PAH

• Dyspnea	60%
• Fatigue	19%
• Near syncope/syncope	13%
• Chest pain	7%
• Palpitations	5%
• LE edema	3%
• Hoarseness of voice (Ortners syndrome)	2%

Physical Exam Findings in PH



BLOOD TESTS AND IMMUNOLOGY.

- Routine biochemistry,hematology and thyroid function tests

- CTD are diagnosed primarily on clinical and laboratory
- criteria and an autoimmune screen consists of antinuclear
- antibodies, including anti-centromere antibody,anti-SCL70 and RNP.

- About one third of patients with idiopathic PAH have positive but low antinuclear antibody titers (≥ 1:80 dilutions.

HIV Testing

- HIV-positive patients have a higher rate of IPAH than the general population

Antinuclear Antibody

- Excluding autoimmune disorders is an important part of the workup in a patient with suspected pulmonary hypertension. Reportedly, up to 40% of patients with IPAH have a positive finding on an antinuclear antibody (ANA) assay but no other clinical manifestations of autoimmune disease.

Thyrotropin

- Screen for thyroid abnormalities during the initial workup for IPAH because these abnormalities are common in patients with IPAH. Thyroid abnormalities may be the cause of or contribute to symptoms similar to IPAH. In addition, hyperthyroidism itself may lead to an elevation in pulmonary artery pressure.

TYPE NATRIURETIC PEPTIDE

Levels of B-type natriuretic peptide (BNP) and N-terminal BNP have been shown to be elevated in patients with IPAH, and levels appear to be prognostic.

Specialized Investigations

- ❑ *Chest Radiography*
- ❑ *Electrocardiogram*
- ❑ *Echocardiography*
- ❑ *Lung function testing*
- ❑ *Ventilation-perfusion scanning*
- ❑ *HRCT scanning*
- ❑ *Pulmonary angiography*
- ❑ *Cardiac catheterization*
- ❑ *Exercise testing*

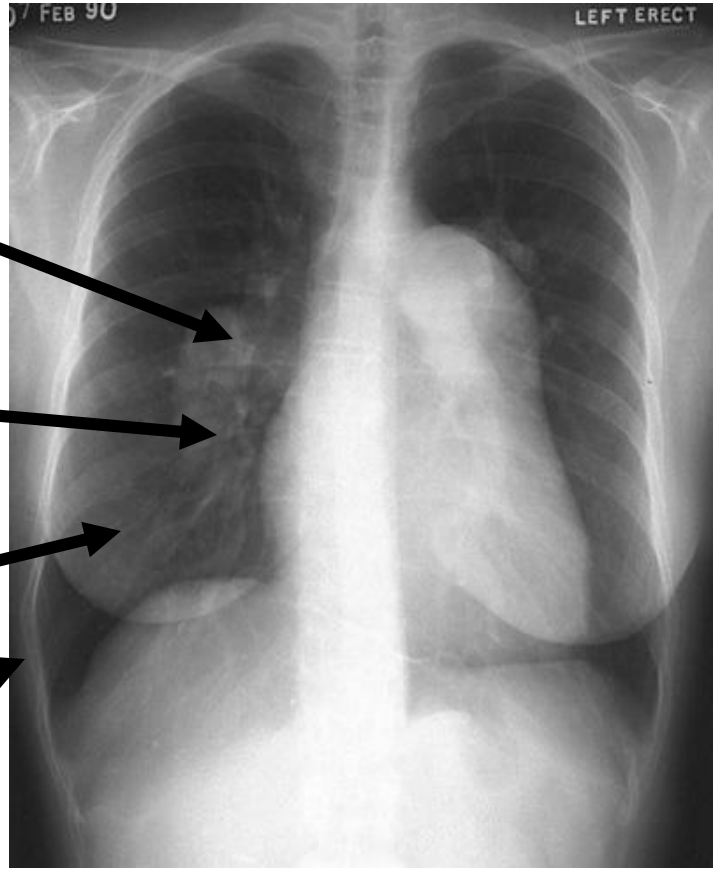
CXR in PH

Large central Pulmonary arteries

Right Ventricular Hypertrophy

Rapid attenuation of pulmonary vessels

Clear Lung Fields



Chest Radiograph

- ❑ *Enlargement of pulmonary trunk*
- ❑ *Pruning of peripheral pulmonary arterial tree*
- ❑ *Right ventricular enlargement*
- ❑ *Findings corresponding to condition leading to PH*

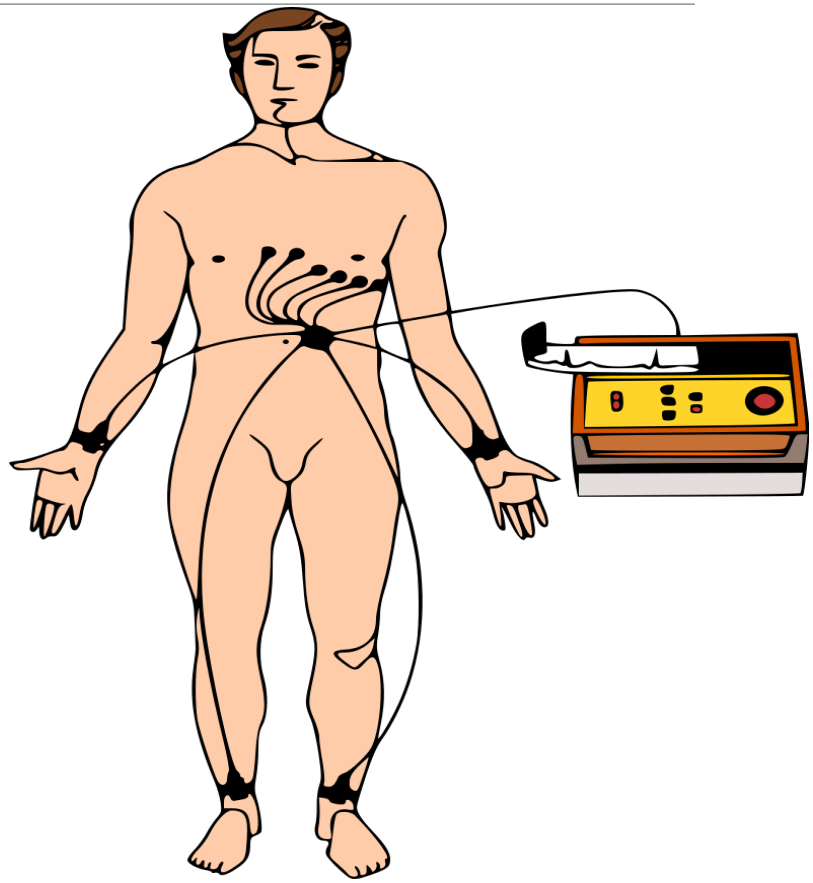
ECG in PH

Right axis deviation

An R wave/S wave ratio greater than one in lead V1

Incomplete or complete right bundle branch block

Increased P wave amplitude in lead II (P pulmonale) due to right atrial enlargement



Echocardiogram Findings

TR

Right atrial and ventricular hypertrophy

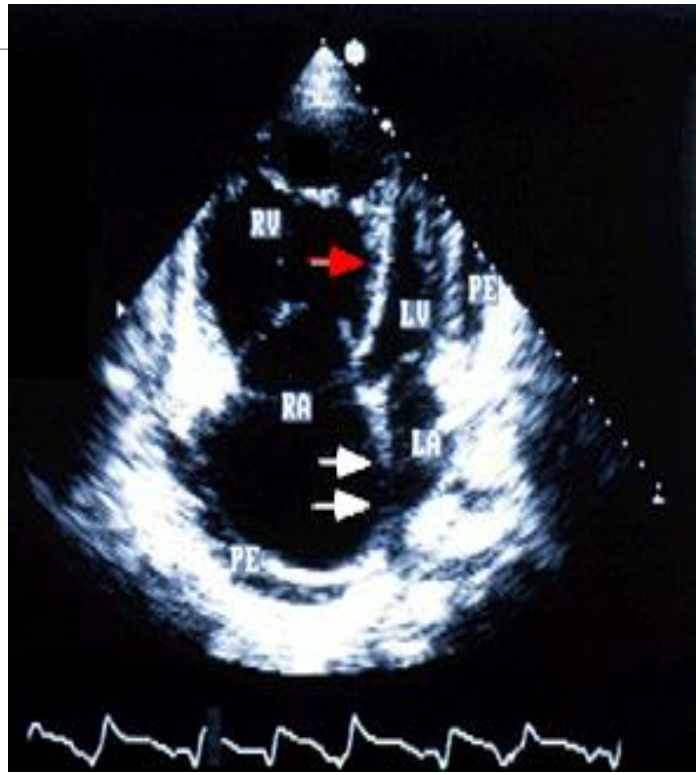
Flattening of interventricular septum

Small LV dimension

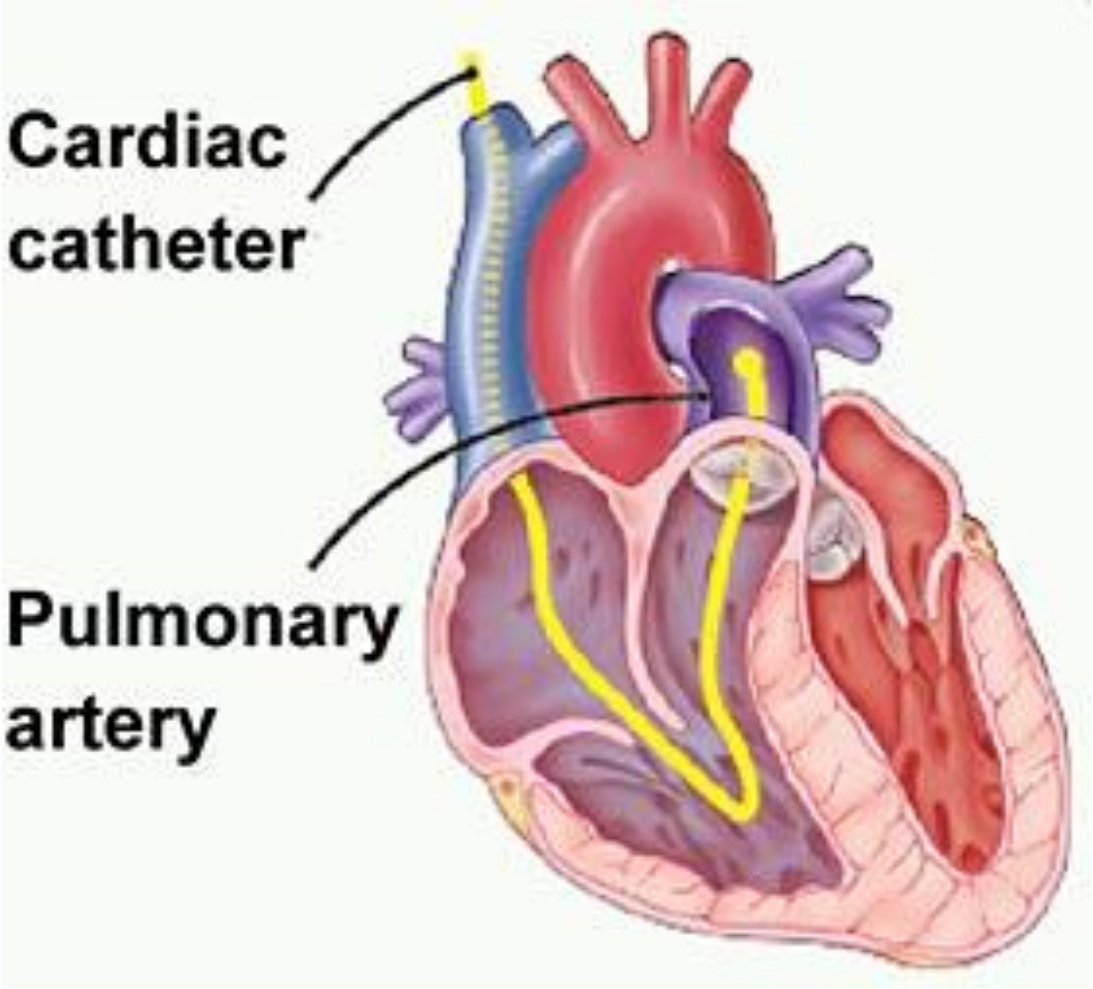
Dilated PA

Pericardial effusion

- Poor prognostic sign
- RA pressure so high it impedes normal drainage from pericardium
- Do not drain, usually does not induce tamponade since RV under high-pressure and non-collapsible



Cardiac catheterization



Cardiac catheterization

Determination of:-

- *Right atrial pressure*
- *Right ventricular pressure*
- *PAP*
- *PCWP*
- *Pulmonary blood flow (cardiac output)*
- *Vasoreactivity*

Grading of pulmonary arterial hypertension*

	Systolic	Diastolic	Mean
Grade 1 (Mild)	30-50	20-25	>20
Grade 2 (Moderate)	50-70	26-35	>40
Grade 3 (severe)	70-110	36-45	>50
Grade 4 (Systemic or supra systemic)	>110	46-55	>60

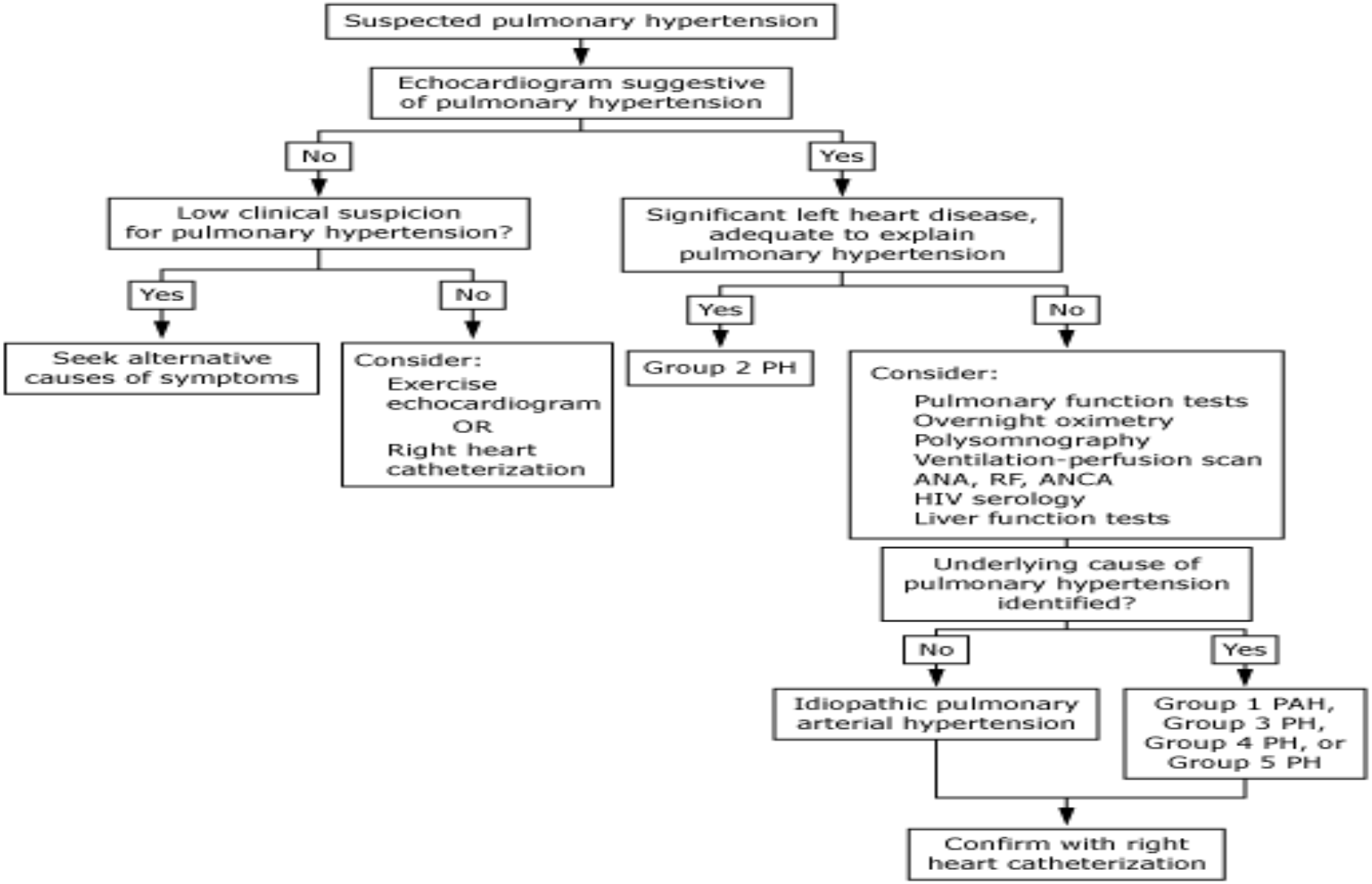
*Data from 100 patients of PAH and rheumatic heart disease. Quintile 1 & 2 (Grade 1) qunitile 3 & 4 (Grade 2) quintile 5 (Grade 3) top 3%(Grade 4)

Definition	Characteristics	Clinical group(s)b
Pulmonary hypertension	Mean PAP 25 mmHg	All
Pre-capillary PH	Mean PAP 25 mmHg PWP 15 mmHg CO normal or reduced	1. Pulmonary arterial Hypertension 3. PH due to lung diseases 4. Chronic Thromboembolic PH 5. PH with unclear and/or Multifactorial mechanisms
Post-capillary PH Passive TPG 12 mmHg Reactive (out of proportion) TPG .12 mmHg	Mean PAP 25 mmHg PWP .15 mmHg CO normal or reduced	2. PH due to left heart disease

Other Investigations

- ❑*Lung function testing*
- ❑*Sleep studies*
- ❑*Ventilation-perfusion scanning*
- ❑*HRCT scanning*
- ❑*Lung biopsy*
- ❑*Pulmonary angiography*
- ❑*Exercise testing*

Diagnostic Work-up of PAH



FINAL DIAGNOSIS

Idiopathic Pulmonary Hypertension

Why Treat PAH?

Survival & Prognosis of PAH

- Prognosis of the disease is very poor
- The median survival of patients with IPAH is 2.8 yrs
- Estimated survival rates are:
  - 68% at 1 year
  - 48% at 3 years
  - 34% at 5 years
- The estimated incidence of PAH among HIV-infected patients is 0.5% (1/200)
- PAH is found in 7-29% of patients with systemic sclerosis
- Median survival of patients who have scleroderma & PAH is approx 1 year

Clin Chest Med 2007; 28(1):1-22

Poor prognostic factors

- Age >45 years
- (WHO) functional class III or IV
- Failure to improve to a lower WHO functional class during treatment
- Echocardiographic findings of a pericardial effusion, large right atrial size, elevated right atrial pressure, or septal shift during diastole
- Decreased pulmonary arterial capacitance (ie, the stroke volume divided by the pulmonary arterial pulse pressure)
- Increased N-terminal pro-brain natriuretic peptide level (NT-pro-BNP)
- Prolonged QRS duration
- Hypocapnia
- Comorbid conditions (eg, COPD, diabetes)

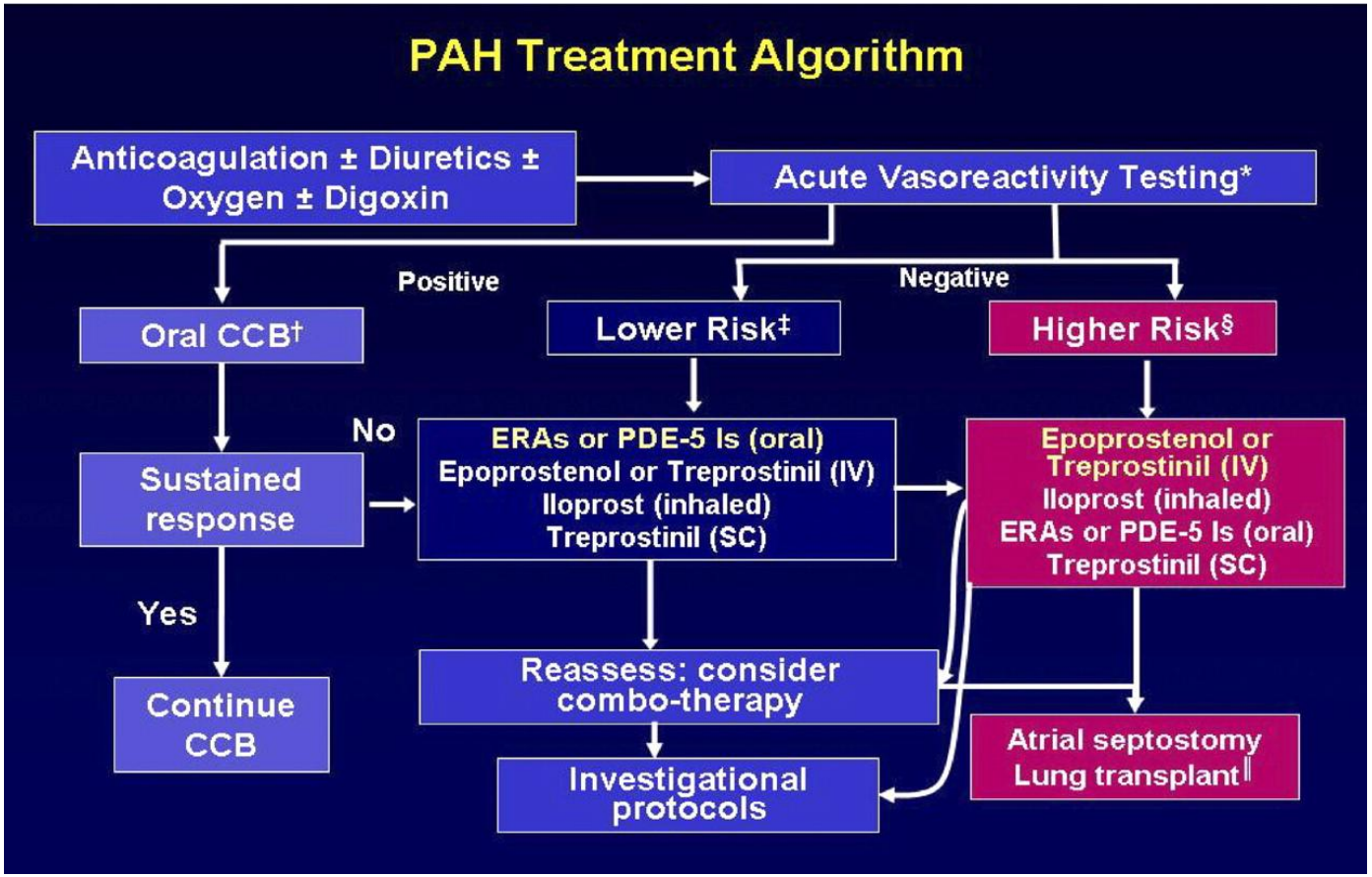
How do we Treat Them?

General measures:

- Avoid pregnancy
  - Contraception imperative
  - Maternal mortality 30%
- Immunizations for respiratory illnesses

  Influenza & pneumonia vaccinations
- Minimize valsalva maneuvers—increase risk of syncope
  - Cough, constipation, heavy lifting, etc

Treatment Algorithm for PAH



McLaughlin, V. V. et al. J Am Coll Cardiol 2009;53:1573-1619

Classes of therapy

- MEDICAL
  - Diuretics
  - Anti coagulants (IPAH)
  - Digoxin
  - Oxygen
  - PAH specific therapy
- SURGICAL THERAPY
  - Atrial septostomy
  - Lung transplantation

Anticoagulants

Studies only show benefit in IPAH patients, based on improved survival.

Other PAH groups not as clear, use in them considered expert opinion.

Generally, keep INR 2.0-2.5.

Thought to lessen in-situ thrombosis

Oxygen

Formal assessment of nocturnal and exertional oxygenation needs.

Minimize added insult of hypoxic vasoconstriction

Keep oxygen saturation ≥90%

- May be impossible with large right to left shunt

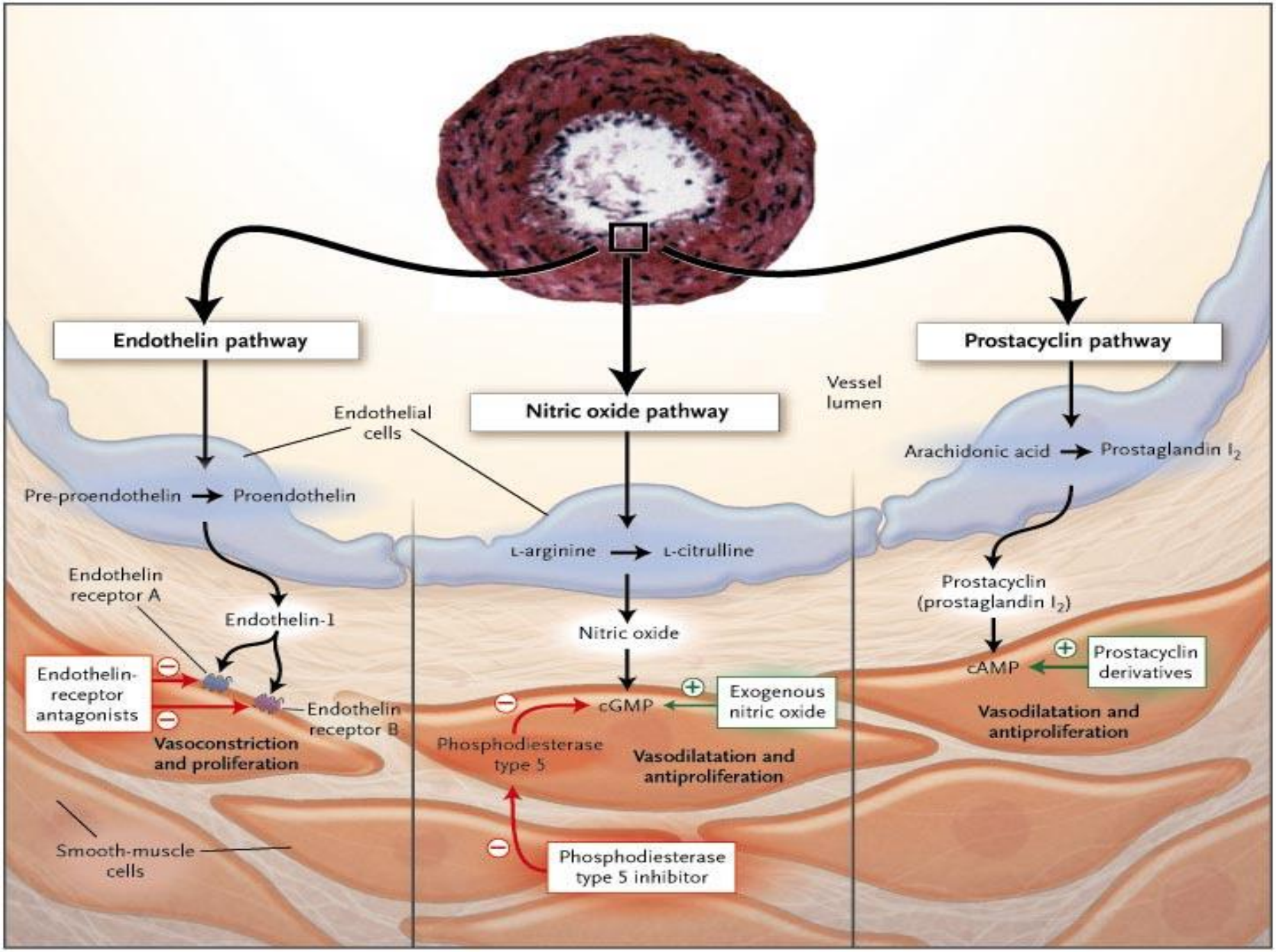
Exclude nocturnal desaturation

- Overnight oximetry

Rule out concomitant obstructive sleep apnea and hypoventilation syndromes

PAH-Specific Therapies

1) Calcium channel blockers
2) Endothelin receptor antagonists (ERAs)—Bosentan, Sitaxsentan, Ambrisentan
3) Phosphodiesterase (type 5) inhibitors (PDE 5-I)—Sildenafil, Tadalafil, Vardenafil.
4) Prostanoids—Epoprostenol, Treprostinil, Iloprost
5) Guanylate cyclase stimulant- Riociguat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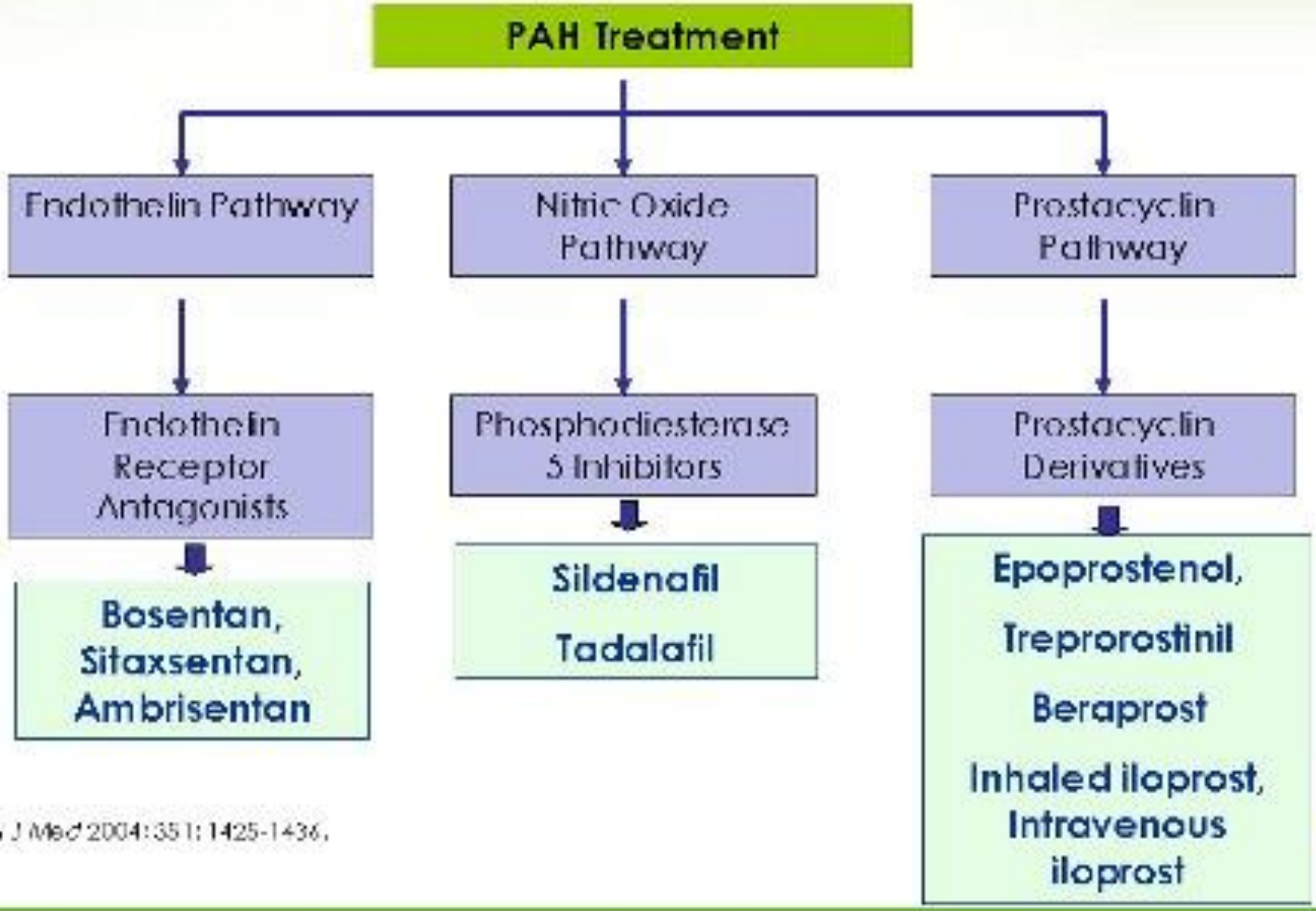
Vessel lumen
Endothelial cells
Pre-proendothelin
Proendothelin
L-arginine
L-citrulline
Arachidonic acid
Prostaglandin I_2
Endothelin receptor A
Endothelin-1
Nitric oxide
Prostacyclin (prostaglandin I_2)
Endothelin-receptor antagonists
Endothelin receptor B
Vasoconstriction and proliferation
cGMP
Exogenous nitric oxide
cAMP
Prostacyclin derivatives
Vasodilatation and antiproliferation
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor

Targeted Therapies for PAH



N Engl J Med 2004;351:1425-1436.

Calcium Channel Blockers

only when demonstrated vasoreactivity in RHC (about 10% or less of patients)

Diltiazem or nifedipine preferred.

Titrate up to maximum tolerated dose.

Systemic hypotension may prohibit use

Only 50% of patients maintain response to CCB.

Not in FC IV patients or severe right heart failure

Failure of medical therapy:

Surgical Care

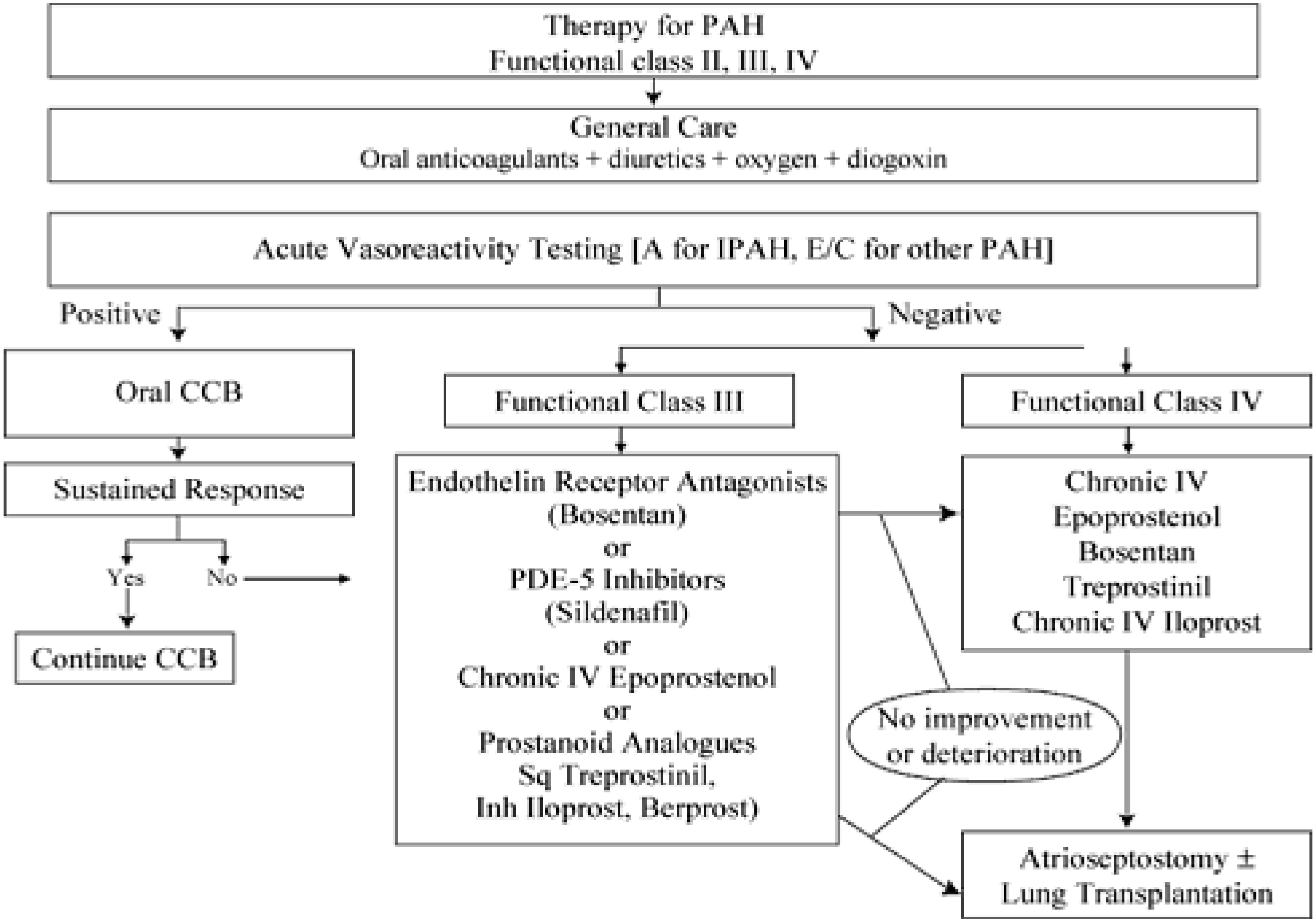
- A single- or double-lung transplant is indicated for patients who do not respond to medical therapy.

- Atrial septostomy is a palliative procedure allowing interatrial right-to-left shunting to occur, thus delivering more overall oxygen content to the respiring tissues, albeit with a lower overall saturation.

Future Therapies

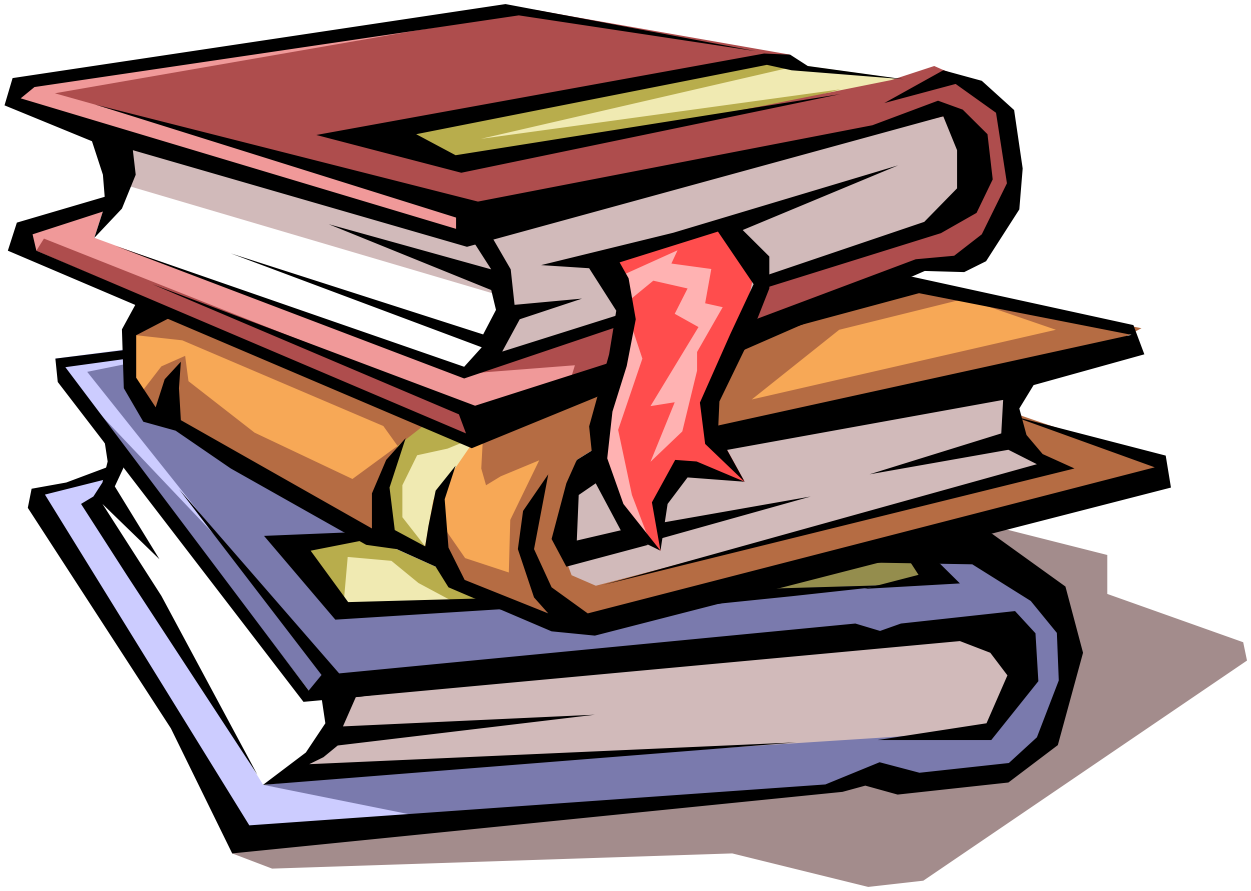
TYROSINE KINASE INHIBITORS

CINACIGUAT, RIOCIGUAT - ACTIVATORS OF GUANYLYL CYCLASE


Therapy for PAH
Functional class II, III, IV
General Care
Oral anticoagulants + diuretics + oxygen + diogoxin
Acute Vasoreactivity Testing [A for IPAH, E/C for other PAH]
Positive
Negative
Oral CCB
Sustained Response
Yes
No
Continue CCB
Functional Class III
Endothelin Receptor Antagonists
(Bosentan)
or
PDE-5 Inhibitors
(Sildenafil)
or
Chronic IV Epoprostenol
or
Prostanoid Analogues
Sq Treprostinil,
Inh Iloprost, Berprost)
Functional Class IV
Chronic IV
Epoprostenol
Bosentan
Treprostinil
Chronic IV Iloprost
No improvement
or deterioration
Atrioseptostomy ±
Lung Transplantation

Assessing disease severity, stability and prognosis

Better prognosis	Determinants of prognosis	Worse prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (>500 m)[a]	6MWT	Shorter (<300 m)
Peak O_2 consumption >15 mL/min/kg	Cardio-pulmonary exercise testing	Peak O_2 consumption <12 mL/min/kg
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE[b] >2.0 cm	Echocardiographic findings[b]	Pericardial effusion TAPSE[b] <1.5 cm
RAP <8 mmHg and CI ≥2.5 L/min/m^2	Haemodynamics	RAP >15 mmHg or CI ≤2.0 L/min/m^2



KNOWLEDGE PUT TO WORK IS WISDOM IN ACTION