ПЕРМСКИЙ ГОСУДАРСТВЕННЫЙ
МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
имени академика Е. А. Вагнера

Pulmonary Hypertension-Pathways, Diagnostic.

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3rd year, PSMU

PH - History

- History of smoking
- ETOH/recreational drug use
- Systemic hypertension
- Cyanosis/murmur as a child
- Joint/musculoskeletal pain
- Raynaud's Syndrome
- FH of unexplained early cardiopulmonary disease
- Use of appetite suppressant drugs

Pulmonary circulation

- Low resistance, high compliance vascular bed
- Only organ to receive entire cardiac output (CO)
- Changes in CO as well as pleural/alveolar pressure affect pulmonary blood flow
- Different reactions compared to the systemic circulation
- Normally in a state of mild vasodilation

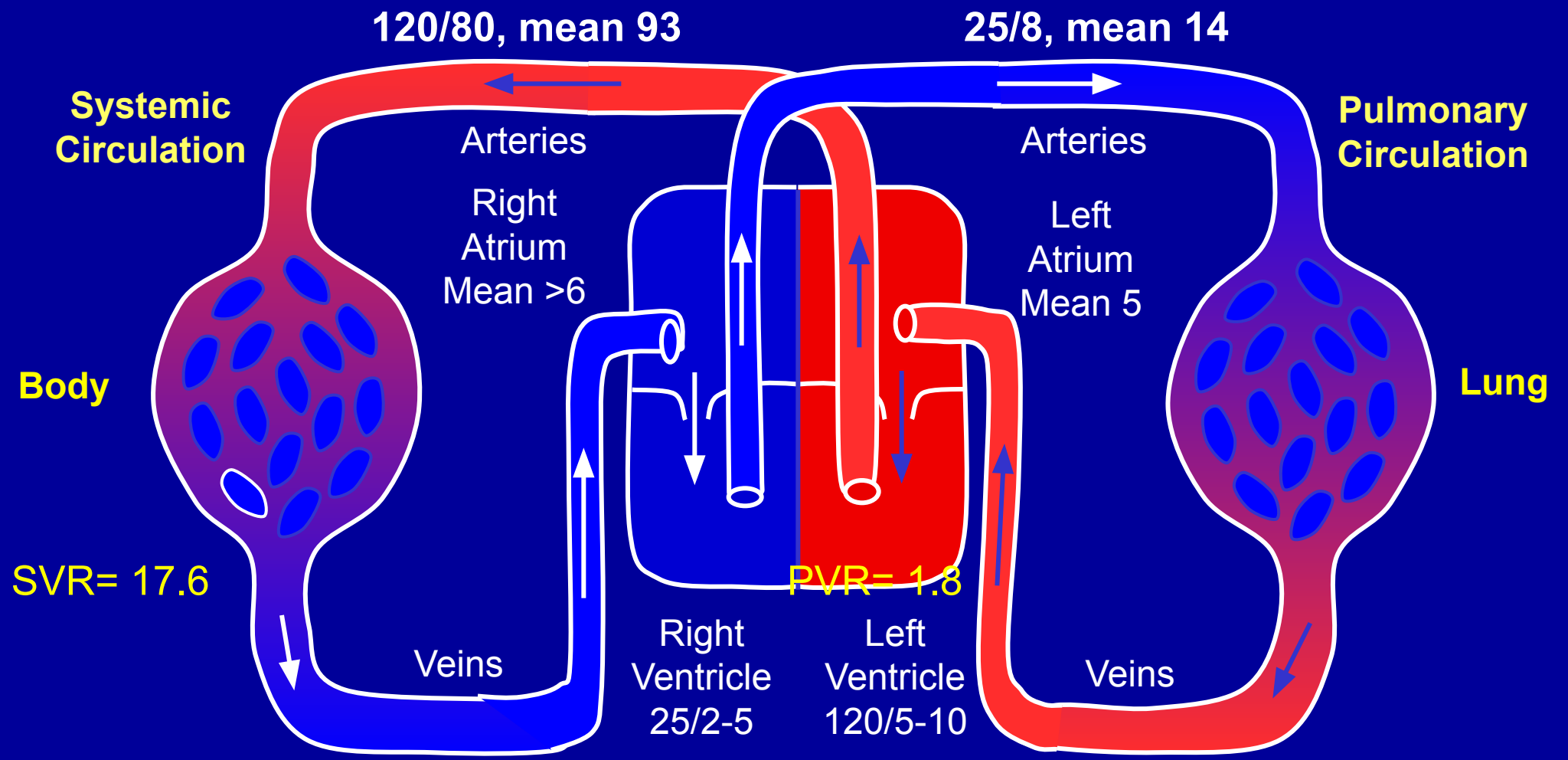
Outline

- Review classification of pulmonary hypertension (PH)
- Pulmonary arterial hypertension (PAH)
- Evaluation of PH and how to differentiate PAH from other forms of PH
- PH and cardiac, renal and hepatic transplantation
- Review PAH-approved therapy and treatment of non-Group 1 PH

Classification of Pulmonary Hypertension (PH)

- 1) Pulmonary arterial hypertension
- 2) Pulmonary hypertension due to left heart disease
- 3) Pulmonary hypertension due to lung diseases and/or hypoxia
- 4) Chronic Thromboembolic pulmonary hypertension (CTEPH)
- 5) Pulmonary Hypertension with unclear and/or multifactorial mechanism

Vascular Pressure in Systemic and Pulmonary Circulations (mm Hg)



PH- Symptoms

- DOE
- Fatigue, weakness
- Chest pain
- LE or abdominal swelling
- Syncope
- Not typical of PAH: orthopnea

TREATMENT OF PH

- Early identification and treatment PH is generally suggested because advanced disease may be less responsive to therapy .
- Treatment begins with a *baseline assessment* of disease severity, followed by primary therapy.
- *Primary therapy* is directed at the underlying cause of the PH.
- Some patients progress to *advanced therapy*, which is therapy directed at the PH itself, rather than the underlying cause of the PH.
- It includes treatment with prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, or, rarely, certain calcium channel blockers.

BASELINE ASSESSMENT

- The baseline severity assessment is essential because the response to therapy will be measured as the change from baseline.
- The functional significance of the PH is determined by measuring exercise capacity.
- From the exercise capacity, the patient's WHO functional class can be determined .
- Pulmonary artery systolic pressure and right ventricular function can be estimated by echocardiography, and then used to make a presumptive diagnosis of PH.
- Right heart catheterization must be performed to accurately measure the hemodynamic parameters and confirm that PH exists.

PRIMARY THERAPY

Primary therapy refers to treatment that is directed at the underlying cause of the PH.

Group 1 PAH

- There are no effective primary therapies for most types , advanced therapy is often needed.

Group 2 PH — Patients with group 2 PH have PH secondary to left heart diseases.

- Primary t/t of the underlying heart disease.

Group 3 PH — Patients with group 3 PH have PH secondary to various causes of hypoxemia.

- treatment of the underlying cause of hypoxemia and correction of the hypoxemia with supplement of oxygen

PRIMARY THERAPY

Group 4 PH — Patients with group 4 PH have PH due to thromboembolic occlusion .

- Anticoagulation is primary medical therapy for patients .
- Surgical thromboendarterectomy is primary surgical therapy for selected patients with thromboembolic obstruction of the proximal pulmonary arteries .
- Perioperative mortality for this procedure is less than 10 percent

Group 5 PH — Group 5 PH is uncommon and includes PH with unclear multifactorial mechanisms.

- Primary therapy is directed at the underlying cause.

GENERAL MEASURES

- All groups — Several therapies should be considered in all patients with PH. .

Diuretics —

- Diuretics are used to treat fluid retention due to PH .
- Should be administered with caution to avoid decreased cardiac output , arrhythmias induced by hypokalemia, and metabolic alkalosis.

Oxygen therapy —

- Oxygen the cornerstone of therapy in patients with group 3 PH.
- Oxygen is generally administered at 1 to 4 L/min and adjusted to maintain the oxygen saturation above 90 percent .
- Supplemental oxygen will not significantly improve the oxygen saturation of patients who have Eisenmenger physiology.

GENERAL MEASURES

Digoxin —

- Improves the right ventricular ejection fraction of patients with group 3 PH due to COPD and biventricular failure
- helps control the heart rate of patients who have SVT associated with RV dysfunction .

Anticoagulation –

- increased risk for intrapulmonary thrombosis and thromboembolism, due to sluggish pulmonary blood flow, dilated right heart chambers, venous stasis, and a sedentary lifestyle.
- indicated in patients with IPAH , hereditary PAH , drug-induced PAH , or group 4 PH.
- The anticoagulant of choice is warfarin.
- Goal of an INR of approximately 2.

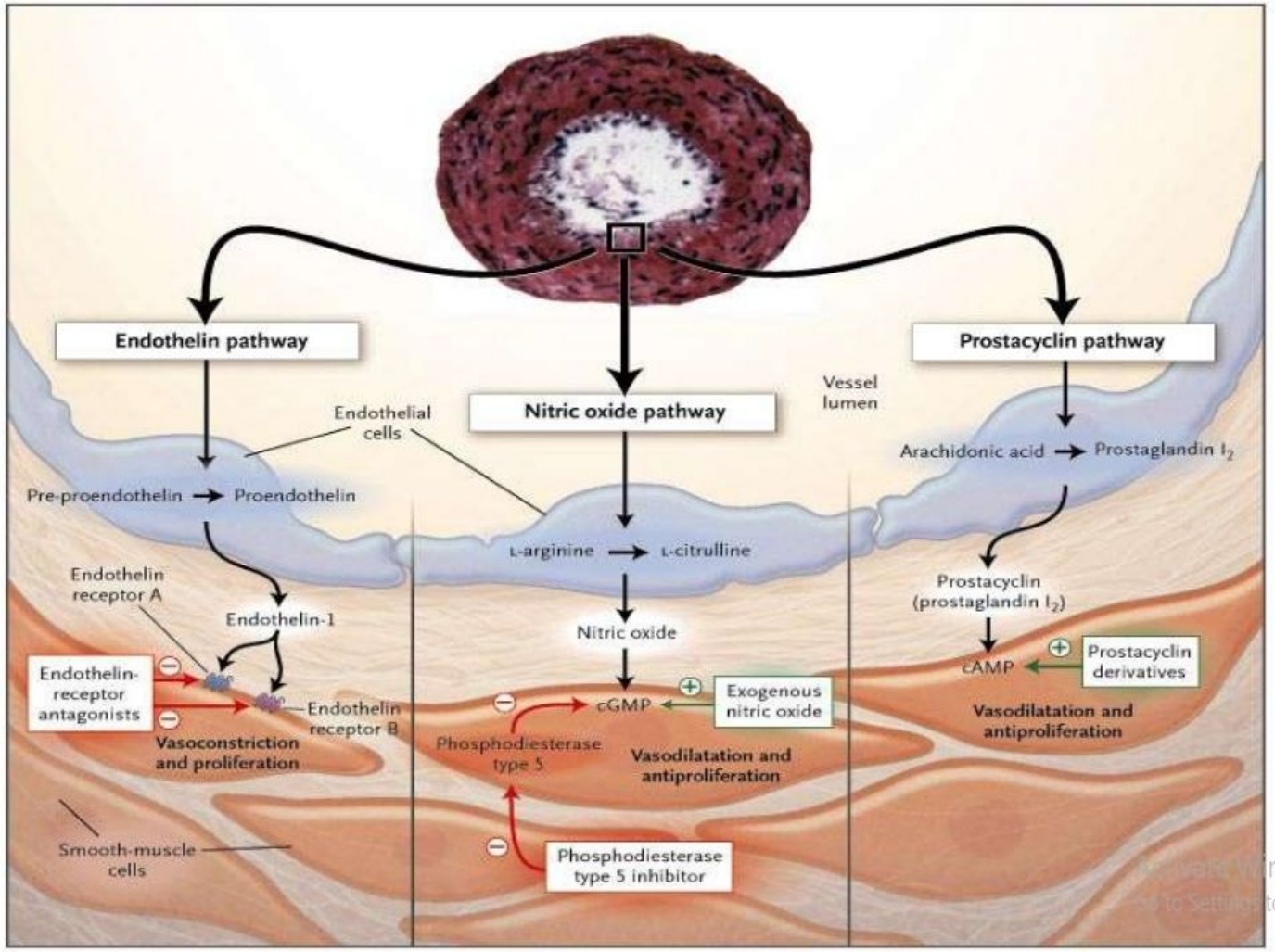
GENERAL MEASURES

- It is recommended to avoid pregnancy
- Immunization against influenza and pneumococcal infection is recommended.
- Psychosocial support should be considered in patients with PAH.
- Epidural anaesthesia instead of general anaesthesia should be utilised, if possible, for elective surgery.
- Excessive physical activity that leads to distressing symptoms is not recommended in patients.

ADVANCED THERAPY

- Advanced therapy is directed at the PH itself, rather than the underlying cause of the PH.
- It includes treatment with prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, or, rarely, certain calcium channel blockers.
- Patient selection — Advanced therapy is considered for patients who have evidence of persistent PH and a World Health Organization WHO functional class II, III.

THERAPY TARGETS FOR PAH



CALCIUM CHANNEL BLOCKERS(CCB)

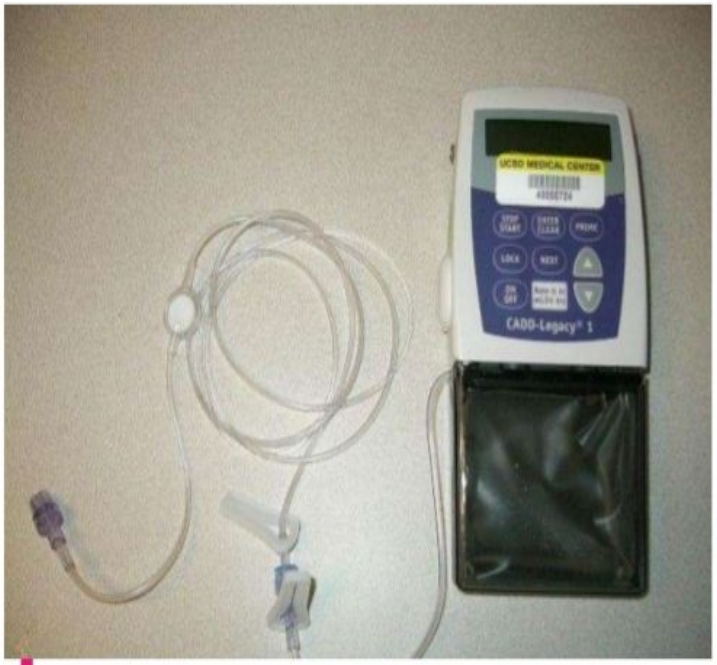
- Patient who may benefit from CCB therapy can be identified acute vasodilator response test in PAH.
- The dosages used are quite high; 90–180 mg/day for nifedipine (up to 240 mg/day) and 240–720 mg/day for diltiazem (up to 900 mg/day). or amlodipine, 20 mg/d
- <20% of patients respond to calcium channel blockers in the long term.
- Not effective in patients who are not vasoreactive.
- Patients with BMPR2 receptor mutation do not respond .
- Side effects –
  constipation, nausea, headache, rash, edema, drowsiness, dizziness, low blood pressure

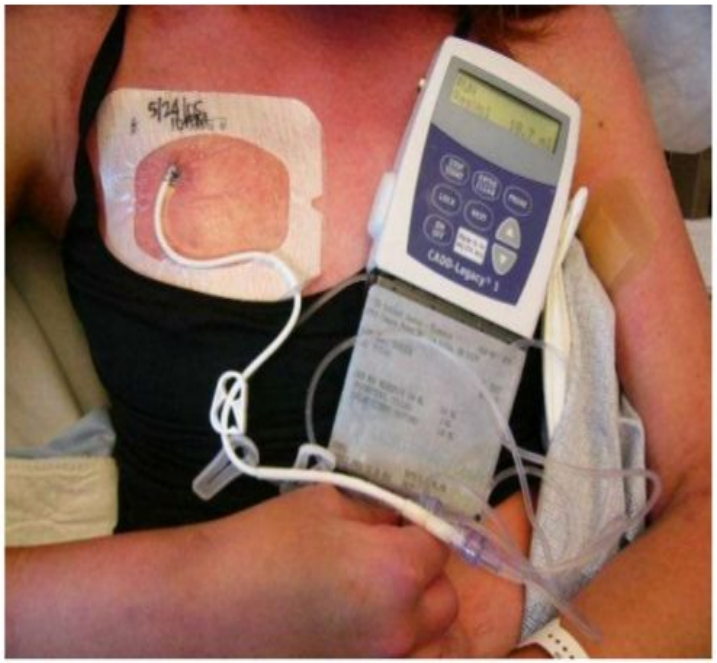
PROSTACYCLIN

- The main product of arachidonic acid in the vascular endothelium causes relaxation of smooth muscle
- Also results in inhibition of growth of smooth muscle cells.
- Intravenous prostacyclin was first introduced in the early 1980s.
- Successfully used in the treatment of PH resulting from left to right shunt, portal hypertension and HIV infection.

EPOPROSTENOL

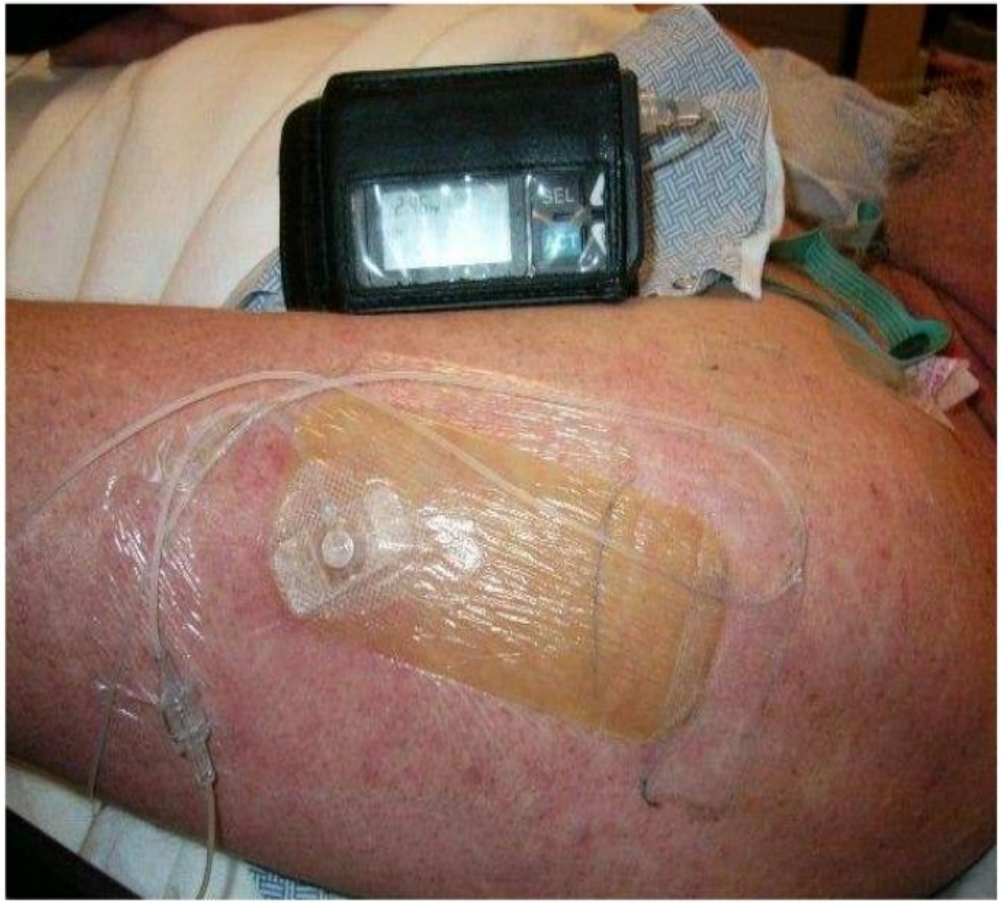
- Potent vasodilator ,Unstable at acidic pH, not taken orally.
- Very short half life,<6 min requires constant Iv administration
- Initial dose: 1 – 2 ng/kg/min
- Titrating in increments of 1- 2 ng/kg/min, based upon side effects and tolerance to reach a “plateau” between 20 – 40 ng/kg/min
- Side effects: Flushing, headache, jaw pain with first bite of food, diarrhea, nausea, erythematous rash and musculoskeletal pain.
- Chronic IV therapy: Line related infections, catheter associated venous thrombosis, thrombocytopenia
- Not available in India.





TREPROSTINIL

- Stable prostacyclin analogue.
- Can be given intravenously or subcutaneously and Inhalation.
- Half life of 3 hours.
- Stable at room temperature
- Initially 1.25 ng/kg/min up to maximum of 22.5 ng/kg/min.
- Side effects: Headache, diarrhea, nausea, rash, jaw pain, infusion site pain, erythema or induration.



ILOPROST

- Prostacyclin analogue.
- Serum half-life of 20 – 25 mins
- For functional class 3 – 4.
- Administered via nebulized aerosol.
- Administered 6 – 9 times a day, each inhalation requires 10 – 15 mins.
- Dose: 2.5 – 5 ug, median inhaled dose of 30 ug/day.
- Side effects: Cough, headache and flushing.

BERAPROST

- First chemically stable and orally active prostacyclin analogue.
- Peak concentration is reached after 30 minutes and elimination half-life is 35 – 40 minutes after oral administration.
- Median dose of 80 ug PO daily.

ENDOTHELIN RECEPTOR ANTAGONISTS

- Endothelin-1 is a potent vasoconstrictor and smooth muscle mitogen.
- High concentrations of endothelin-1 have been recorded in the lungs of patients with group 1 PAH, including scleroderma and congenital cardiac shunt lesions .
- Emerged as an initial therapy for group 1 PAH in the late 1990s.

BOSENTAN

- Nonselective endothelin receptor antagonist,
- improves hemodynamics and exercise capacity in patients with group 1 PAH.
- Orally active nonpeptide antagonist of both endothelin receptor subtypes.
- Prevents and even reverses the development of PH, pulmonary vascular remodelling and right ventricular hypertrophy.
- Initial dose of 62.5 mg bid for first 4 weeks and followed by target dose of 125 mg bid.
- Side effects: Hepatotoxicity and teratogenicity.
- Available in India.

SITAXSENTAN

- Selective ET_A antagonist
- Has oral bioavailability and a long duration of action ($t_{1/2}$, 5-7h) .
- Side effects: ↑ INR and PT .

AMBRISENTAN

- ET_A selective antagonist
- Under research

PHOSPHODIESTERASE INHIBITORS

SILDENAFIL

- Orally administered cyclic GMP phosphodiesterase 5 (PDE5) inhibitors that prolong the vasodilatory effect of NO in group 1 PAH.
- Approved dose is 20 mg t.i.d., but the durability of effect up to a up-titration beyond 20 mg t.i.d. (mainly 40–80 mg t.i.d.) is needed quite frequently.
- Contraindicated with Nitrates and nicorandil.
- Prevent rebound pulmonary vasoconstriction

Tadalafil and vardenafil also appear to improve outcomes in patients with group 1 PAH.

NITRIC OXIDE

- Inhaled form.
- Acts as direct smooth muscle relaxant via activation of the guanylate cyclase system.
- Short therapeutic half life.
- Ameliorates hypoxemia and lowers PVR by direct pulmonary vasodilatation.

SURGICAL INTERVENTIONS

Balloon Atrial Septostomy

- Allow R - L shunting to increase systemic output that
- In spite of fall in the systemic arterial oxygen saturation, will produce an increase in systemic oxygen transport.
- Shunt at the atrial level would allow decompression of the RA and RV, alleviating s/s of right heart failure.
- Considered after short term failure of maximal medical therapy.
- Severe IPAH has been the main indication other include PAH associated with surgically corrected CHD, CTD, distal CTEPH, PVOD, and pulmonary capillary haemangiomatosis.

HEART / LUNG TRANSPLANTATION

- 1 year survival of 70%.
- 5 year survival of 50%.
- Effective therapy for patients with end stage pulmonary vascular disease.

Other areas of research for treatment of PH includes

- Gene therapy
- serotonin transporter
- vasoactive intestinal peptide and tyrosine kinase inhibitors.
- Angiogenic factors and stem cells .
- Imatinib

SPECIFIC CONDTIONS ASSOCIATED WITH PH

COLLAGEN TISSUE DISEASES

- Occurs commonly with the CREST syndrome .
- Often have coexistent interstitial pulmonary fibrosis.
- Fall in diffusing capacity precede the development of PH.
- Treatment is identical to that of patients with IPAH but is less effective.
- The treatment of the PH, not affect the natural history of the underlying collagen vascular disease.
- Immunosuppressive may result in clinical improvement in patients with PAH associated with SLE or mixed CTD

CONGENITAL SYSTEMIC TO PULMONAY SHUNTS

- It is common for large post-tricuspid cardiac shunts (e.g.VSD, PDA) less common, in pre tricuspid shunts (e.g. ASD).
- 3-year survival rate of 77% compared with 35% for untreated IPAH.
- Prevalence of PAH in adult CHD, 5–10%.
- Secondary erythrocytosis is beneficial for adequate O2 transport and delivery.
- Bosentan is currently approved in Europe for WHO-FC III Eisenmenger's syndrome patients.
- Heart–lung or lung transplantation with heart surgery is an option in special cases

PORTAL HYPERTENSION

- 1–2%of patients with liver disease and portal hypertension develop PAH.
- The pathogenesis may be related to toxic substances derived from the gastrointestinal tract, due to portosystemic shunts, causing damage to the lung endothelium.
- Another possibility is high CO state is inducing PAH.
- Epoprostenol,bosentan, and sildenafil may exert beneficial haemodynamic and clinical effects in patients.
- Anticoagulation is not recommended
- Significant PAH is a contraindication to liver transplantation if mean PAP is 35 mmHg

LV DIASTOLIC DYSFUCTION

- PH as a result of LV diastolic failure is common but often unrecognized .
- It can occur with or without LV systolic failure.
- The most common risk factors are hypertensive heart disease; coronary artery disease; and impaired LV compliance related to age, diabetes, obesity, and hypoxemia.
- Symptoms of orthopnea and paroxysmal nocturnal dyspnea are prominent.
- Many patients improve considerably if LV end-diastolic pressure is lowered.

MITRAL VALVE DISEASE

- Mitral stenosis and mitral regurgitation represent important causes of PH from reactive pulmonary vasoconstriction resulting in marked elevations in PAP.
- In patients with MS, corrective surgery predictably results in a reduction in PAP and PVR.
- Patients with MR, however, may not have as dramatic a response to surgery because of persistent elevations in LV end-diastolic pressure.

CHRONIC OBSTRUCTIVE LUNG DISEASE(COPD)

- COPD associated with mild PH in the advanced stages .
- Incidence of PH in COPD with at least one previous hospitalization for exacerbation is 20%.
- In advanced COPD, PH is highly prevalent 50% .
- Echocardiography is recommended as a screening .
- Continuous oxygen therapy relieves the pulmonary vasoconstriction, reverses chronic ischemia and improves survival.
- Long-term oxygen therapy is indicated if the resting arterial Po_2 remains <55 mmHg.
- vasodilators can worsen gas exchange and not used.

INTERSTITIAL LUNG DISEASE

- PH in interstitial lung disease that results from parenchymal and vascular remodelling .
- The prevalence of PH is between 32 and 39%.
- Coexisting hypoxemia occurs frequently and contributes to morbidity.
- ILD often associated with the collagen vascular diseases.
- Many patients have pulmonary fibrosis of unknown etiology.
- The pulmonary vasodilators approved for PAH have not been shown to be helpful.

THROMBOEMBOLIC DISEASES

- Most patients treated for acute PTE with IV heparin and oral warfarin do not develop chronic PH.
- Pulmonary thromboendarterectomy is an established surgical treatment in patients whose thrombi are accessible .
- Lifelong anticoagulation using warfarin is mandatory
- Target INR 2.0 .

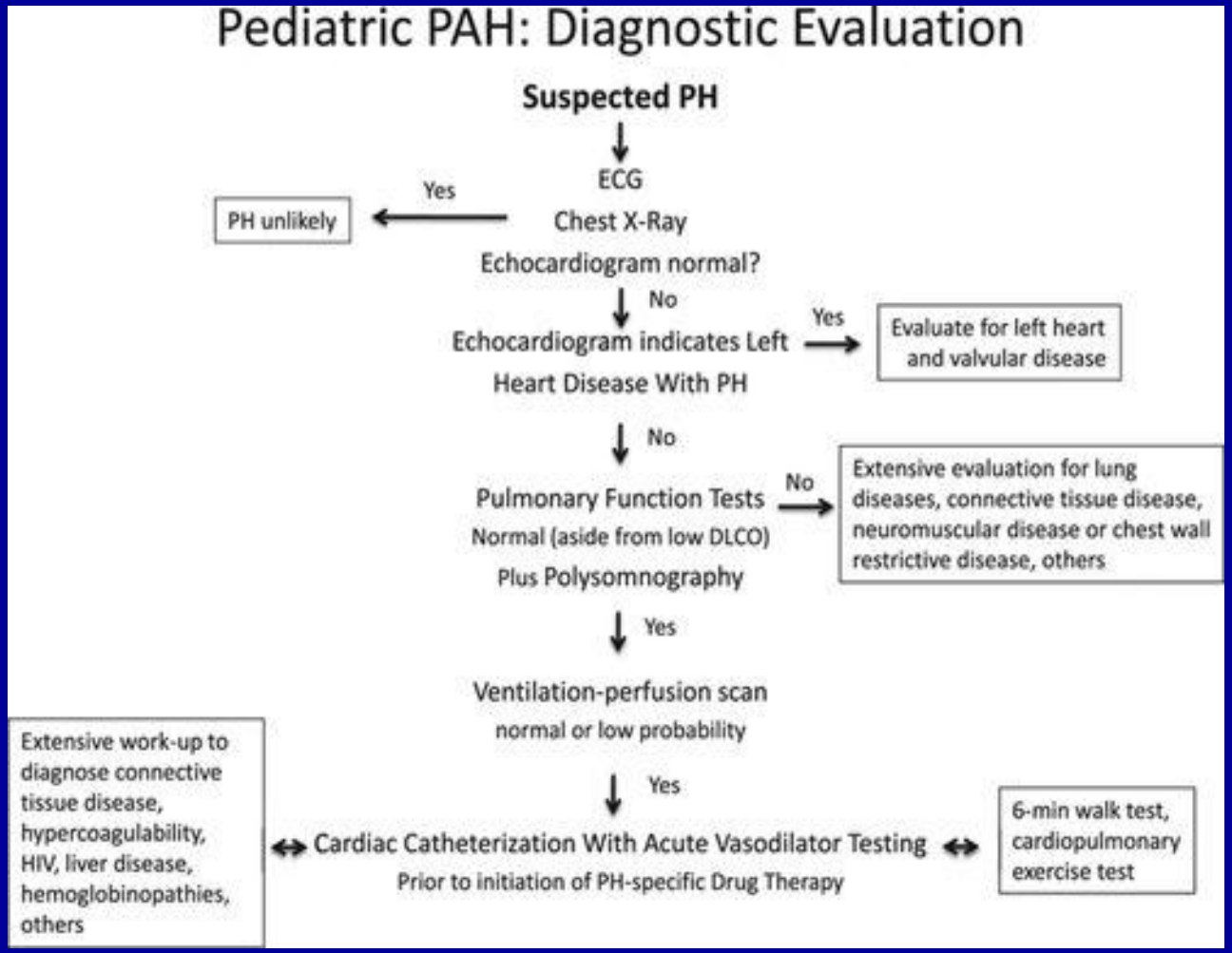
SICKLE CELL DISEASE

- The etiology is multifactorial, including hemolysis, hypoxemia, thromboembolism, chronic high cardiac output, and chronic liver disease.
- Intravascular hemolysis leading to NO deficiency is hypothesized as a major pathogenetic mechanism for PAH in SCD.
- Prevalance 32 and mortality is 40% in 45 month gldwin etal
- Intensification of SCD–specific therapy appears to reduce the morbidity.

HIV INFECTION

- Pathogenesis of HIV-related PAH remains unclear
- Incidence is estimated at 1 per 200 cases.
- Treatment is less well established in comparison with other forms of PAH.
- Epoprostenol, inhaled iloprost may improve exercise tolerance, haemodynamics and symptoms
- 3-year survival rate as low as 21% in the most advanced cases (WHO-FC III/IV)

Algorithm illustrating general diagnostic workup for pediatric pulmonary arterial hypertension



Classification of PAH, Group 1

- Idiopathic PAH (formerly primary pulmonary hypertension, PPH)
- Heritable

  Drug/toxin induced
- Associated with:
  - Connective tissue diseases
  - HIV infection
  - Portal hypertension
  - Systemic to pulmonary shunts
  - Schistosomiasis
  - Chronic hemolytic anemia

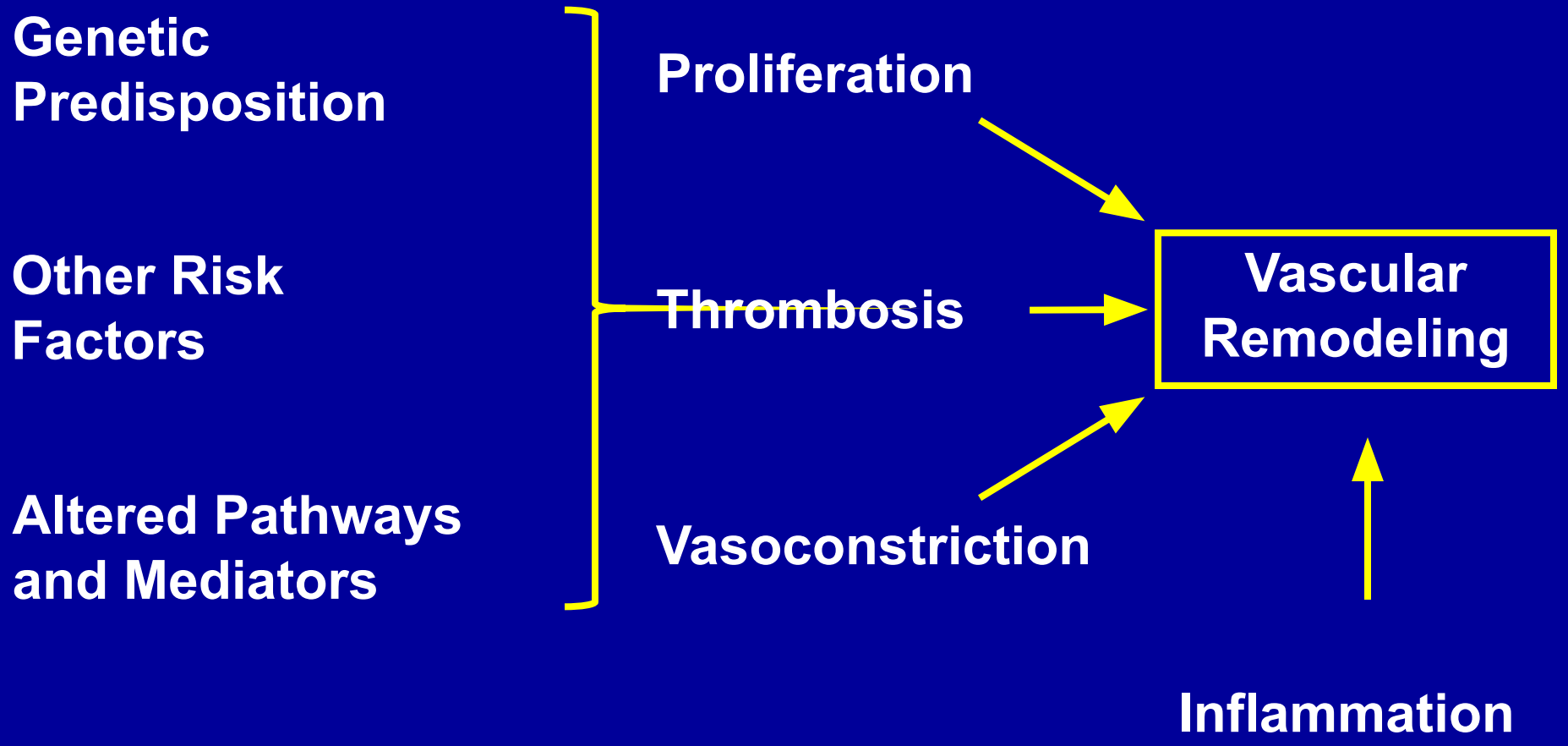
Group 2 PH

- Pulmonary hypertension owing to left heart disease
  - Systolic dysfunction
  - Diastolic dysfunction
  - Valvular disease
  - Pulmonary venous obstruction

PH with unclear or multifactorial mechanisms: Group 5

1. Hematologic disorders
2. Systemic disorders: vasculitis
3. Metabolic disorders
4. **Others: chronic renal failure on dialysis**

Pathogenesis : An Integrated View



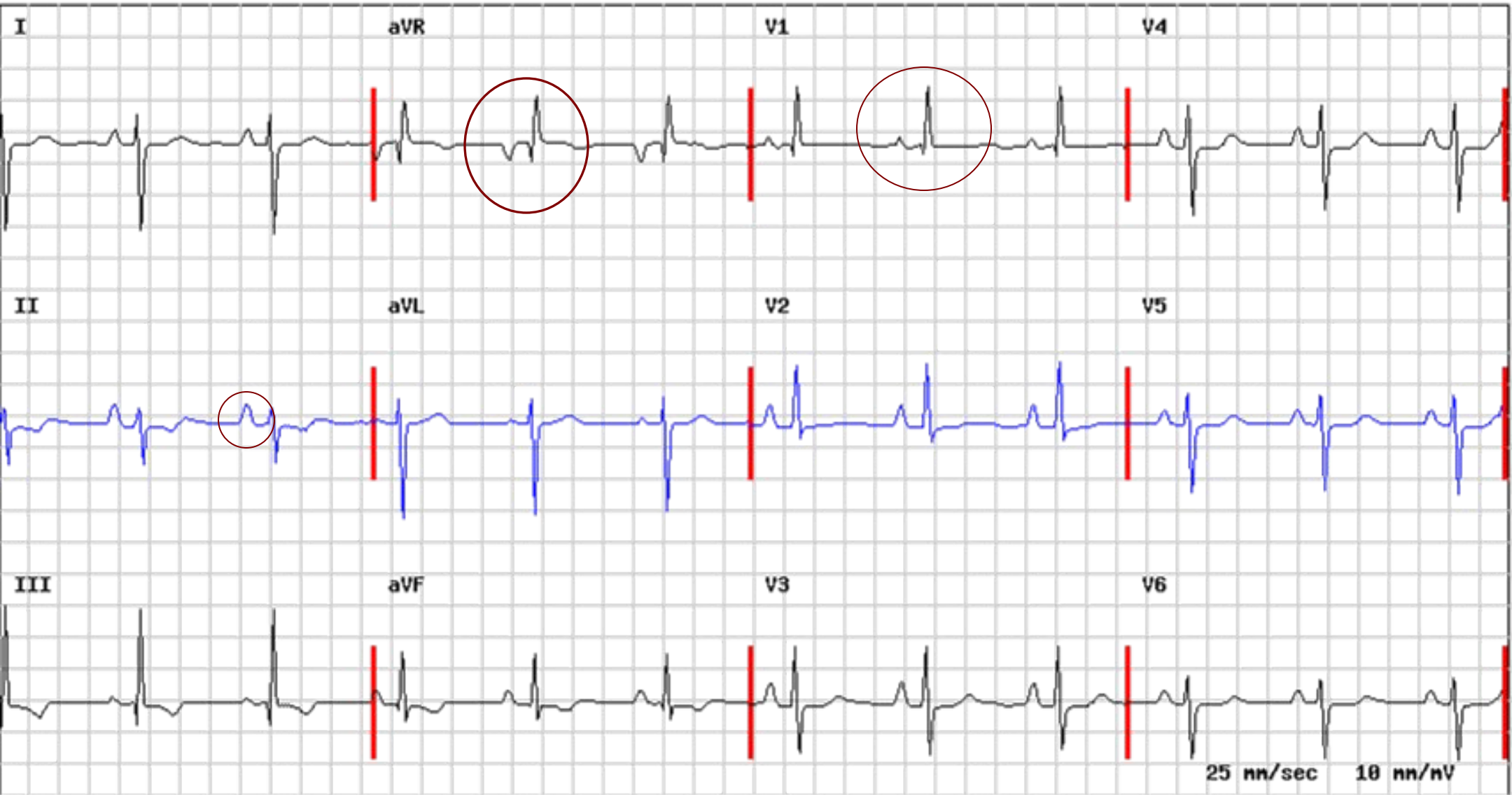
Evaluation for PH

- ECG
- Chest x-ray
- V/Q scan or contrasted spiral CT (+/- angiogram)
- PFTs
- Exercise oximetry
- Echocardiogram
- Right heart catheterization w/vasodilator testing
- Labs: CBC, CMP, INR, ANA, HIV, TFTs

ECG Impression: Normal sinus rhythm, rate 67. Right axis deviation. Right atrial enlargement. RVH with ST-T abnormalities

PR Interval: 189	QT Interval: 413	Axes: P: 40		ST: -56
QRS Duration: 85	QT Interval Corrected: 436		MEAN QRS: 156	T: -32

ECG Severity: - ABNORMAL ECG -



PH - Radiographic studies

- CXR:

  -large proximal PA with peripheral tapering (pruning)

  -cardiomegaly due to enlarged RA, RV

  -pleural effusion is uncommon

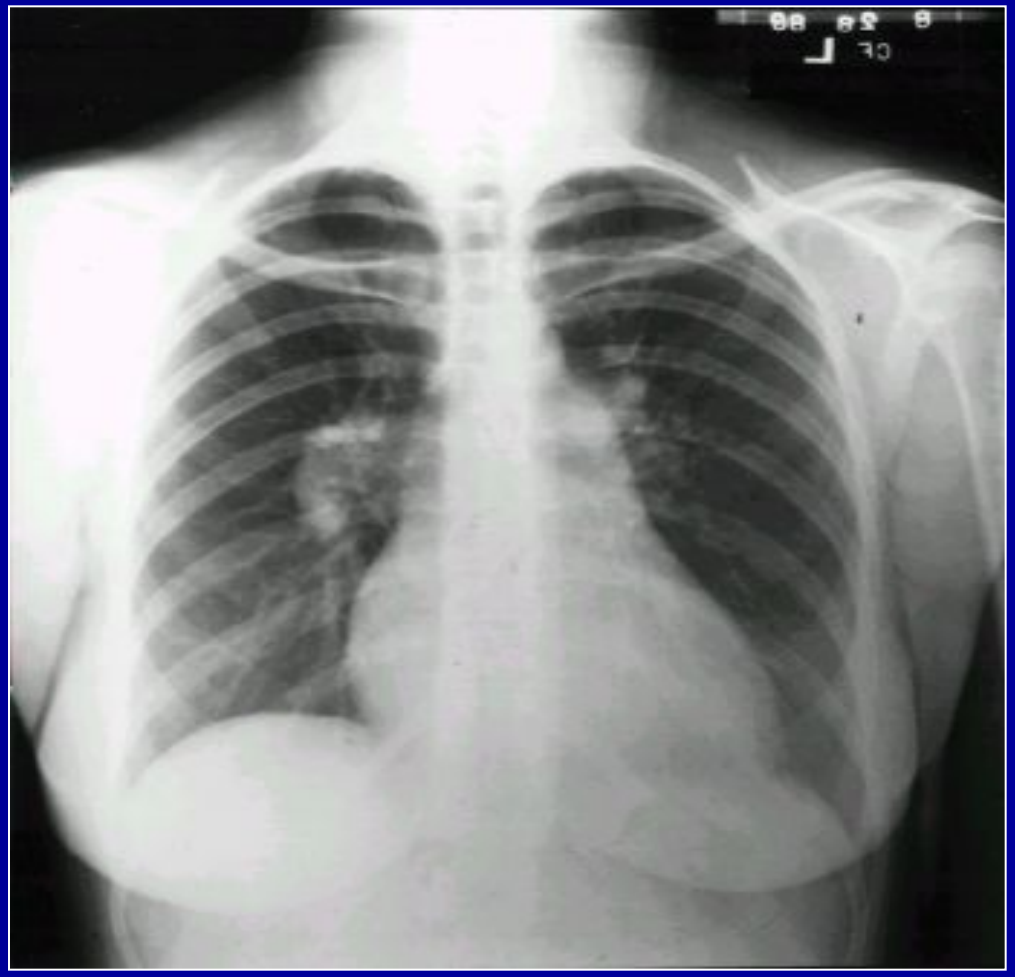
- CT:

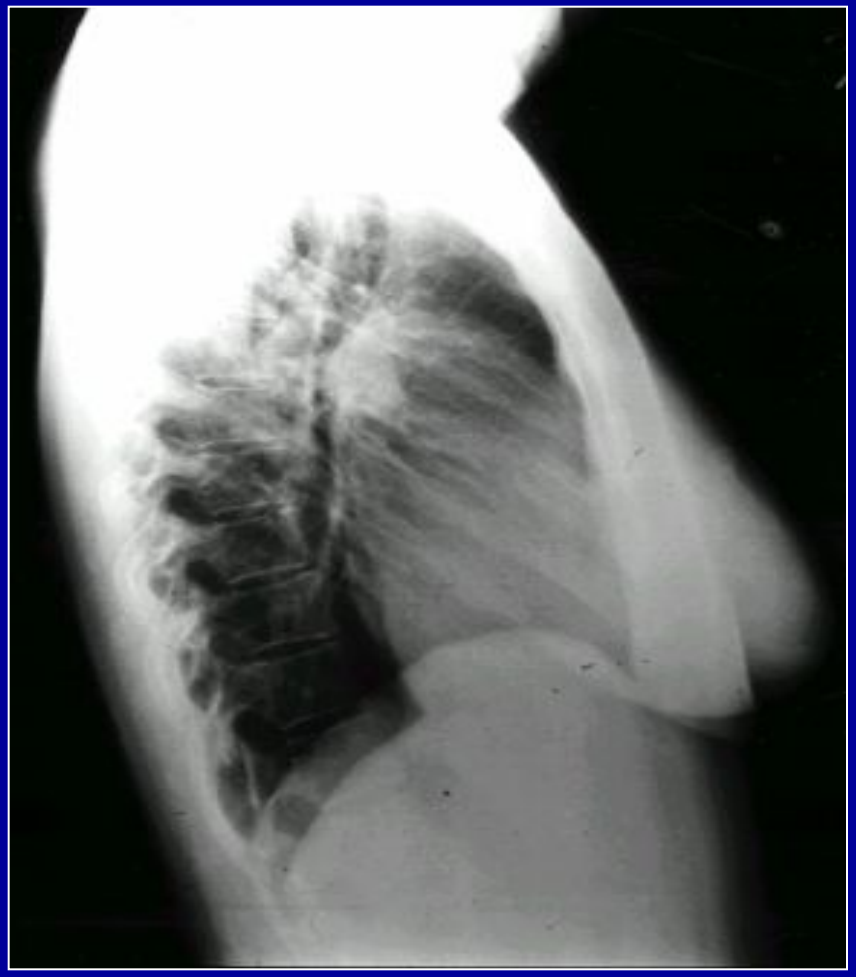
  -PA >aorta

  -cardiomegaly, enlarged RV

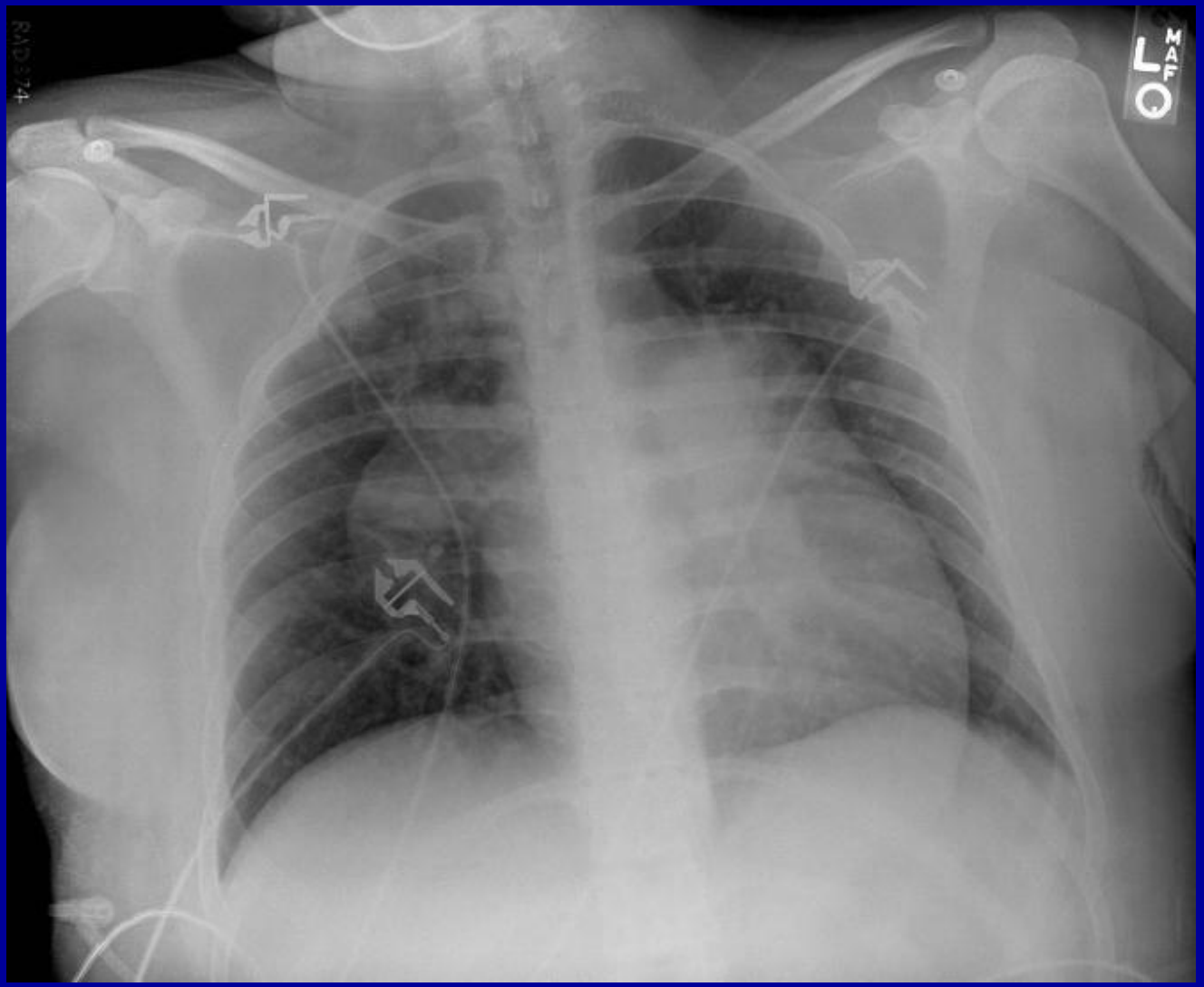
  -pericardial effusion

CXR in PAH

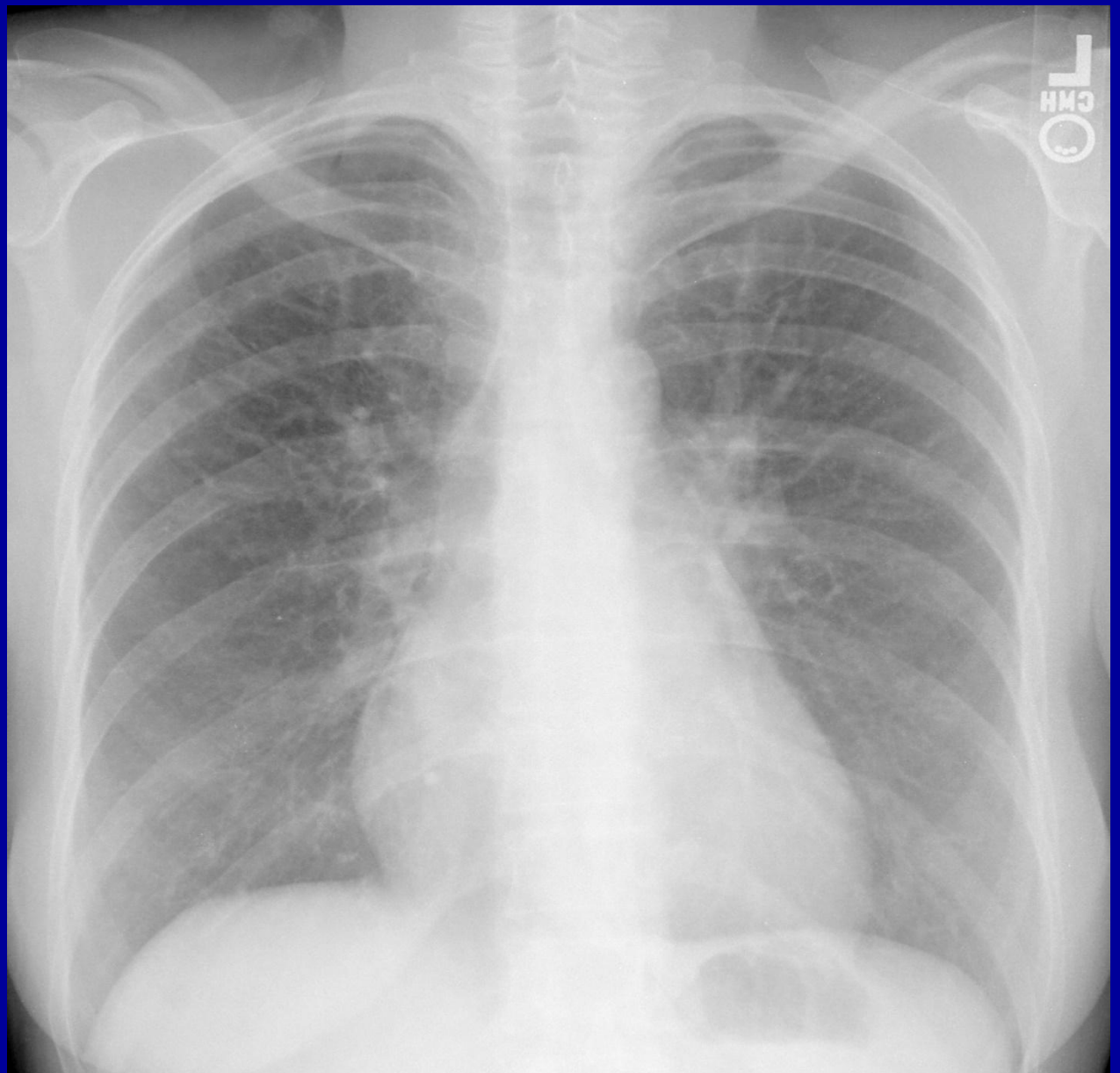




CXR in Eisenmenger Syndrome

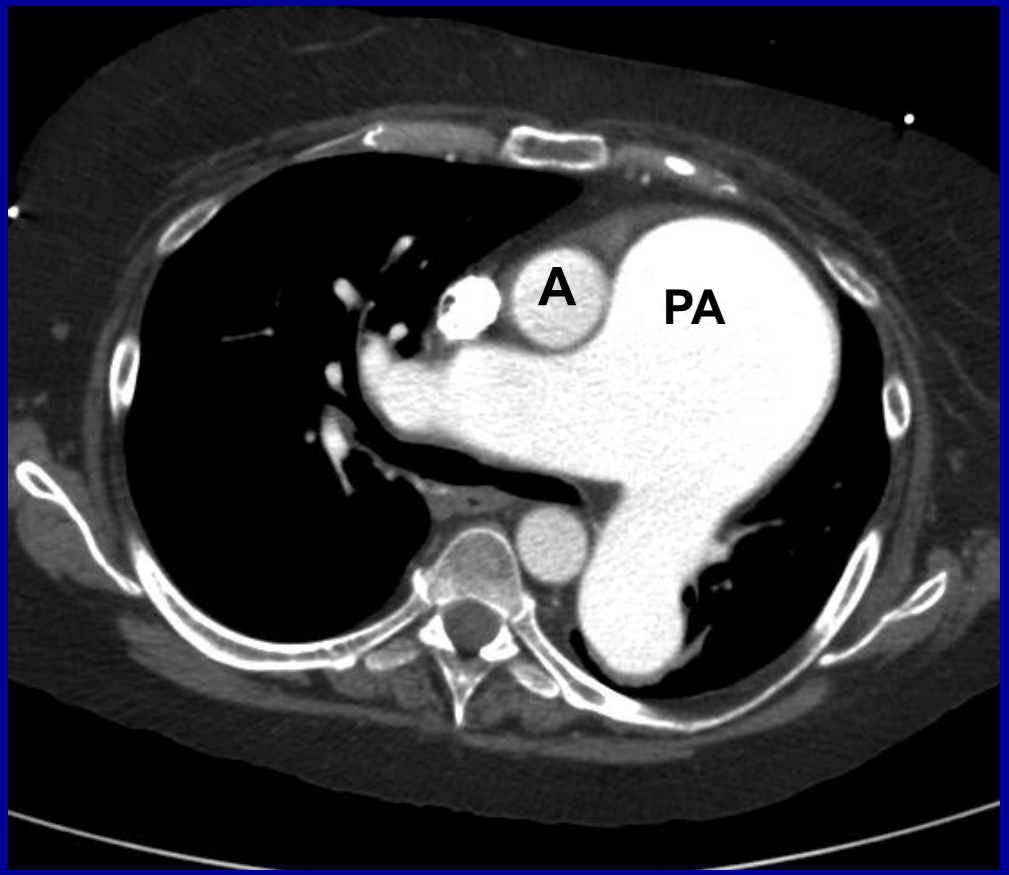


Mitral Stenosis

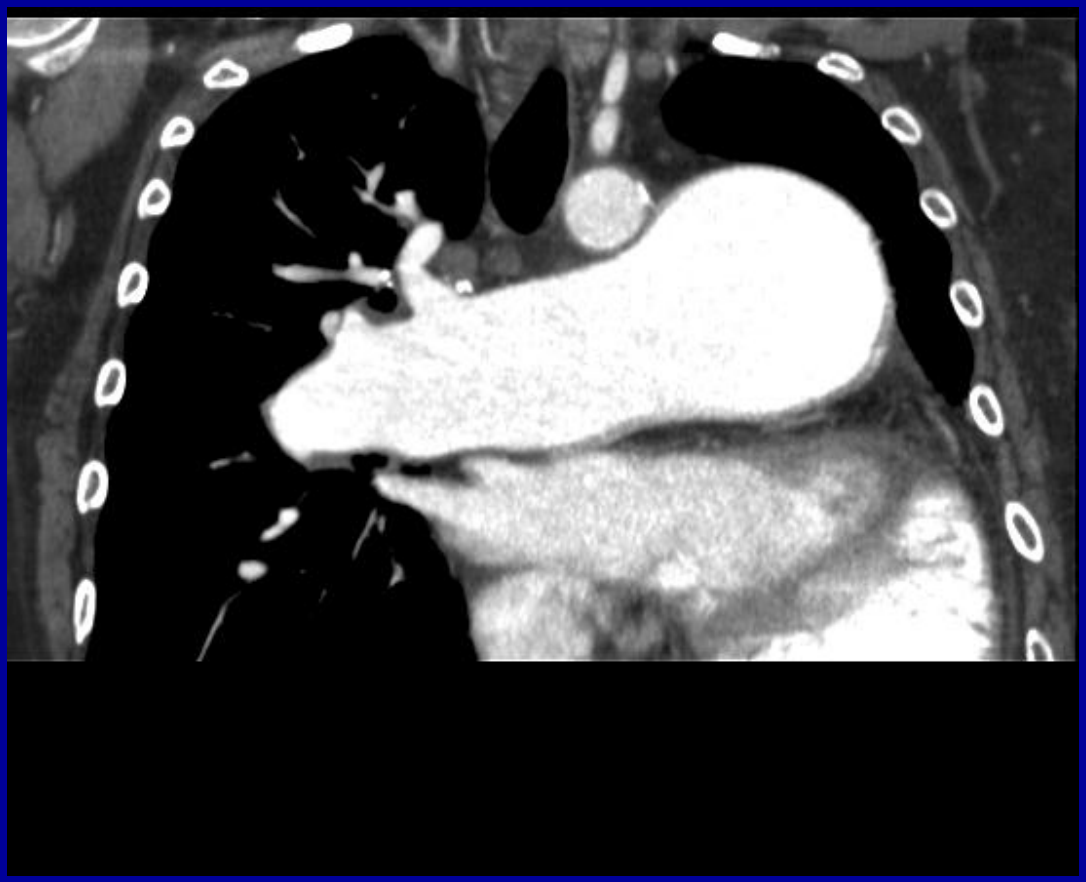


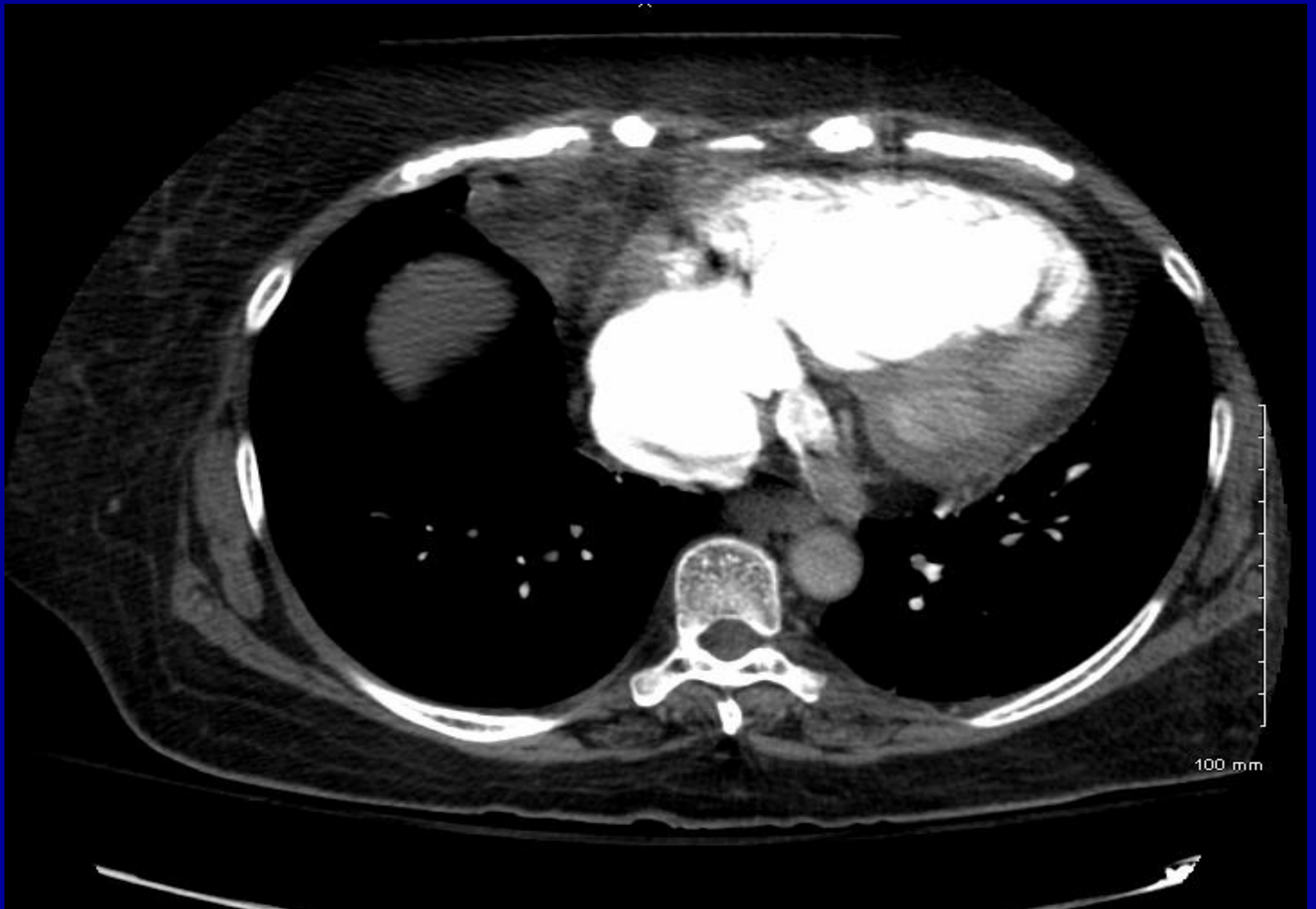
Enlarged main PA on CT

Standard view



Coronal view

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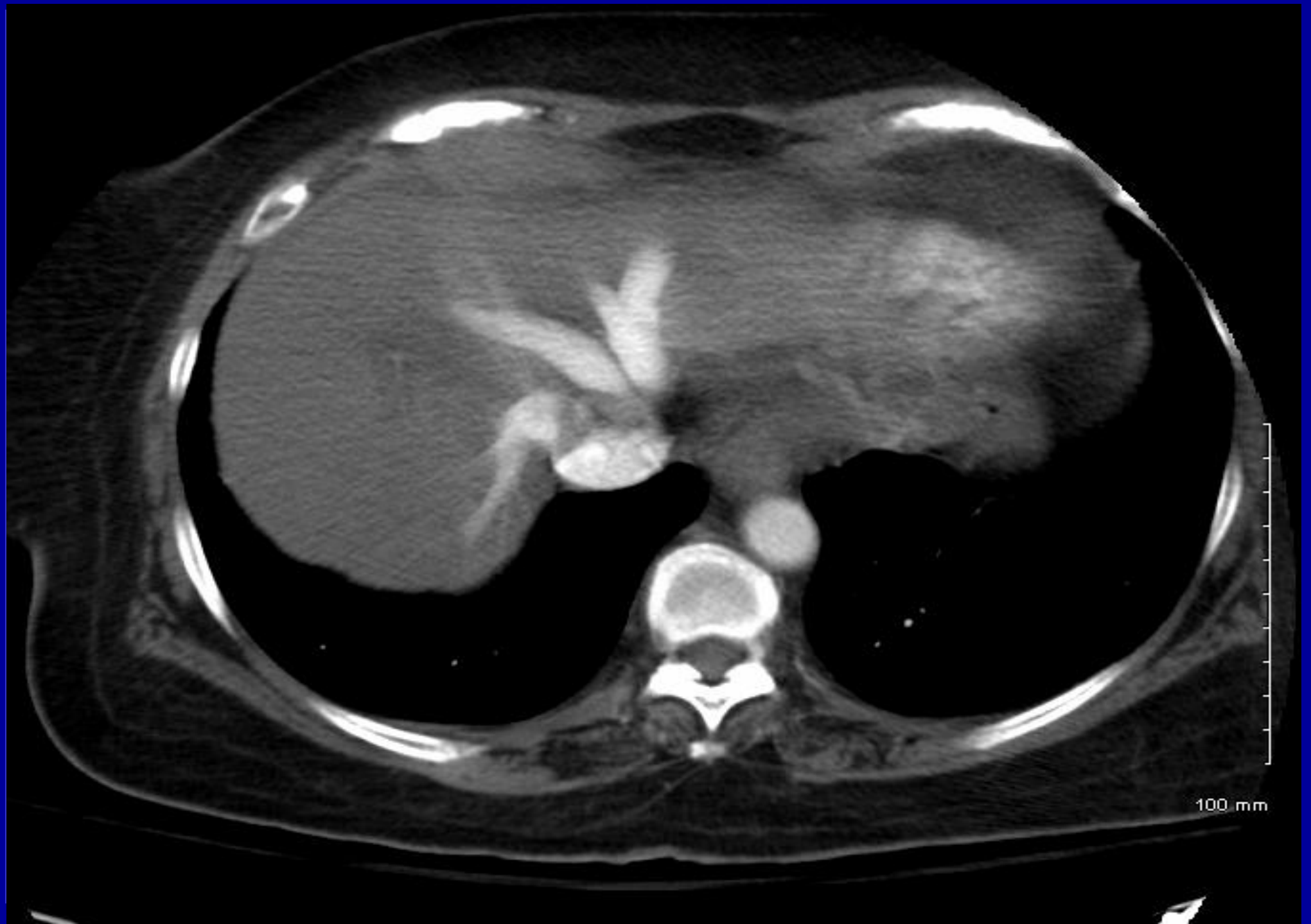
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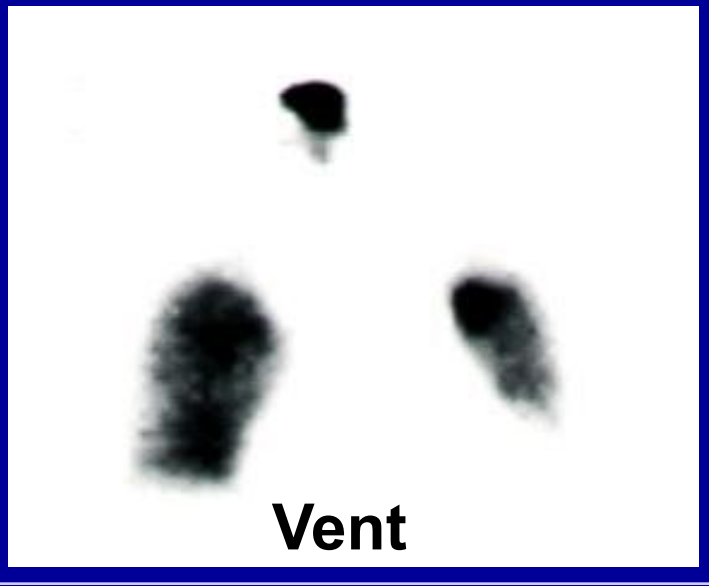
Ventilation Perfusion Lung Scan

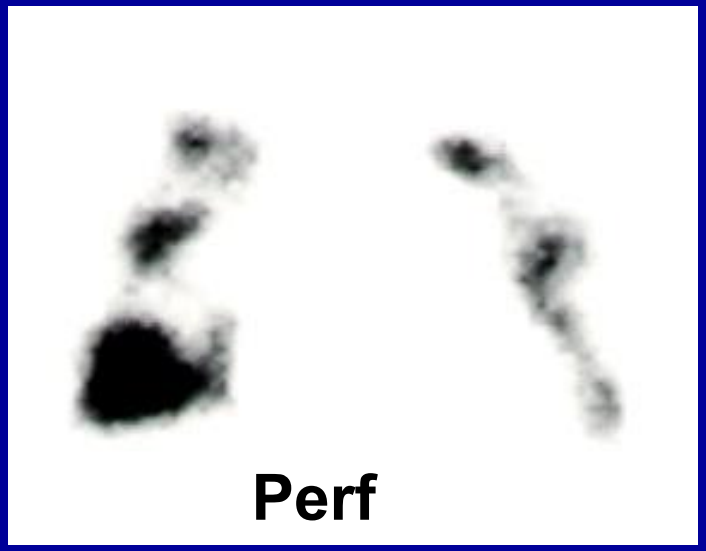
PAH

Perf



Vent

CTEPH



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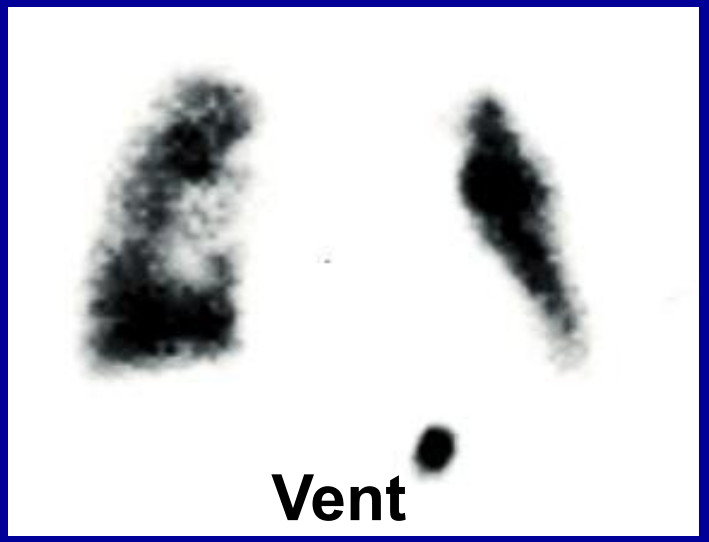
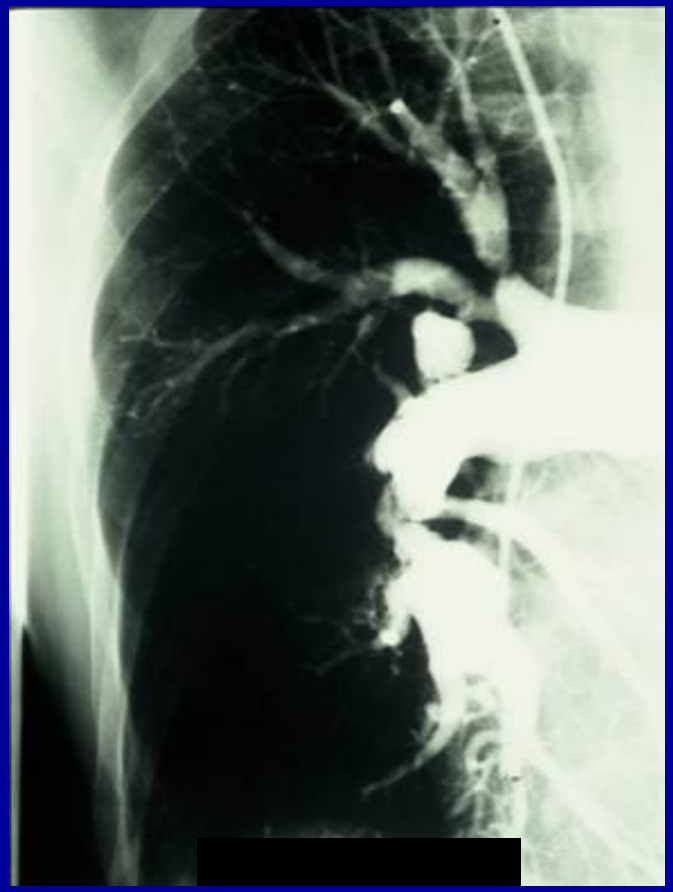


Vent

CTEPH: Pulmonary Angiography



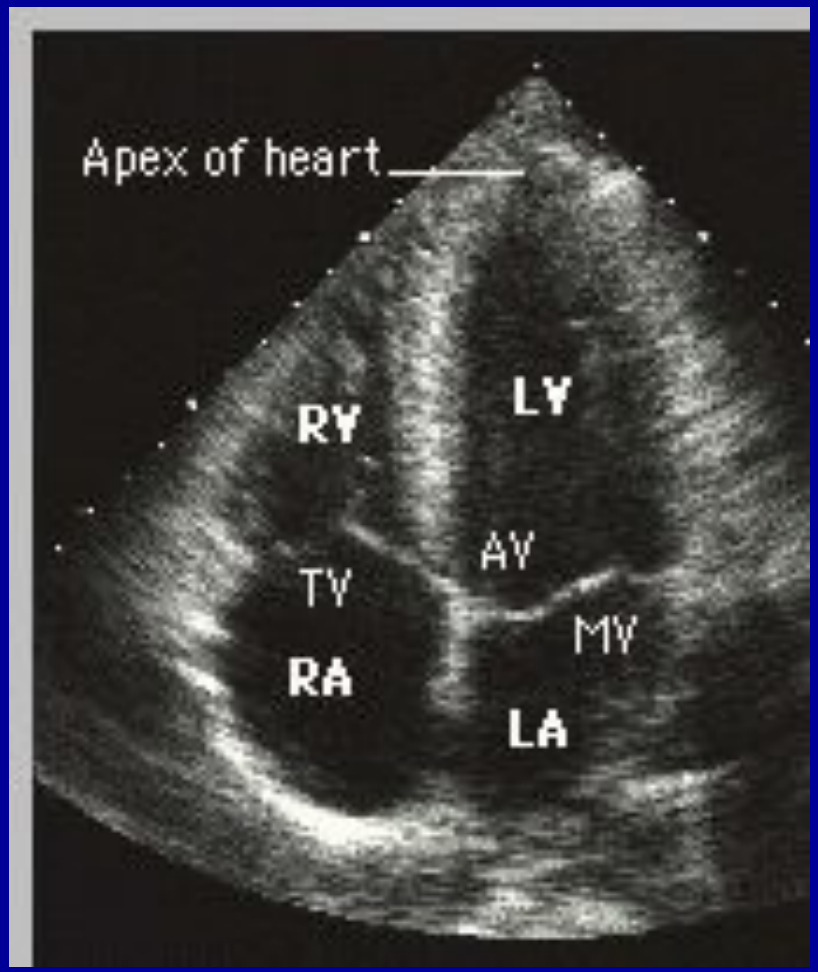
- Confirms diagnosis of CTEPH in patients with PH
- Assess thrombus accessibility
- Distinct angiographic patterns
  - "Web" narrowing
  - Poststenotic dilatation
  - Proximal occlusion
  - "Pouch" defects

Organized Clot Removed at Surgery

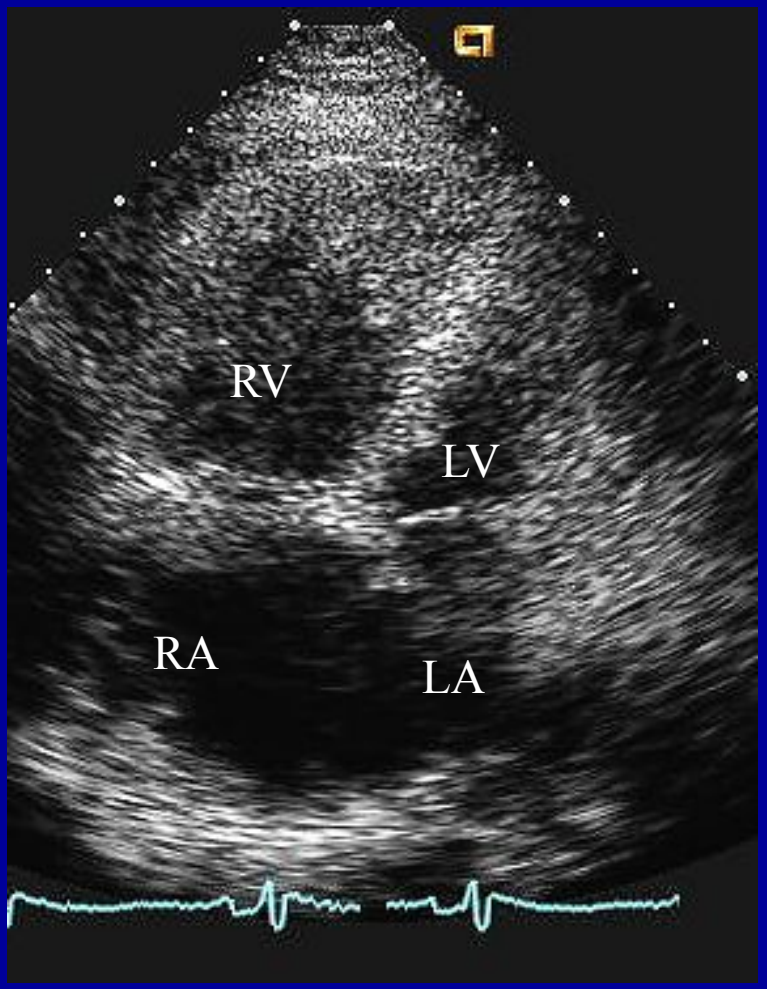
Pulmonary Function tests

- No characteristic changes
- Mandatory to screen for significant restrictive or obstructive lung disease
- Diffusing capacity often significantly reduced in patients with scleroderma (<50%)

RV, RA Enlargement on Echocardiogram



Normal



PH

Other Helpful Diagnostic Tests
(Determined by patient's history)

- High resolution chest CT
- Cardiopulmonary exercise study
- Polysomnography
- Arterial blood Gas
- Hepatitis serologies
- Left heart catheterization, evaluation of coronary arteries

Echocardiographic findings in ESRD patients undergoing transplant

Echocardiographic Data	Patients With PHT (*n* = 85)	Patients Without PHT (*n* = 415)	*P* Value
LV, diastole (cm)	4.9 ± 0.5	4.7 ± 2.0	.3
LV, systole (cm)	3.2 ± 0.5	3.1 ± 0.5	.8
Right ventricle (cm)	3.3 ± 0.5	3.2 ± 0.4	.8
Left atrium (cm)	**4.0 ± 0.7**	**3.5 ± 0.6**	**<.0001**
Right atrium (cm)	3.7 ± 0.5	3.3 ± 0.4	<.0001
Diastolic dysfunction (%)	18.8	21.4	.6
Systolic dysfunction (%)	**22.4**	**13.5**	**.04**
LV ejection fraction (%)	49.7 ± 7.9	52.3 ± 6.9	.002
LV hypertrophy (%)	**78.8**	**59.8**	**.001**

Treatment of non PAH-pulmonary hypertension

- Pulmonary Venous Hypertension:
- Treat heart failure with afterload reduction
  - Systolic or diastolic
- MV or AV disease
  - Replace the valve
- Pulmonary vein stenosis
  - Pulmonary vein stenting

Treatment of non PAH-pulmonary hypertension

- PH associated with disorders of the respiratory system and/or hypoxemia:
  - Rx of hypoxemia is often the main therapy

- PH due to chronic thromboembolic disease:
  - Thromboendarterectomy for proximal disease
  - Can consider PAH therapy for distal disease

Adjunctive treatments of PAH

- Anticoagulation
- Diuretics
- Digoxin
- Oxygen
- Calcium channel blockers
- Exercise
- Salt restriction

Specific PAH Treatment

- Epoprostenol (generic and Flolan®)
- Treprostinil (Remodulin®)
- Iloprost (Ventavis®)

Prostaglandins

- Bosentan (Tracleer®)
- Ambrisentan (Letairis®)

Endothelin receptor antagonists (ERAs)

- Tadalifil (Adcirca®)
- Sildenafil (Revatio®)

Phosphodiesterase 5 inhibitors (PDE5 inhibitors)

PAH Determinants of Risk

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	WHO class	IV
Longer (>400 m)	6MWD	Shorter (<300 m)
Minimally elevated	BNP	Very elevated
Minimal RV dysfunction	Echocardiographic findings	Pericardial effusion, significant RV dysfunction
Normal/near normal RAP and CI	Hemodynamics	High RAP, low CI

Take Home Points

- PH can not be diagnosed by Echo alone, need a thorough evaluation for all patients
- Right heart catheterization is necessary in ALL patients to accurately diagnose PH
- PAH is a progressive disease, even with Rx
- Make sure the patient has PAH before treating
- Despite multiple therapies, lung transplantation is the only curative treatment for PAH
- PH negatively impacts outcome of all solid organ transplants


Thank
You