Pulmonary Arterial Hypertension

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Pulmonary Arterial Hypertension

- I have no conflicts of interest relevant to this presentation

Admission: 10/12/18

- 60yo F with PMH of sarcoidosis (diagnosed by bx in 2002) chronic respiratory failure on 3L O2 and HFpEF (EF 50% in 8/25/18) was transferred from Banner Estrella.

- Pt was noted to be dyspneic the past week, with worsening dyspnea and lethargy x1 day, + chest pain, cough, dizziness and significant weight gain, swelling of extremity and abdomen, and nausea.

- At baseline, pt is able to walk but sits in a chair most days, can do some ADLs, but very limited by dyspnea.
-
- Of note, pt had multiple hospital admissions with similar presentations x 3 past year, last discharged 10/9/18

Hospital Course:

- EMS reported pt to be tachycardic and hypoxic to 80% on 3L O2, and was placed on non-rebreather with 94% saturation.
- BP 80/50. CTA no PE

- Physical exam was significant for JVD, rhonchi, 3+ LE pitting edema, and bilateral LE ulcers.

- Labs:
- Wbc: 18.9, BUN/Cr 67/1.4 (baseline 0.8-1),
- Trop 0.6, proBNP 1144
- ALT 253, AST 271, ALP 124,
- lactic acid 2.7-> 4.6.
- ABG 7.15/75/162/26 on 50% FiO2..

Imaging:

- Echocardiogram:
- LVEF 70%, severe RA/RV enlargement with severe septal flattening, hypokinetic RV, moderate TR, RVSP 117mmHg, dilated IVC.

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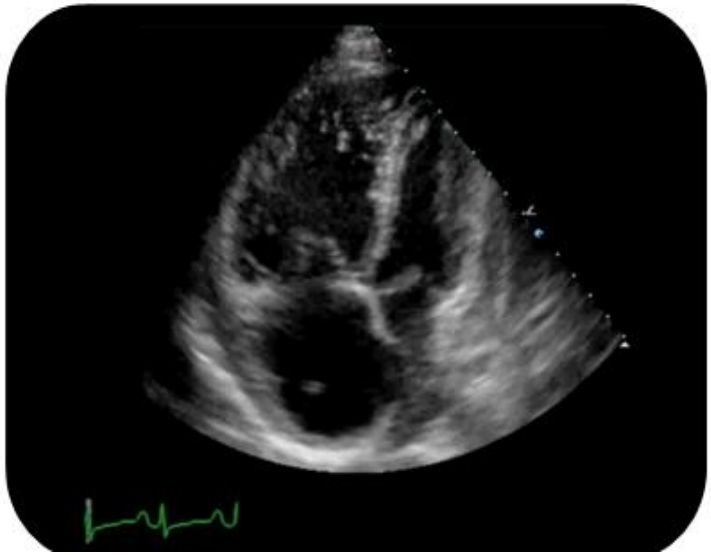


Clinical Course

- Labs:
- Wbc: 18.9, BUN/Cr 67/1.4 (baseline 0.8-1),
- Trop 0.6, proBNP 1144
- ALT 253, AST 271, ALP 124,
- lactic acid 2.7-> 4.6.
- ABG 7.15/75/162/26 on 50% FiO2..

- Intubated at 4am:
- NE: 20mcg/kg/min
- CVP 22
- BP 90/60

History and Patient Presentation

- Age: 41
- Gender: female
- Ethnicity: Caucasian
- Attorney, Married, Non smoker, neg etoh, neg drugs, no children

- Morbidly obese – in Feb 2008 (over 400 lbs), started exercise program, but by july had increase in diffuse body swelling – outside MD dx lymphedema.

- Consulted bariatric surgeon (8/2008) had echo which showed increased RVSP (84) Normal LV size and fxn. RV severely dilated. Bilateral lower extremity dopplers and dobutamine stress test were negative.

History and Patient Presentation

- Afib in late sept 08 and hospitalized until sometime in October. Started on Amiodarone, Aggressively diuresed with lasix and developed renal insuff. Echo at this time showed RVSP of 70, RV severely dilated concentric LVH, EF 60%

- Despite above PA pressures she underwent an attempted laproscopic Gastric Sleeve surgery. Discontinued after Trocars placed into abd cavity resulted in large amts of ascites.

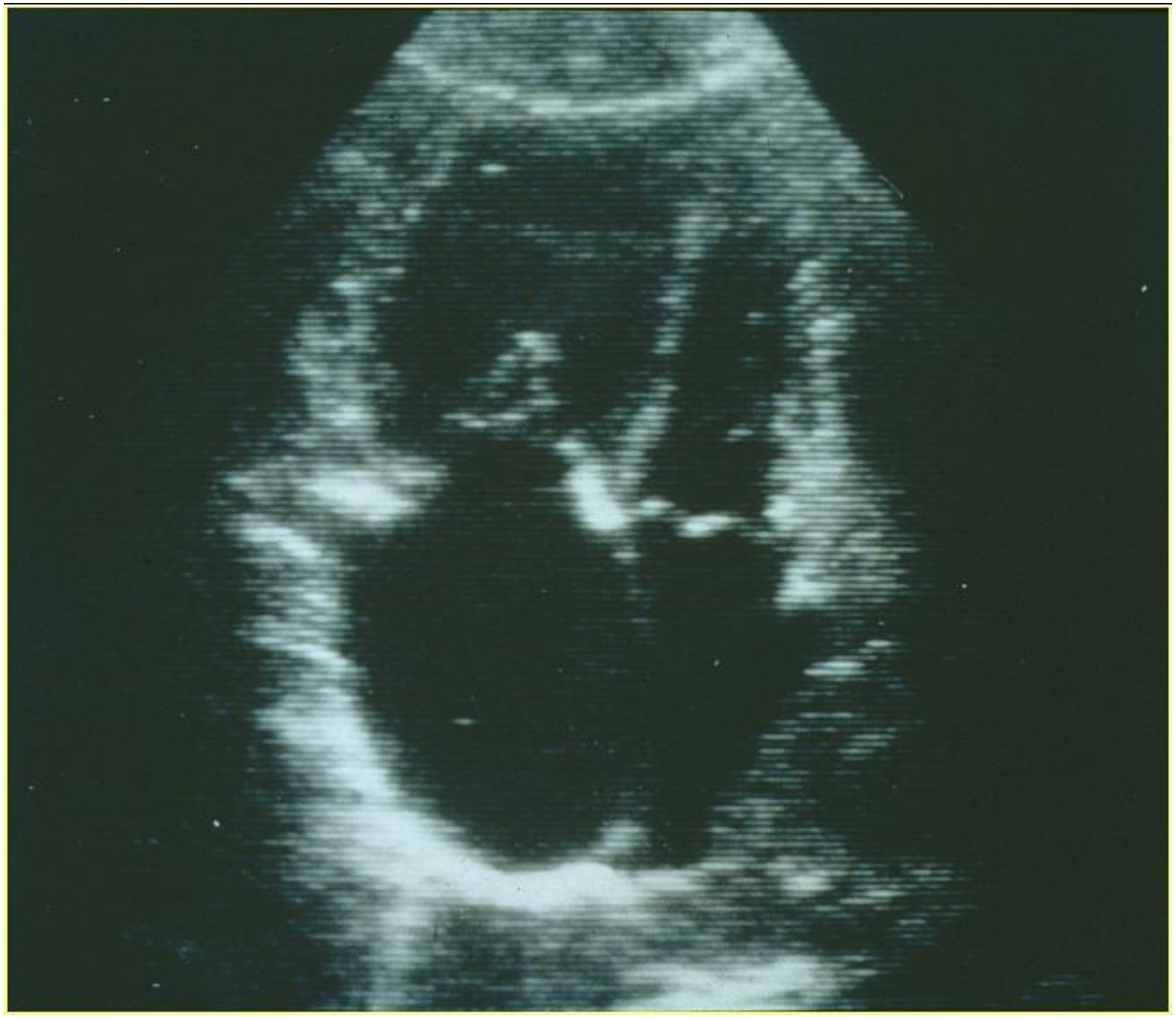
- Liver bx showed "cirrhosis".
- Long hospitalization due to non healing abdominal incision and d/c'd 12/09

- Transferred for higher level of care due to 80lb weight gain in 6 months, worsening dyspnea.

Physical Exam & Labs

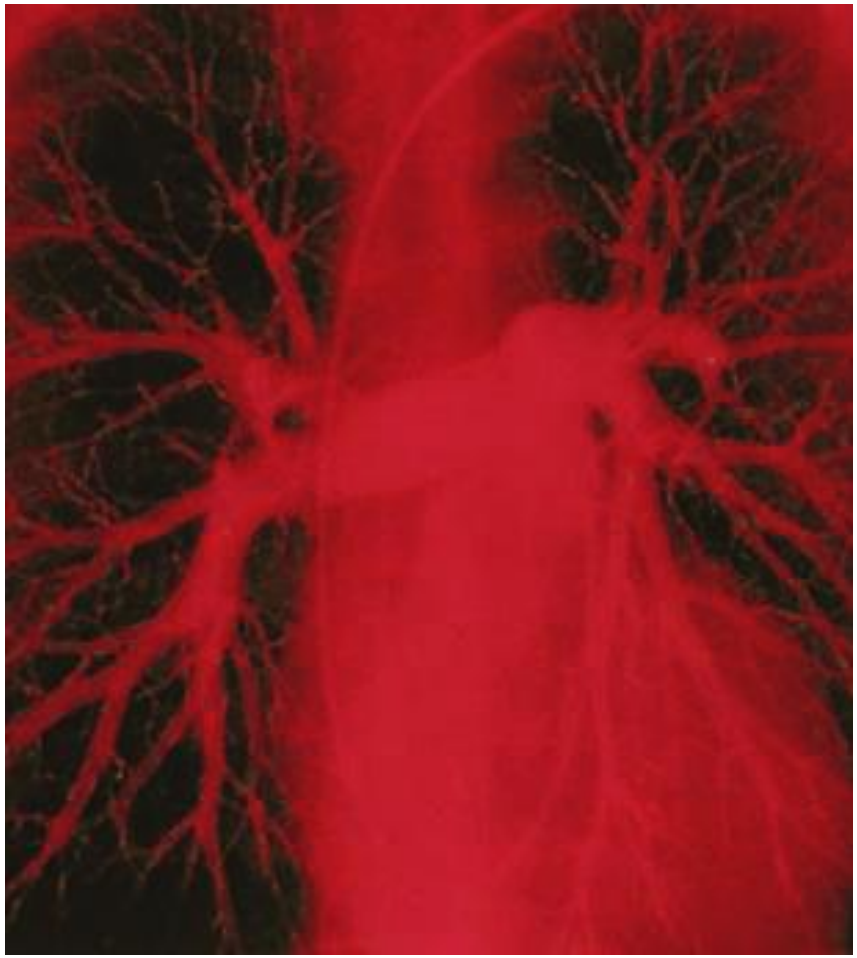
- T 36.9, HR 90, BP 105/62, R 18, sat 93% 2L, WT 475lbs
- HEENT: PERRL, EOMI, no jaundice
- Neck: too large to assess JVP
- Pulm: dec BS throughout, no crackles, wheeze
- CV: RRR, II/VI systolic m in mid sternum, inc P2
- Abd: obese, protuberant, pitting edema
- Ext: 3+ edema to low back

Results:



Characteristics of the Pulmonary Circulation

- Low pressure system
  - One fifth the pressures of systemic circulation, despite same CO as systemic circulation
- Low resistance
  - ~One seventh the resistance of systemic circulation
- High capacitance
  - Accommodates 5- to 6-fold ↑ in blood flow with only 2-fold ↑ in PAP
- Dynamic vascular bed
  - V:Q matching; vasodilatation and recruitment



Badesch et al., *J Am Coll Cardiol*. 2009;54:S55–66.

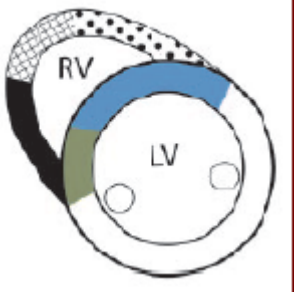
5th World Symposium on Pulmonary Hypertension (WSPH) Consensus Definitions

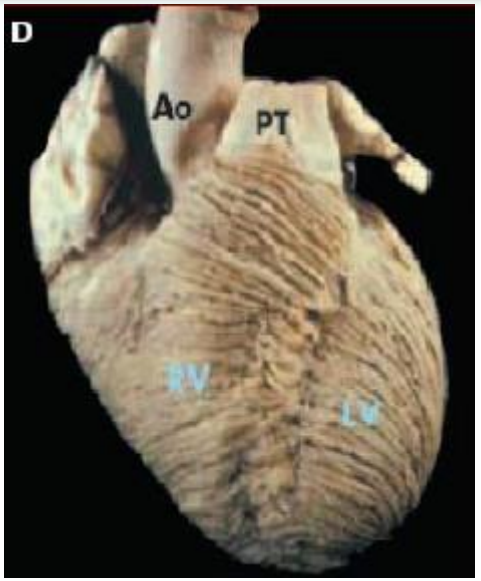
Pulmonary Hypertension (PH)	
Mean pulmonary artery pressure (mPAP)	≥25 mm Hg
Pulmonary Arterial Hypertension (PAH)	
Mean pulmonary artery pressure (mPAP)	≥25 mm Hg
with	
Mean pulmonary artery occlusion pressure (PAOP)	≤15 mm Hg
and	
Pulmonary vascular resistance (PVR)	>3 Wood units

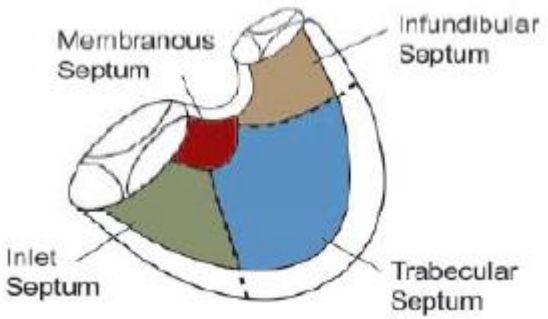
Badesch et al., *J Am Coll Cardiol*. 2009;54:S55–66.

Right Ventricular Structure

- The RV is triangular in shape
- Divided into 3 regions
  - Inlet
  - Apex
  - Infundibulum or Conus
- Contraction proceeds from inlet to infundibulum
- Capacitance of large PAs accommodates stroke volume, keeps pressure low







Nice 2013 WHO Group Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.2.1 BMPR2
- 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
- 1.2.3 Unknown
- 1.3 Drug and toxin induced
- 1.4 Associated with:
- 1.4.1 Connective tissue disease
- 1.4.2 HIV infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart diseases
- 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

1". Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

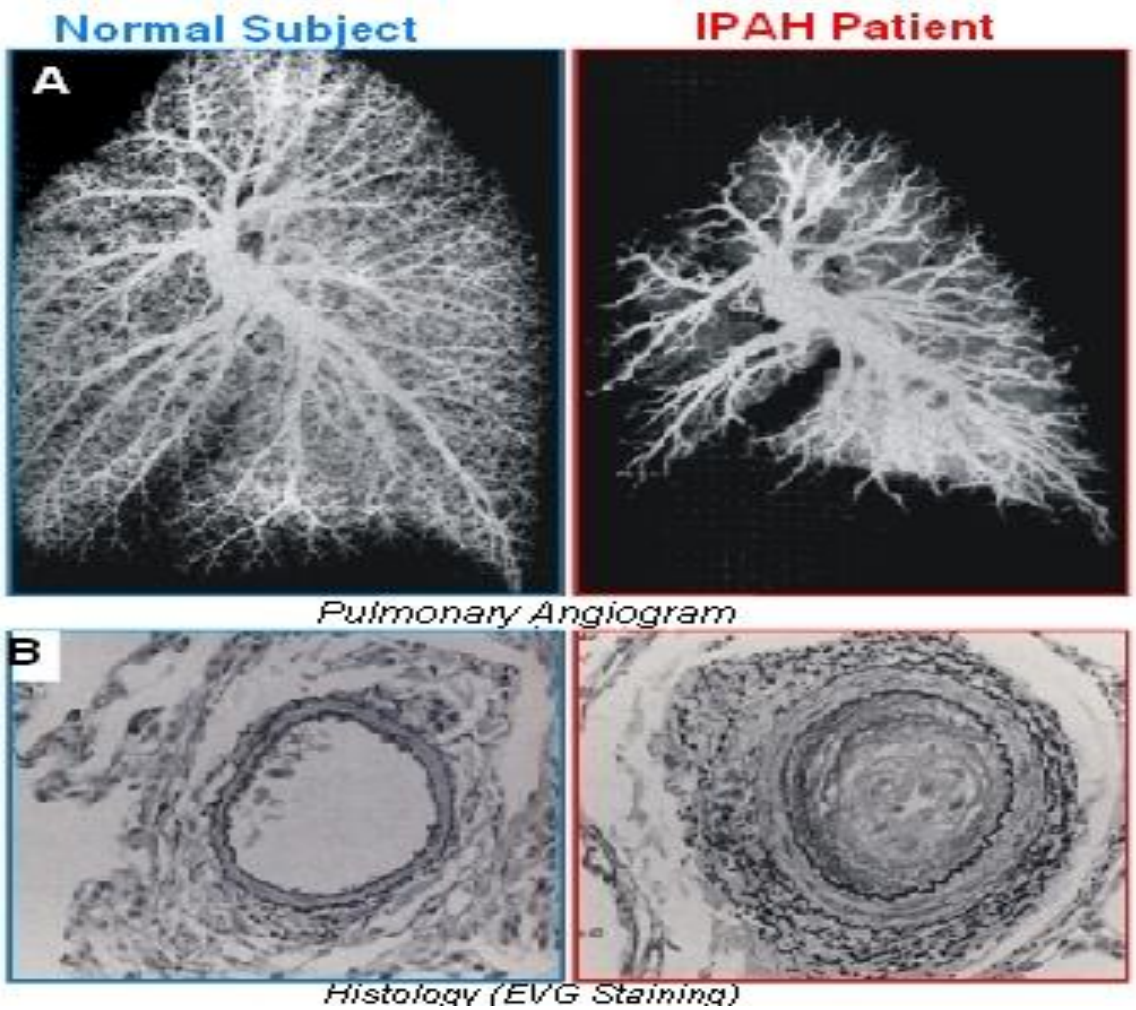
5. Pulmonary hypertension with unclear multifactorial mechanisms

- 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis: lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

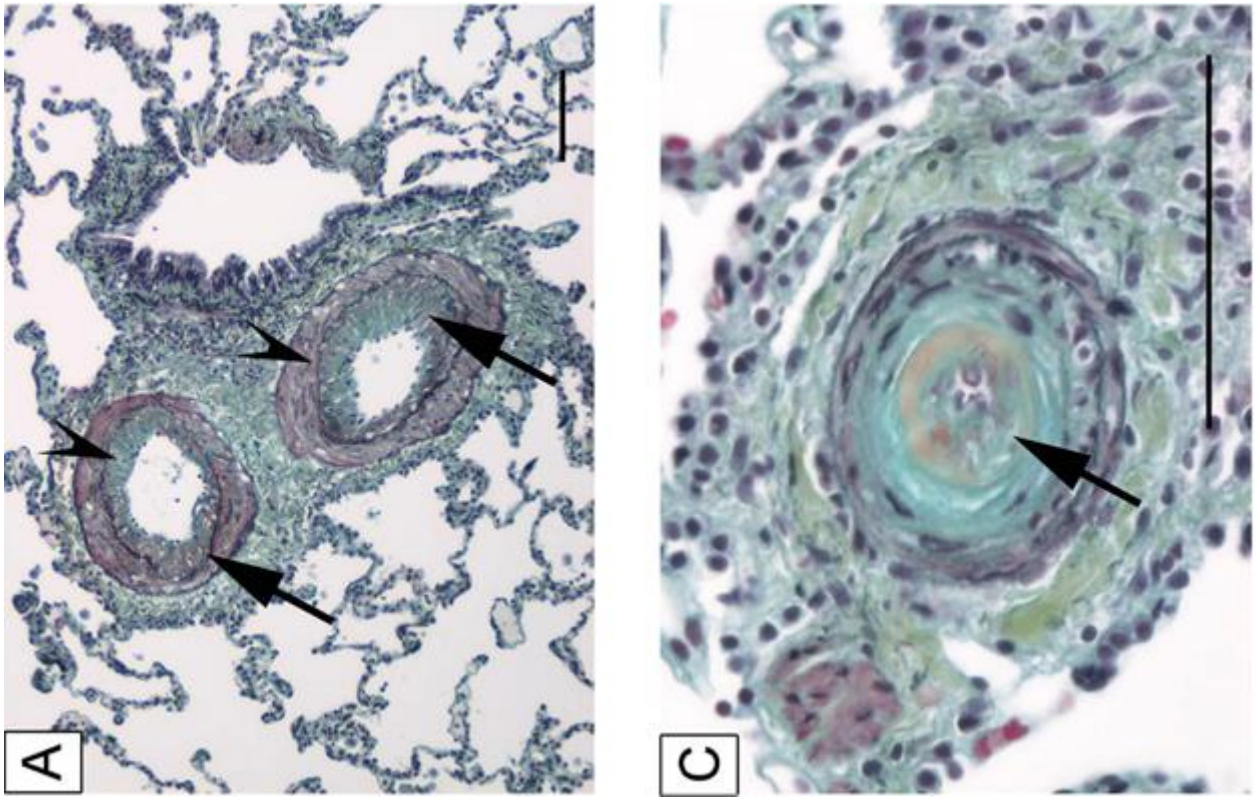
WHO = World Health Organization; BMPR2 = bone morphogenic protein receptor type 2; ALK-1 = activin-like receptor kinase-1; ENG = endoglin; SMAD9 = mothers against decapentaplegic 9; CAV1 = caveolin-1; KCNK3 = potassium channel super family K member-3; HIV = human immunodeficiency virus

Simonneau G, et al. *J Am Coll Cardiol*. 2013;62(25, suppl D):D34-D41.

Normal vs. Idiopathic PAH

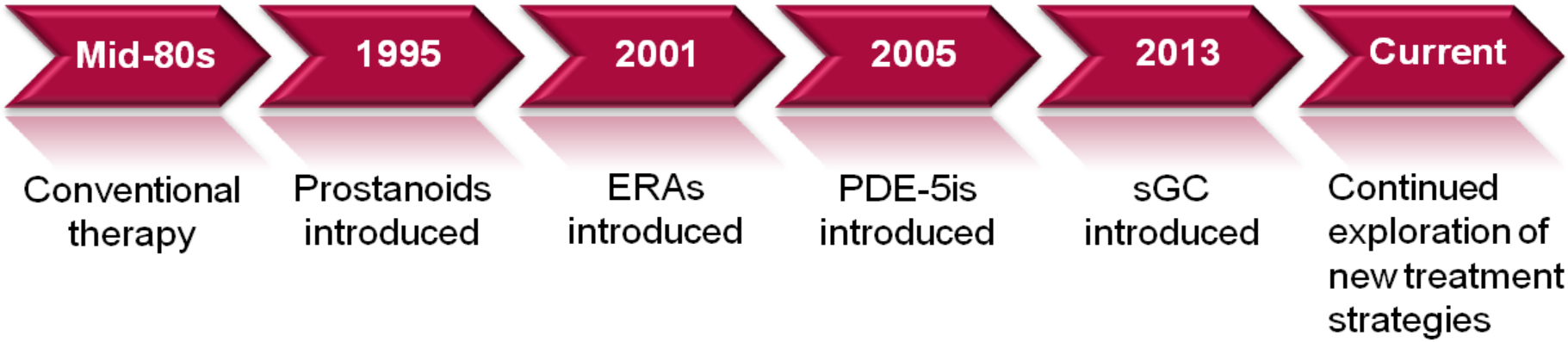


Idiopathic PAH

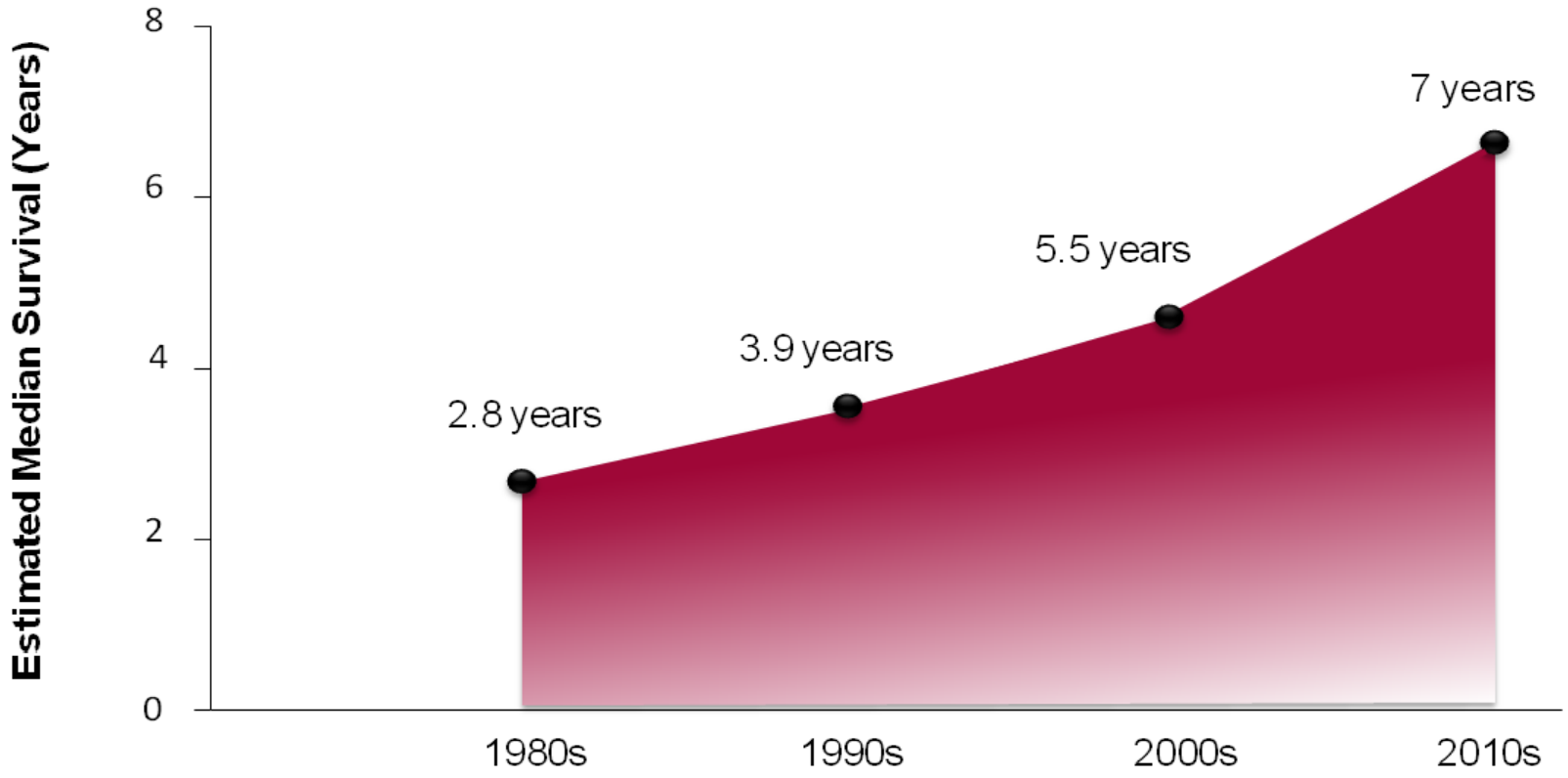


Stacher et al: AJRCCM 186: 261-272

Introduction of PAH Therapies



Progress in PAH Survival



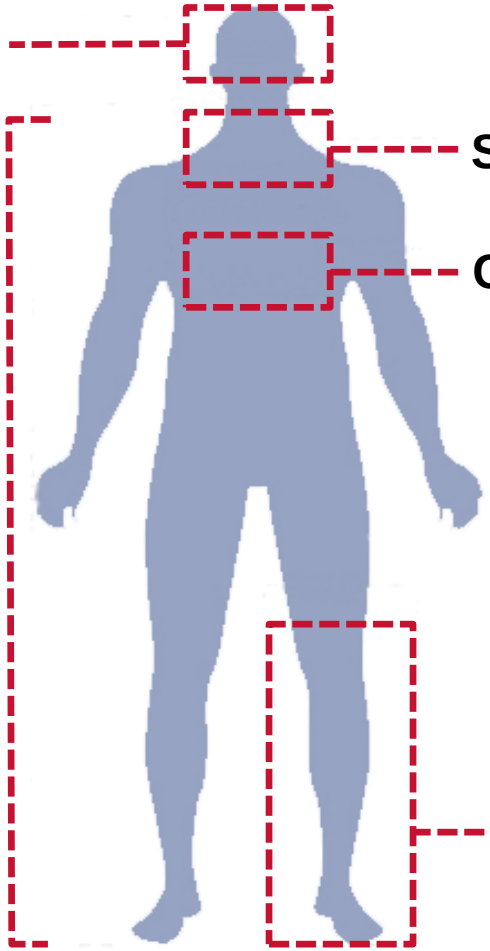
D'Alonzo GE, et al. *Ann Intern Med*. 1991;115:343-349; Thenappan T, et al. *Eur Respir J*. 2010;35:1079-1087; Humbert M, et al. *Eur Respir J*. 2010;36:549-555; Benza RL, et al. *Chest*. 2012;142:448-456.

Screening for PAH

- Patient profile and physical exam
- Chest x-ray
- Electrocardiogram (ECG)
- Doppler echocardiography is the preferred screening tool
- Ventilation/perfusion lung scan
- Pulmonary function tests
- Functional assessment
  - Exercise capacity, 6-minute walk test most common
- Right Heart Catheterization (RHC) definitive diagnosis of PAH
- As needed:
  - Chest CT
  - Sleep study or overnight oximetry
  - Connective tissue disease serologies

McLaughlin VV, et al. *J Am Coll Cardiol*. 2009;53(17):1573-1619.

Symptoms of PAH



Dizziness and/or fainting (syncope)

Shortness of breath (dyspnea)

Chest pain (angina)

Feeling tired or worn out (fatigue)

Swollen ankles and legs (edema)

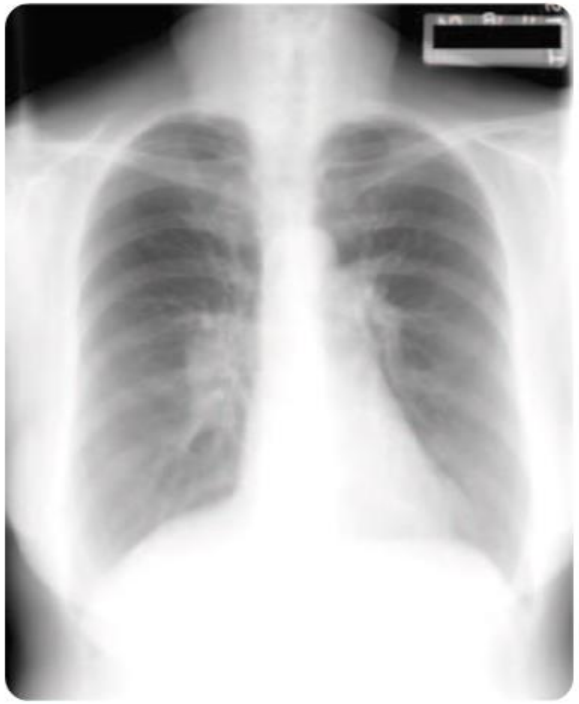
McLaughlin et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

WHO Functional Classification Assessment of PH Severity

Class	Description
I	
II	Mild limitation of usual activities No discomfort at rest Normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope
III	Marked limitation of physical activity No discomfort at rest Less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope
IV	Patient unable to perform any physical activity at rest and may have signs of right ventricular failure Dyspnea and/or fatigue and/or syncope/near-syncope may be present at rest, and symptoms are increased by almost any physical activity

Diagnostic Workup: Chest X-Ray

- Chest x-ray is abnormal at diagnosis in 90% of IPAH patients
- Findings include:
  - Central pulmonary arterial dilatation
  - "Pruning" (loss) of peripheral blood vessels
  - Right atrial and ventricular enlargement (more advanced cases)



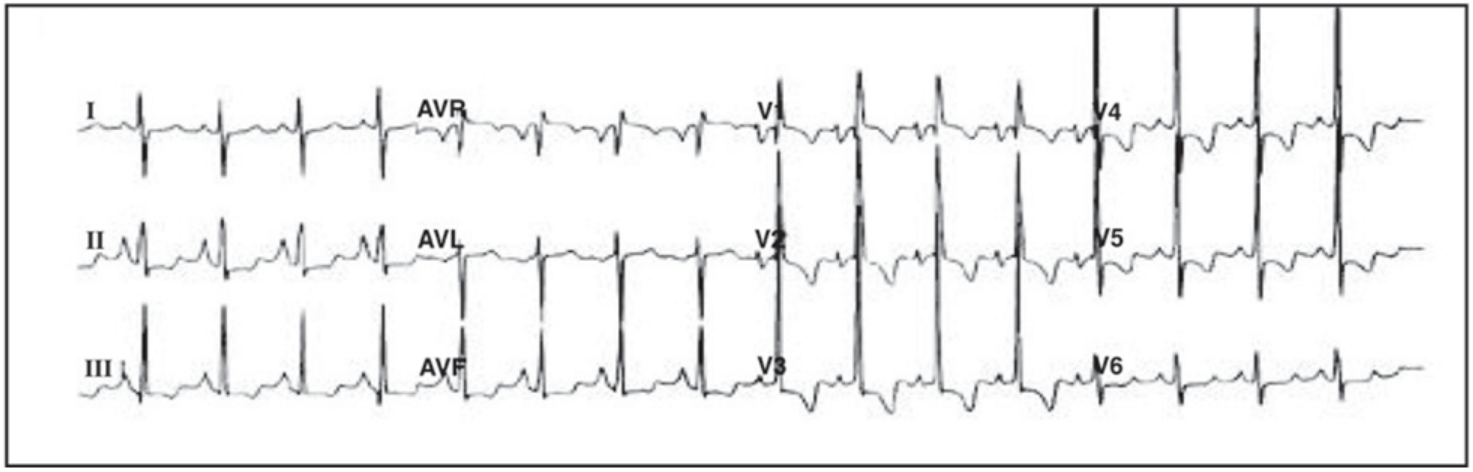
Chest radiography in PAH demonstrating enlargement of the central pulmonary arteries with peripheral pruning of the pulmonary vasculature on the postero-anterior view.

Image source: McLaughlin VV and McGoon MD. *Circulation.* 2006;114(13):1417-1431. Reprinted with permission.

Galiè N, et al. *Eur Heart J.* 2004;25(24):2243-2278.

Diagnostic Workup: Electrocardiogram (ECG)

- ECG may suggest PAH by revealing:
  - Right ventricular hypertrophy (87% of patients with IPAH)
  - Right axis deviation (79% of patients with IPAH)
- However, ECG has inadequate sensitivity and specificity to be considered a reliable screening tool
- A patient may have severe PAH in the presence of a normal ECG



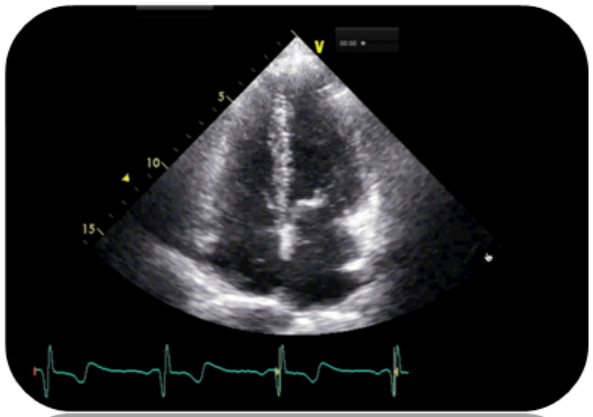
ECG in PAH demonstrating right-axis deviation, right ventricular hypertrophy, and anterior ST- and T-wave abnormalities consistent with a right ventricular strain pattern.

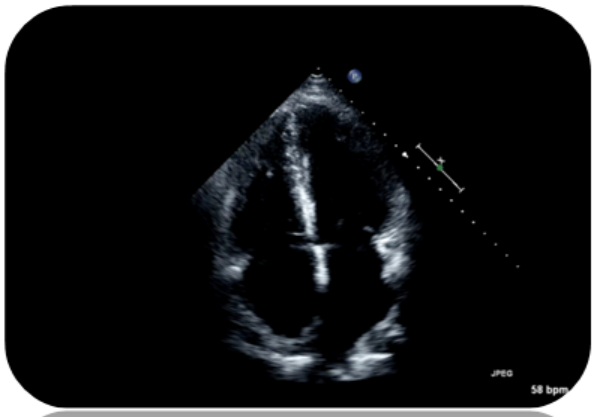
Galiè N, et al. *Eur Heart J*. 2004;25(24):2243-2278.
Image Adapted from McLaughlin VV, et al. J Am Coll Cardiol. 2009;53(17):1589.

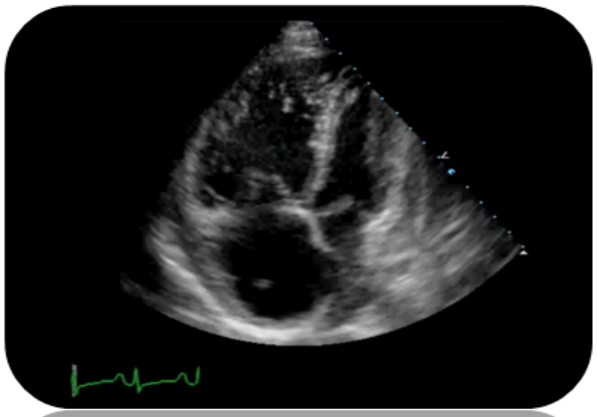
Echocardiography

- Echocardiography and other tests are useful for screening and evaluation
- Doppler echocardiography is the preferred screening tool

Early Stage Compensated	*Moderate Severity Decompensating*	*Severe Decompensated*

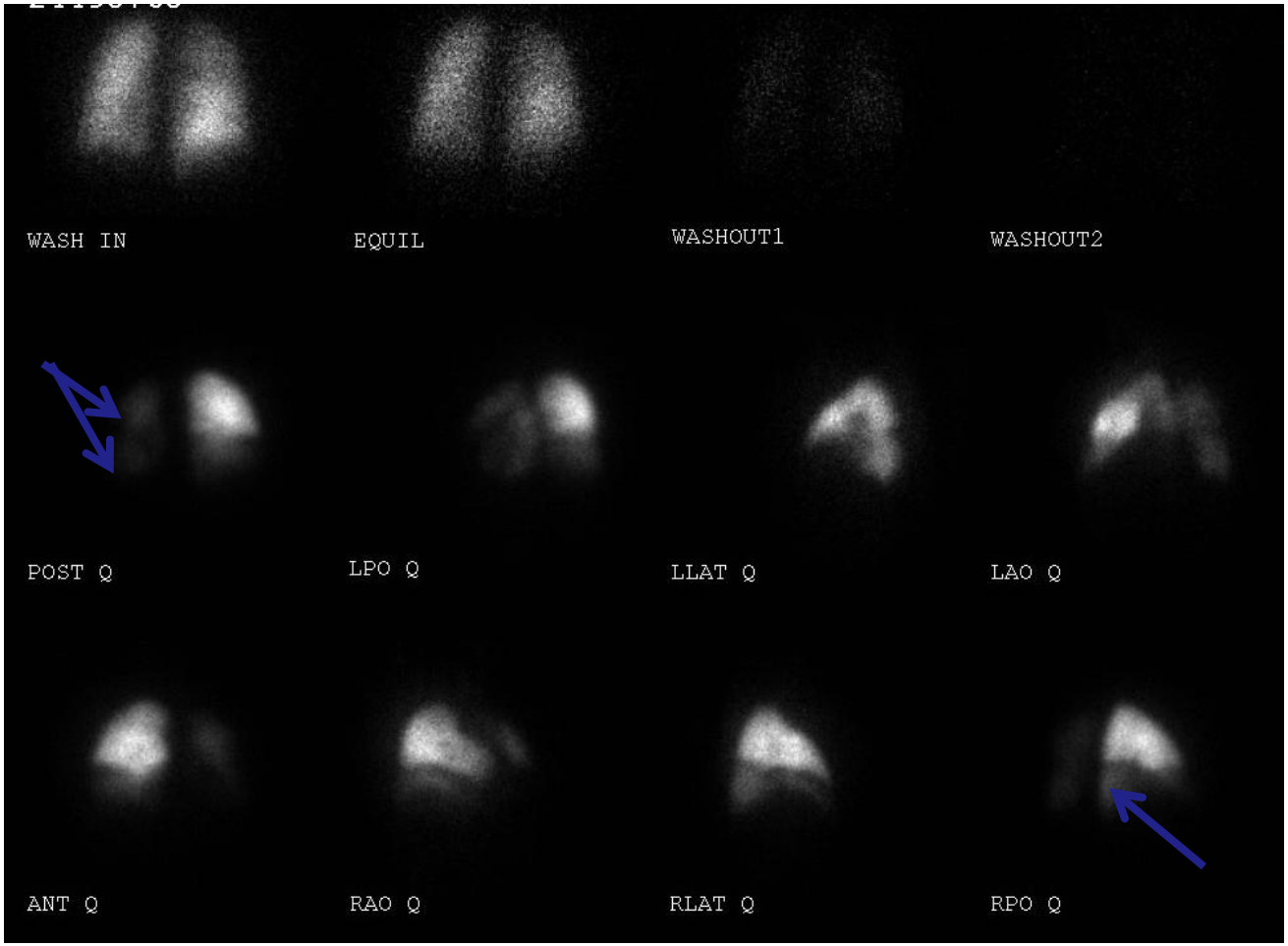






McLaughlin VV, Archer SL, Badesch DB, et al. *J Am Coll Cardiol*. 2009;53(17):1573-1619.

Ventilation Perfusion (VQ) Scintigraphy: Gold Standard for CTEPH

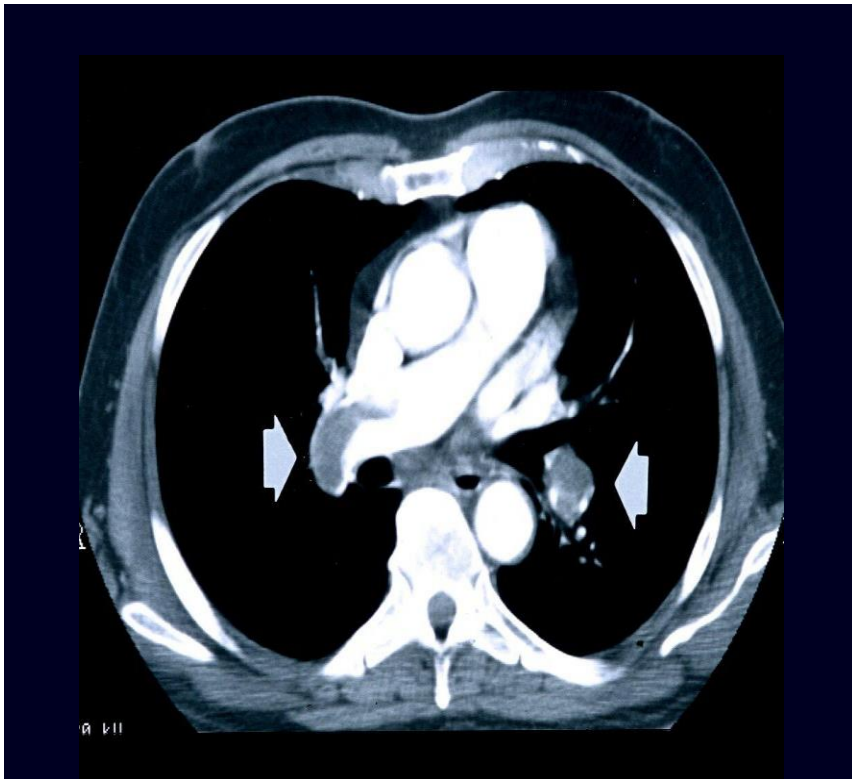


Case Example: Perfusion is intact primarily to the right upper lobe

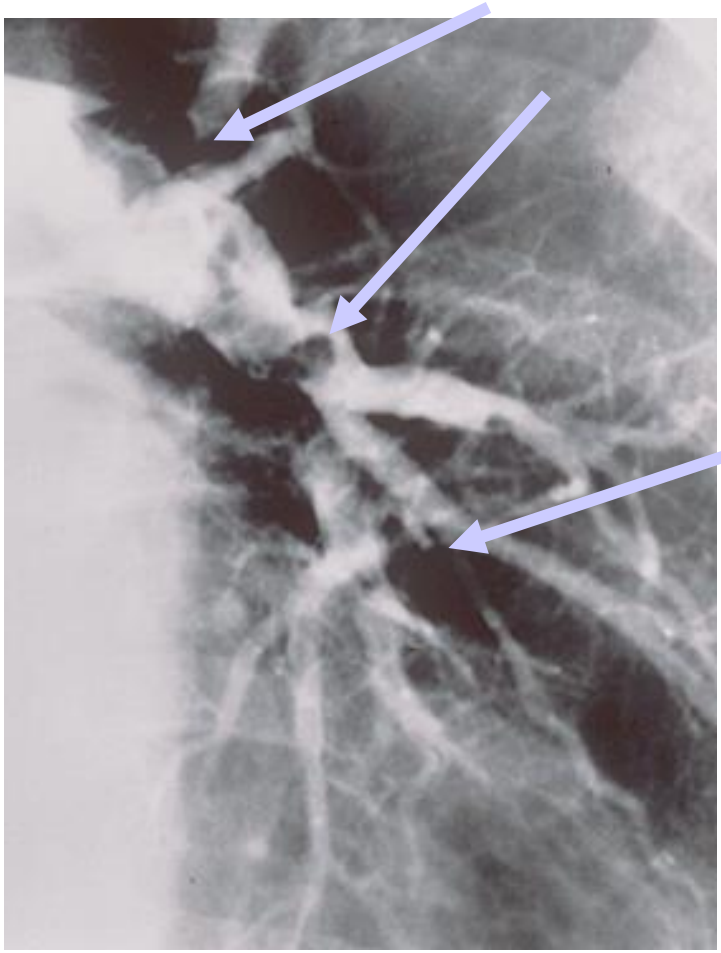
Blue Arrows: hypo-perfused regions representing perfusion defects

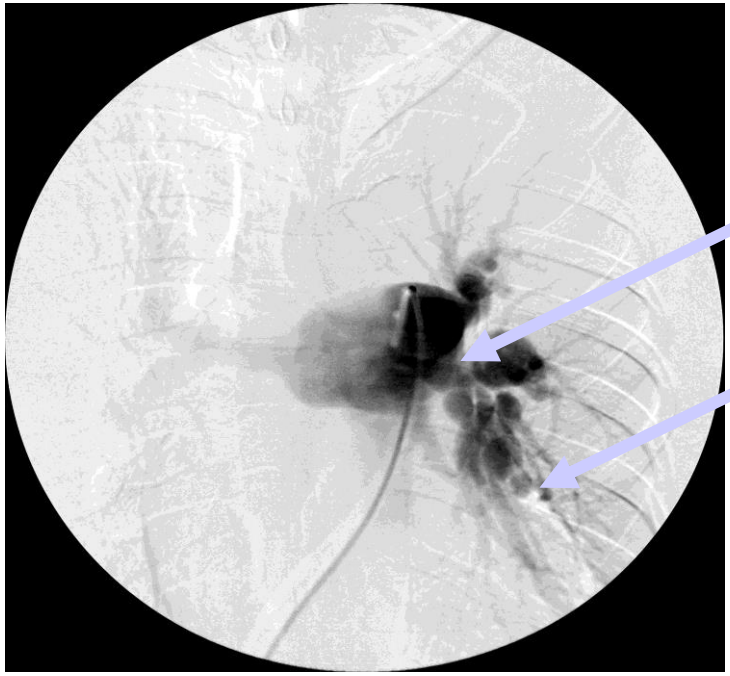
CT Chest (PE protocol)

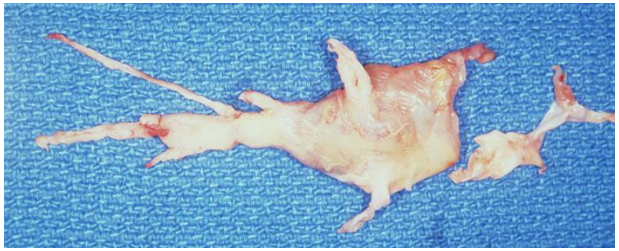
- CT scanning or MRI should not be used to <u>exclude</u> CTEPH:



Pulmonary Angiogram





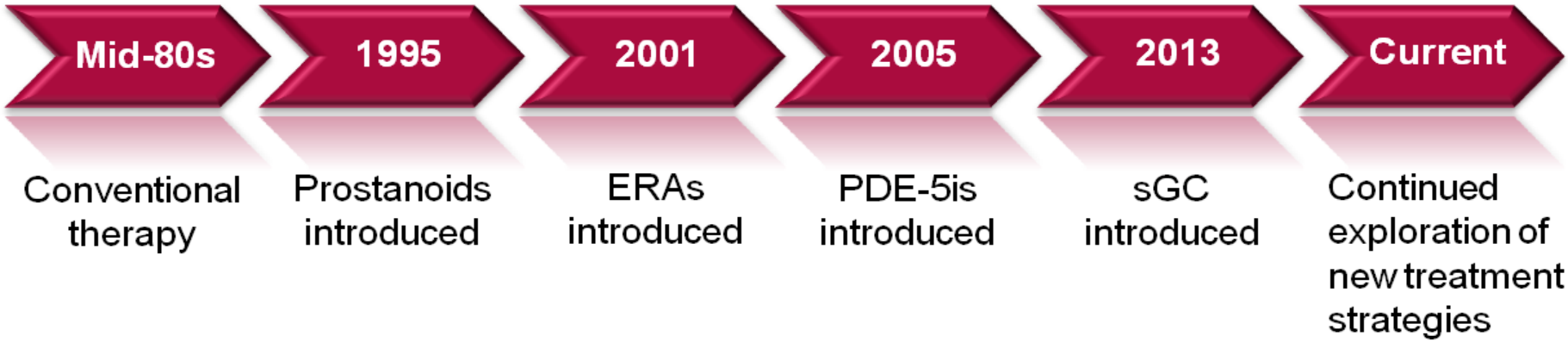


5th WSPH: Prognostic Variables Used in Clinical Practice To Set Treatment Goals

Variable	Recommended Goal
WHO Functional class (FC)	I or II
Echocardiography/CMRI	Normal/near normal RV size and function
Hemodynamics	Normalization of RV function •RAP < 8 mm Hg and •CI > 2.5 to 3.0 L/min/m^2
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg and $EqCO_2$ <45 L/min/L/min
B-type natriuretic peptide	Normal

McLaughlin VV, et al. *J Am Coll Cardiol.* 2013;62:D73-81

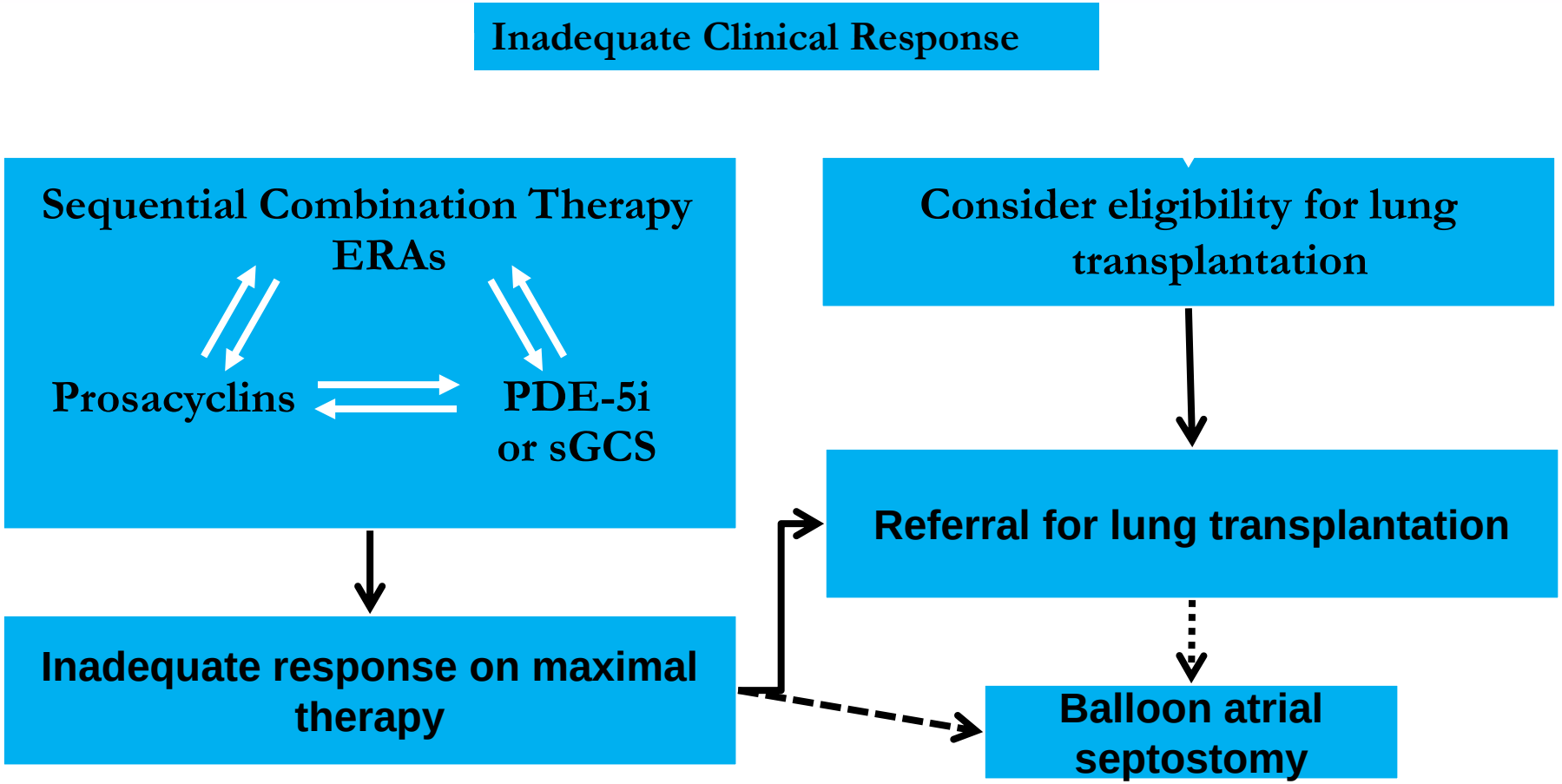
Introduction of PAH Therapies



PAH-specific Treatment Options:

Oral Therapy				Inhaled Therapy	Continuous Parenteral Therapy
ERAs	**PDE5 Inhibitors**	**sGC Stimulator**	**Prostacyclin**	**Prostacyclins**	
Ambrisentan	Sildenafil	Riociguat	Treprostinil	Iloprost	Epoprostenol (Flolan®)
Bosentan	Tadalafil			Treprostinil	RTS epoprostenol (Veletri®)
Macitentan					Treprostinil (SC or IV)

Updated Guidelines: Inadequate Clinical Response to Initial PAH Therapy



Adapted from: Galie N, et al. *J Am Coll Cardiol.*

Hospital Course:

- Initial diagnosis: severe pulmonary arterial hypertension and Cor Pulmonale. Acute Right Heart Failure, obstructive sleep apnea (100% compliant with CPAP at 15cm of water)
- Initial therapy: Aggressive Acute Diuresis with IV Lasix ,Sildenafil 50 mg TID, Metolazone and SQ Remodulin
- D/C home 1/31. Amiodarone dc'd (afib) due to risk of associated hypothyroidism, transitioned from IV to oral lasix, CPAP, Remodulin SQ 19 ng/kg/min, Sildenafil
- D/C wt 359 lbs

Catheterization Data

- Right heart Cath 1/10/09, MRAP 22, PAP 91/41/60, wedge 15, CO 6.0 L/min, CI 2.1L/min PA Sat 58% negative vasodilator test
  - 50mg tid revatio
- Right heart Cath 5/13/09 MRAP 11, PAP 78/28/46, Wedge 15, CO (thermodilution) 11. 1, CI 5.18 no change in hemodynamics with NO 40 ppm
  - 20mg tid revatio
  - 47ng/kg/min treprostinil

Six Minute Walk Data

- 6MWD: unable to walk when admitted in 01/10/09
  - Wt: 475lbs; BNP 789
  - Discharged 19ng/kg/min on 02/02/09
- 6MW 2/9/09 195 meters on 3L 02 saturation 95% baseline – 90% after walk
  - Wt: 303lbs; BNP 209
  - **21ng/kg/min SQ remodulin** + 20mg tid revatio
- 6MW 8/10/09 365 Meters on RA sats 97% baseline to 94%
  - Wt: 222lbs; BNP 22
  - **47ng/kg/min SQ remodulin** + 20mg tid revatio
- 6MW 2/08/10 444 meters on RA
  - Wt: 194lbs
  - **53ng/kg/min SQ remodulin** + 20mg tid revatio
- 6MW 11/15/16 455 meters on RA
  - Wt: 216lbs
  - **90ng/kg/min SQ remodulin** + 20mg tid revatio

Follow up January, 2018

- On Remo 120ng/kg/min; 180lb (started off over 400lbs)
- Huge improvement in overall lifestyle and clinical response
  - married
- FC 2
- Repeat sleep study without evidence of sleep apnea
- Return every 6 months with repeat 6MW, clinical exam, functional class chem 10 +/- BNP, CBC and thyroid q 6 months. Repeat echo yearly.