PULMONARY HYPERTENSION

REVIEW & UPDATE

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Disclosures

- None

Case

A 32-year-old female with no past medical history presents to your office for evaluation of shortness of breath. The patient complains of 4 months of dyspnea on exertion. She denies cough or wheezing. On exam, you note an oxygen saturation of 94% on room air at rest, clear lungs, no edema, and shiny, slightly swollen fingers. What is the next step?

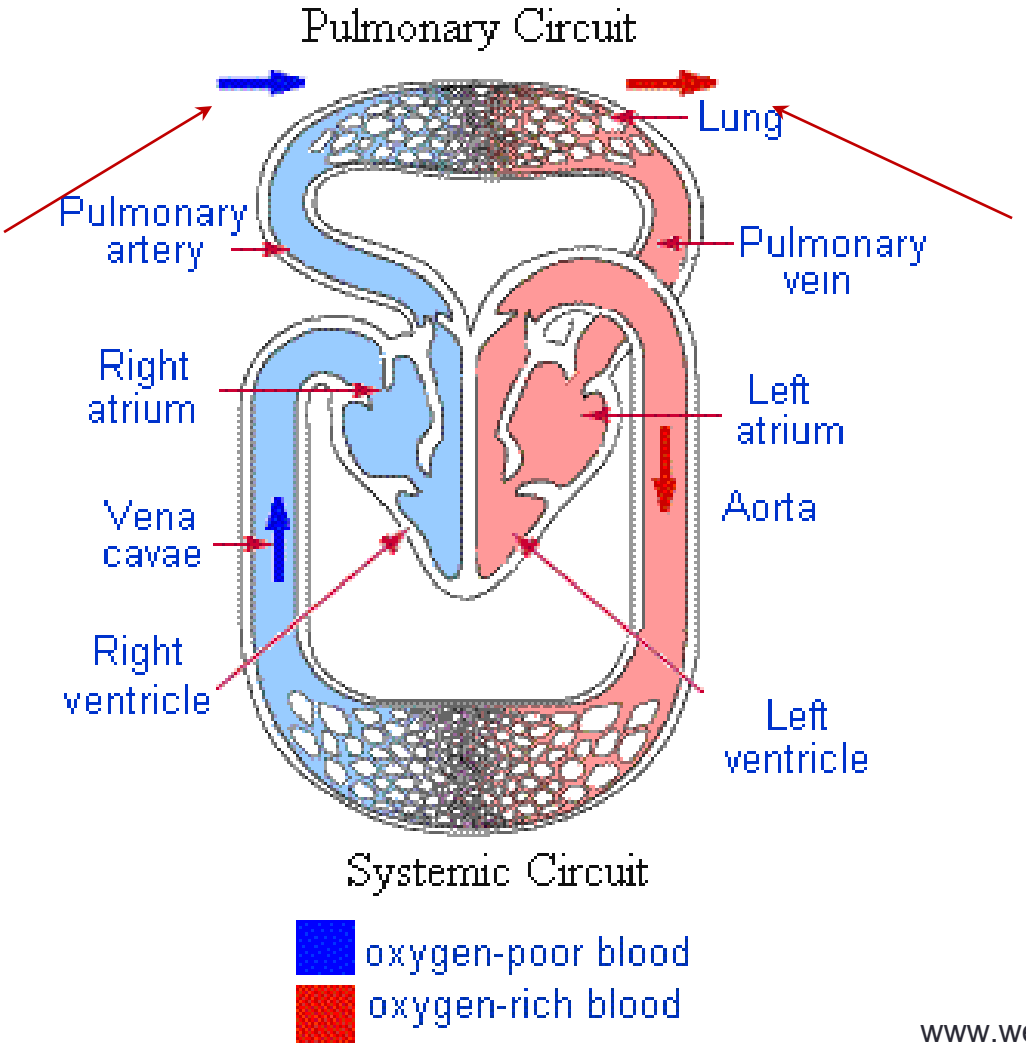
A. It's asthma. Start albuterol.
B. It's a blood clot. Get a d-dimer.
C. It's depression. Start an SSRI.
D. It's pulmonary hypertension. Get an echocardiogram.
E. It's pulmonary fibrosis. Get chest imaging.

What is Pulmonary Hypertension?

- Pulmonary Hypertension (PH) describes a group of conditions that are characterized by elevated pressure inside the pulmonary vasculature
  - Pulmonary arterial pressure (PAP) > 25 mmHg at rest on a right heart catheterization
  - Normal PAP is ~ 14-20 mmHg
- Pulmonary Arterial Hypertension (PAH) is a category of pulmonary hypertension
  - Pulmonary vascular remodeling
  - Restricted flow through the pulmonary arterial circulation
  - Increased pulmonary vascular resistance (PVR)
  - Right ventricular failure
  - One year survival <70% in patients with certain high risk features

Pulmonary Vasculature

"Precapillary or Pulmonary arterial"



"Postcapillary or Pulmonary venous"

Pulmonary Circulation

- High-flow, low-pressure system
- Right ventricle
  - Thin-walled
  - Poorly tolerates acute increases in afterload
  - Ventricular Interdependence (LV and RV share a septum)

Dilated RV → ↓ LV filling

↓ CO

↓ O2 delivery

- What happens to the right ventricle is a major determinant of outcome in PAH

What is Pulmonary Hypertension?

- World Health Organization has classified pulmonary hypertension into 5 groups based on:
  - Underlying mechanism
  - Clinical presentation
  - Prognosis
  - Treatment strategies

Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 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 and/or pulmonary capillary hemangiomatosis

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
   - 3.1 Chronic obstructive pulmonary disease
   - 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**

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in **bold**.
BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Simmonneau et al. J Am Coll Cardiol 2013;62:D34-41

Epidemiology: ***WHO Group 1 PAH***

- ***Idiopathic PAH*** is more common in young women
  - F/M ratio 1.7:1
  - Mean age at diagnosis 37 years
  - Most commonly misdiagnosed as asthma
- ***PAH in HIV***
  - incidence of 0.5% (6-12 times that of the general population)
  - Independent of CD4 count or opportunistic infections
- ***Drugs & Toxins PAH***
  - Association between use of methamphetamines and diet pills for > 3 months and development of PAH

Table 7 **Updated risk level of drugs and toxins known to induce pulmonary arterial hypertension**

Definite	Likely	Possible
• Aminorex • Fenfluramine • Dexfenfluramine • Toxic rapeseed oil • Benfluorex • Selective serotonin reuptake inhibitors[a]	• Amphetamines • Dasatinib • L-tryptophan • Methamphetamines	• Cocaine • Phenylpropanolamine • St John's Wort • Amphetamine-like drugs • Interferon α and β • Some chemotherapeutic agents such as alkylating agents (mytomycine C, cyclophosphamide)[b]

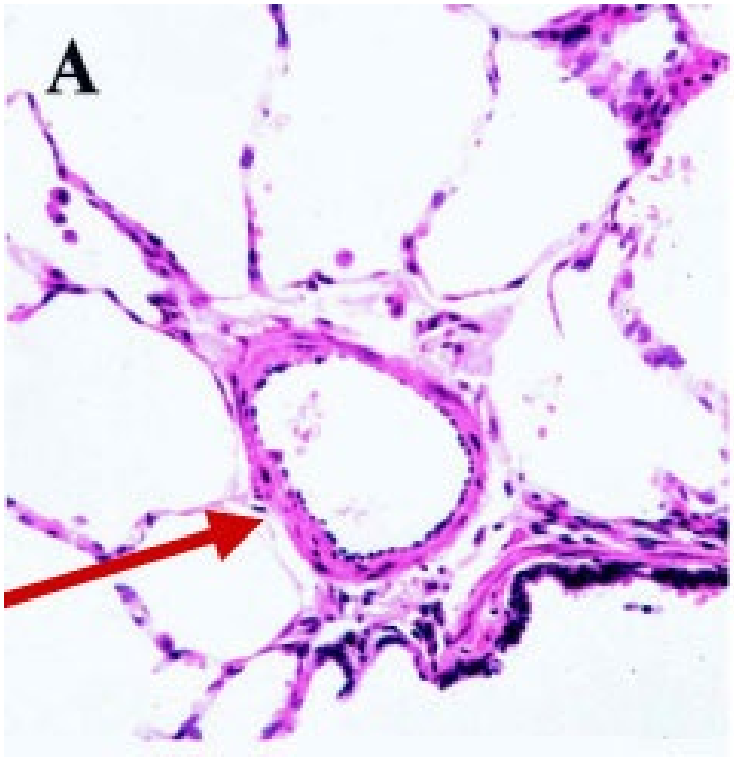
[a]Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors.
[b]Alkylating agents are possible causes of pulmonary veno-occlusive disease.

Galie et al. Eur Heart J 2016; 37(1):67-119.

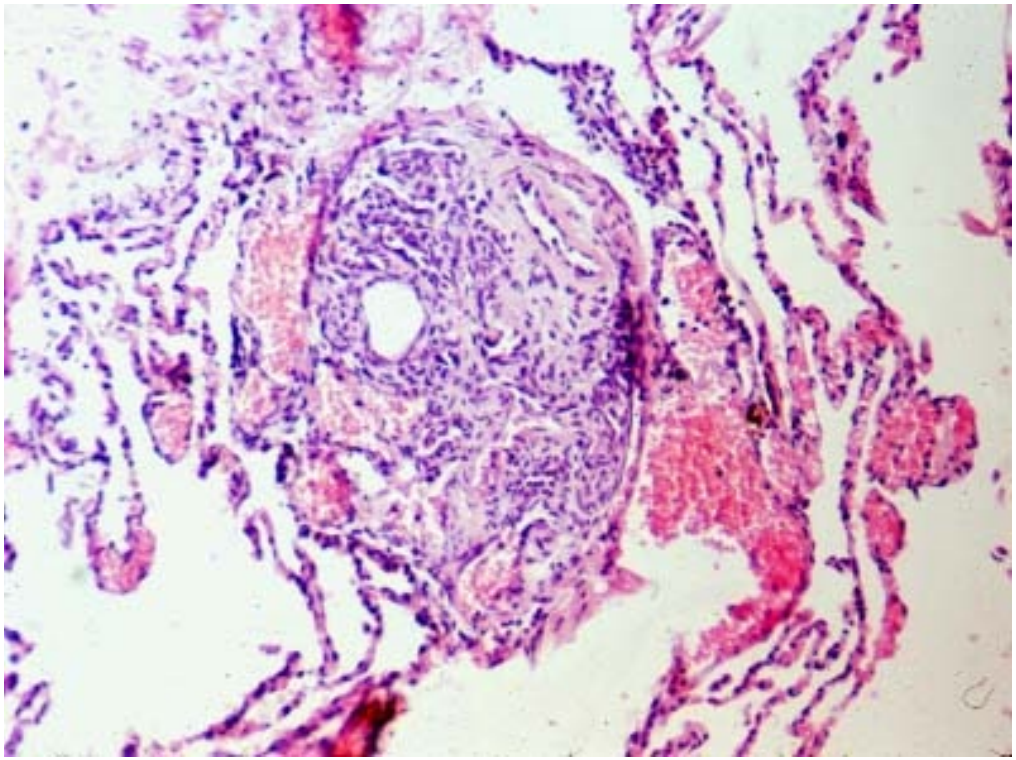
Epidemiology: ***WHO Group 1 PAH***

- ***Connective Tissue Disease associated PAH***
  - Systemic sclerosis >> Mixed CTD > SLE, RA
  - PAH occurs in 10-40% of patients with limited cutaneous systemic sclerosis
- ***Portal Hypertension***
  - Occurs in 3.5 – 16% of patients with end-stage liver disease
  - Worse outcomes than other types of WHO group 1 PAH
  - PAH may persist even after liver transplantation

Pathology: Pulmonary Artery

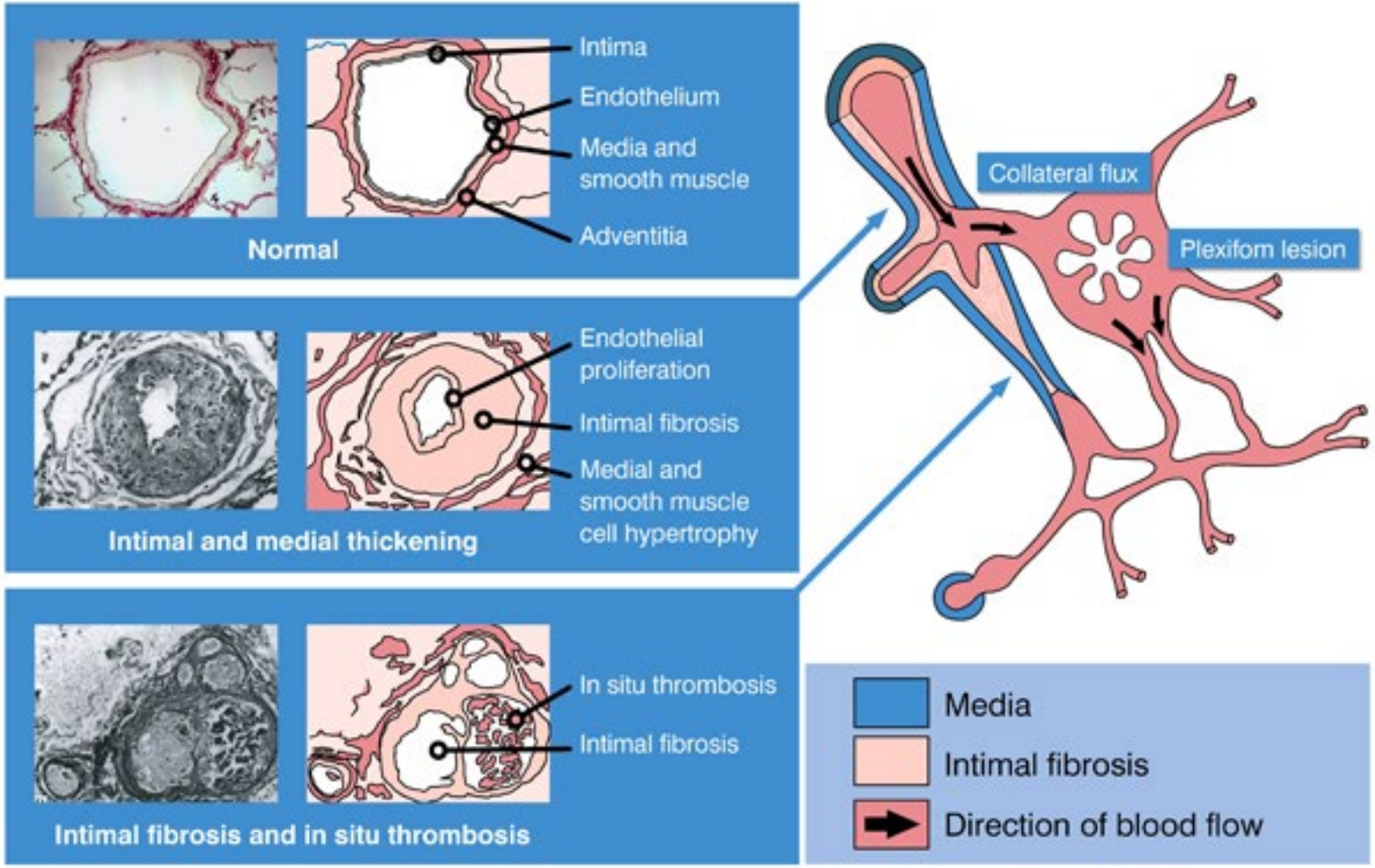


Normal



PAH

Pulmonary Arterial Hypertension: histopathological features



Epidemiology: ***WHO Group 2 PH***

- ***Pulmonary venous (post-capillary) hypertension associated with left heart disease***
- Includes systolic or diastolic heart failure, & valvular disease
  - Prevalence of PH in systolic or diastolic dysfunction has been reported as 25-83% (increases with severity of heart failure)
  - Mechanism: thought to occur due to passive pulmonary venous congestion, vasoconstriction, venous remodeling

The most common cause of right heart failure is…

Left Heart Failure!

Epidemiology: ***WHO Group 3***

- ***Chronic lung diseases***
  - COPD
    - 50% of patients with end-stage disease (hypoxia)
    - Presence of PH in COPD increases mortality
  - Interstitial lung disease (idiopathic pulmonary fibrosis, etc.)
  - Obstructive sleep apnea

- Severe PH is uncommon
- Mechanism: destruction of alveolar capillary bed; hypoxic vasoconstriction

Epidemiology: ***WHO Group 4***

- Chronic Thromboembolic Pulmonary Hypertension ***(CTEPH)***
  - Occurs in 0.5-2% of patients after acute pulmonary emboli
  - Organization/remodeling of clot

Epidemiology: ***WHO Group 5***

- ***Miscellaneous causes***
  - Metabolic
  - Structural (fibrosing mediastinitis)
  - Hematologic (sickle cell disease)
  - Chronic renal failure

Symptoms of PAH

- Nonspecific and often confounded by presence of comorbid conditions
  - Dyspnea on exertion
  - Lower extremity edema
  - Chest pain
  - Dizziness
  - Palpitations
  - Fatigue
  - Syncope
- NIH found that ~2 years from onset of symptoms transpire before a correct diagnosis of PAH is established

History

- Ask about
  - Family history of sudden death at young age
  - Personal or family history of connective tissue disease
  - History of drug use (meth) or diet pills (Fen-Phen)
  - Risk factors for liver disease
  - Personal or family history of DVT/PE

Physical Exam

- JVD
- Lower extremity edema
- High-pitched, holosystolic murmur of TR (LSB)
- Loud P2
- Clear lungs if PAH
- Cyanosis in 20% of IPAH (due to R->L shunt and low CO)
- Clubbing (more likely with congenital heart disease)
- Look for stigmata of connective tissue disease and liver disease

Screening

- No data to suggest screening of asymptomatic patients

- Except…
  - Patients with systemic sclerosis
    - Echocardiogram yearly
    - PFTs
    - BNP

Diagnostic Testing

- If you suspect PH, start with a transthoracic echocardiogram (especially if signs of right heart failure are present)

- Findings suggesting PH on TTE
  - Elevated RVSP or PASP
  - Dilated RA
  - Dilated RV
  - Decreased RV function

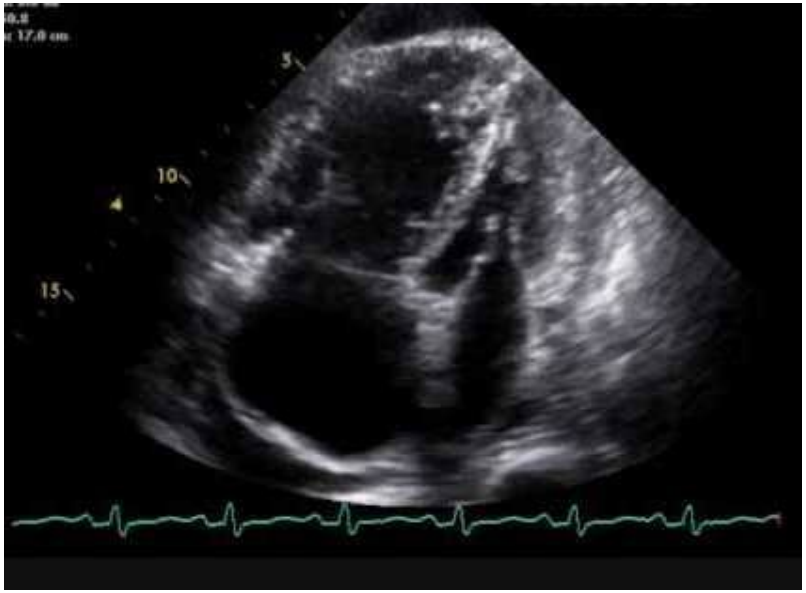


Table 3. Common Causes of Elevated Systolic Pulmonary Arterial Pressure*

Chronic lung disease and sleep disorders (including chronic obstructive pulmonary disease and obstructive sleep apnea)
High cardiac output states (e.g., anemia, hyperthyroidism)
Hypertension
Left heart disease, including heart failure with preserved or reduced ejection fraction
Obesity
Volume overload, particularly in heart failure or in the setting of dialysis and chronic kidney disease

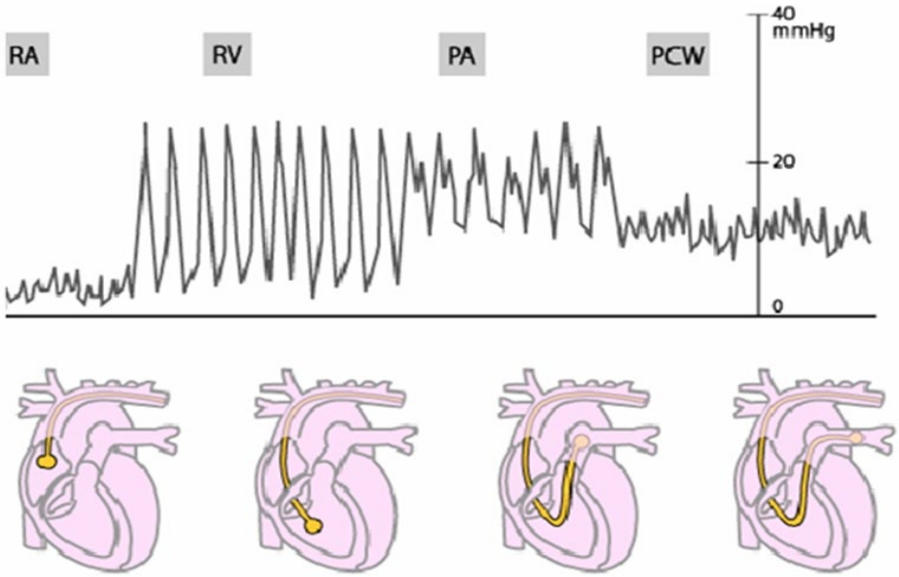
*—*Other than increased vascular resistance.*

Information from references 21 through 23.

Diagnostic work up

- **Right heart catheterization = gold standard for diagnosis!**

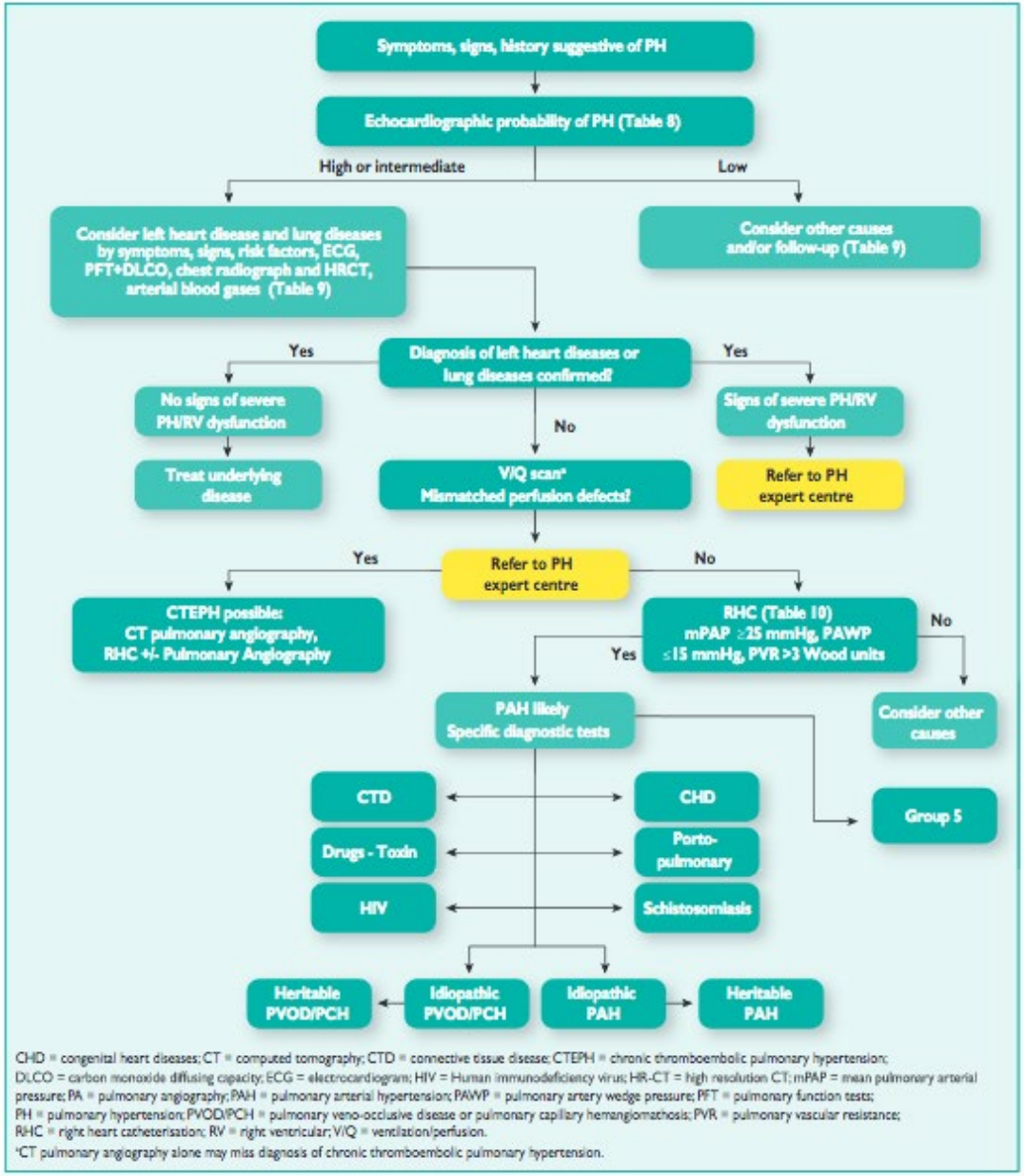
- PAH:
  - mPAP >25 mmHg
  - PAWP <15 mmHg
  - PVR >3 WU



RVSP 40 mmHg on echo ~ mean PA pressure 25 mmHg on right heart catheterization

Diagnostic Testing

- ECG – evidence of RV strain
- Chest x-ray – prominent hila (enlarged pulmonary arteries)
- Pulmonary Function Tests – isolated reduction in DLCO
  - Can also be seen in anemia, early interstitial lung disease, or CHF
- Six minute walk test – desaturation with exercise
- BNP - elevated
- Autoimmune studies
- V/Q scan
  - To evaluate for CTEPH
- HRCT to look for interstitial lung disease
- Sleep study to look for obstructive sleep apnea



CHD = congenital heart diseases; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = Human immunodeficiency virus; HR-CT = high resolution CT; mPAP = mean pulmonary arterial pressure; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PH = pulmonary hypertension; PVOD/PCH = pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; RV = right ventricular; V/Q = ventilation/perfusion.
*CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

Galie et al. Eur Heart J 2016; 37(1):67-119.

Treatment

- ***Pulmonary vasodilator therapies*** are ONLY approved for WHO Group 1 and WHO group 4 CTEPH disease
  - Should only be started after a right heart catheterization confirms hemodynamics and diagnosis
  - Data has not shown benefit in other groups
  - Can be harmful in WHO Group 2 → flash pulmonary edema
  - Can be harmful in WHO Group 3 → worsening V/Q mismatch
- ***Pulmonary endarterectomy*** for CTEPH
- Goal of treatment is to improve symptoms and survival
- Treat underlying problem

- General guidelines:
  - Low salt diet, fluid restriction, and diuretics to manage volume status
  - Supplemental oxygen as needed to keep O2 sat >90%
    - Hypoxia is a potent pulmonary vasoconstrictor
  - Achieve normal sinus rhythm
  - Avoid pregnancy: hemodynamic fluctuations during pregnancy, delivery and postpartum period carry up to 50% maternal mortality rate

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E. It's pulmonary fibrosis. Get chest imaging.

Thank You!

Questions?

References

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