Elevated Pulmonary Artery Pressure on Echocardiogram: Don't Panic, Be Pragmatic!

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Disclosures

I do not have any relevant commercial relationships to disclose

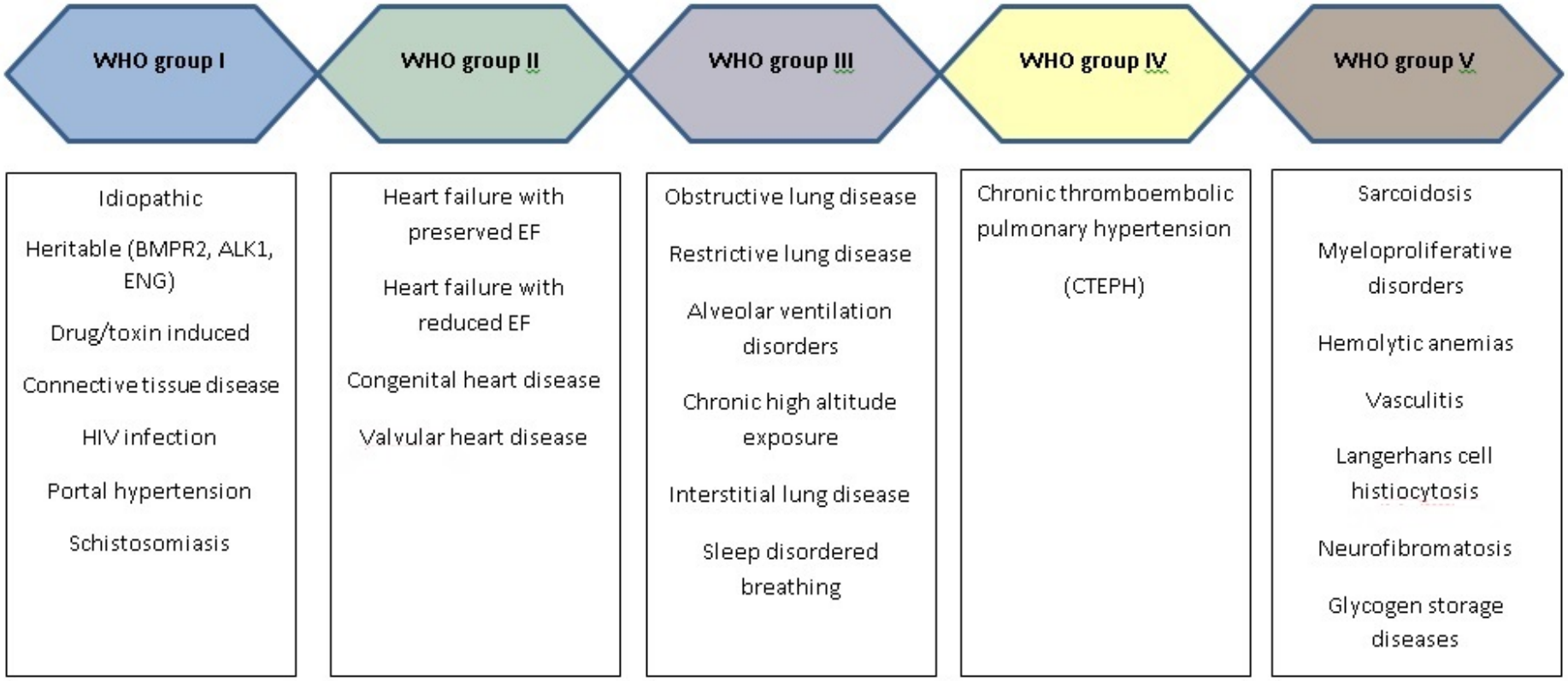
However…..

Go Pens!!

Learning objectives

- At the conclusion of this session, participants should be able to:
  - Distinguish between the various World Health Organization (WHO) classes of pulmonary hypertension (PH)
  - Ascertain the most likely etiology of a patient's PH based on detailed history taking and physical exam
  - Understand the basic physiologic principles of invasive hemodynamic data
  - Determine which PH patients require urgent specialist referral
  - Recognize patients in whom pulmonary vasodilator therapy would be appropriate

Pulmonary Hypertension



Adapted from Simmoneau et al . Eur Respir J. 2019; 53: 1801913

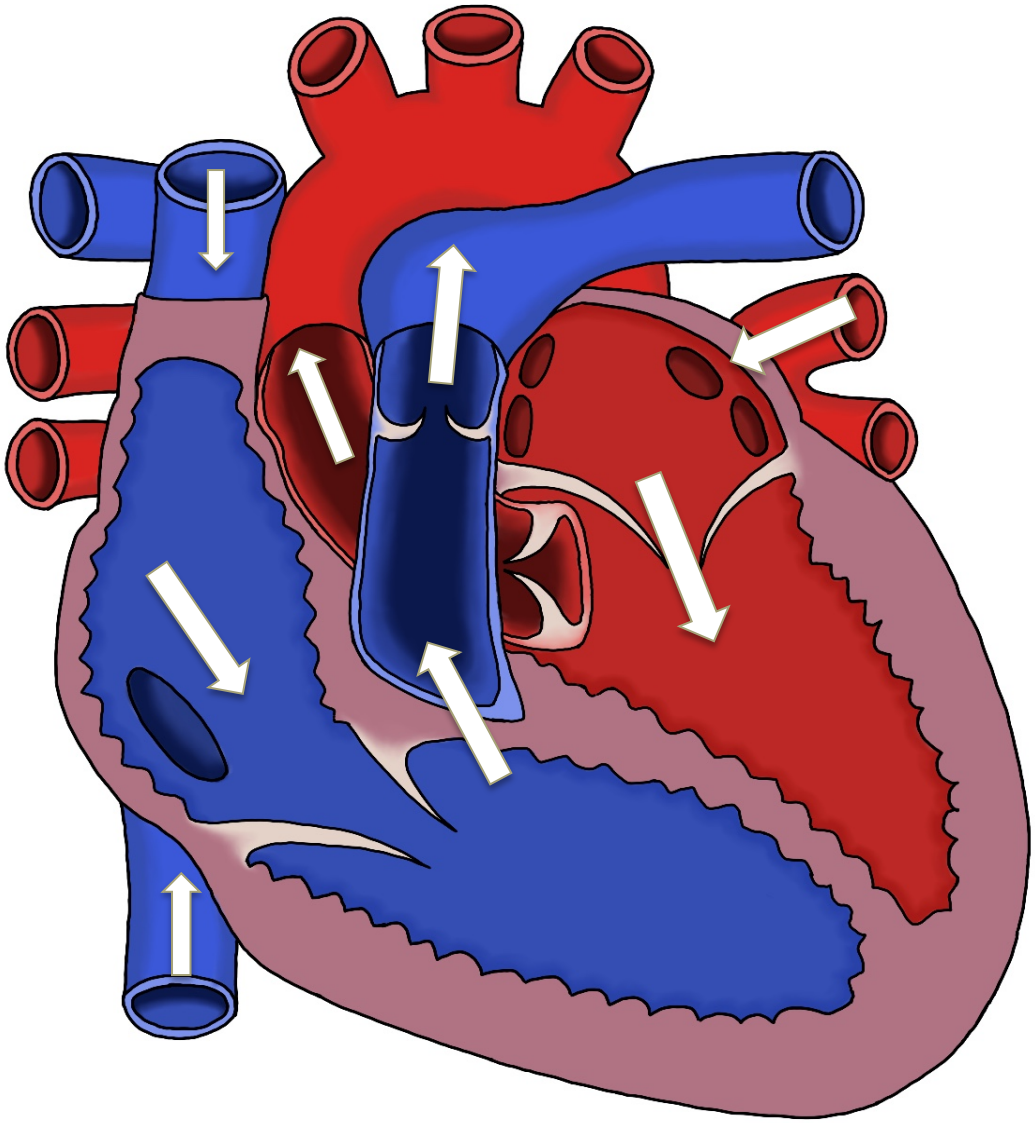
How does this apply to my practice?

- Elevated pulmonary artery pressures have been observed in 60% of patients with reduced left ventricular ejection fraction and 83% of patients with preserved left ventricular ejection fraction on transthoracic echocardiogram (TTE)[1]

1. Lam CS et al. J Am Coll Cardiol. 2009;53(13):1119-26.

Anatomic and physiologic review

The cardiopulmonary circulation can be viewed as a highway



Digital artwork by Jessie Alyward

Why is this concept so important?

- Left ventricle is designed to withstand a high degree of afterload
- Right ventricle is not systemic, therefore it is NOT inherently designed to withstand a high degree of afterload
- Pulmonary hypertension patients do not die from elevated pulmonary artery pressure– they die from resultant right ventricular failure and blunted cardiac output.

Defining pulmonary hypertension

- TTE is a great screening test, and this is usually where we first identify the disease process
  - Right ventricular systolic pressure (RVSP) is considered an echocardiographic surrogate of pulmonary artery pressure
  - RVSP ≥40mmHg suggests an underlying diagnosis of PH[2]
- Historically, PH has always been defined as a mean PAP ≥25mmHg on **right heart catheterization**[3] – however, discussions from the 6th world symposium on PH in 2018 concluded that mean PAP ≥20mmHg should be considered diagnostic[4]
- More on this later…

2. McLaughlin VV et al. J Am Coll Cardiol. 2009;53(17):1573-619

3. Hoeper MM et al. J Am Coll Cardiol. 2013;62(25).

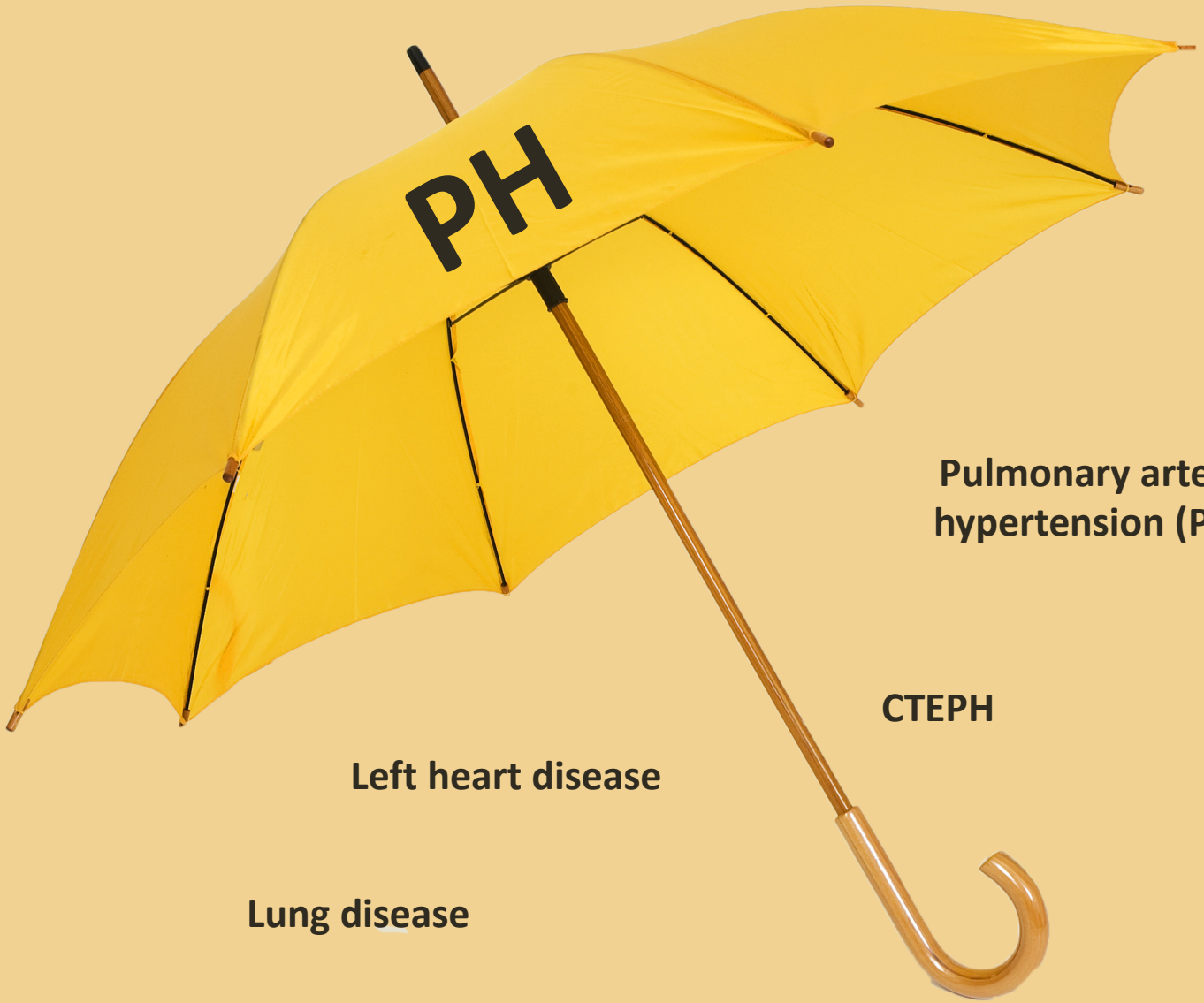
4. Simonneau G et al. Eur [illegible] ir J. 2019;53(1):1801913

Prevalence

- Roughly 20% of the US population has echocardiographic evidence of pulmonary hypertension[5]
- However – only 10 to 15 people **per million** are diagnosed with pulmonary arterial hypertension each year[6]
- How is that possible? Aren't they the same thing?

5. Lam CS et al. Circulation. 2009;119(20):2663-2670.

6. Humbert M et al. A*JRCCM. 2*006;173(31):1023-1030.



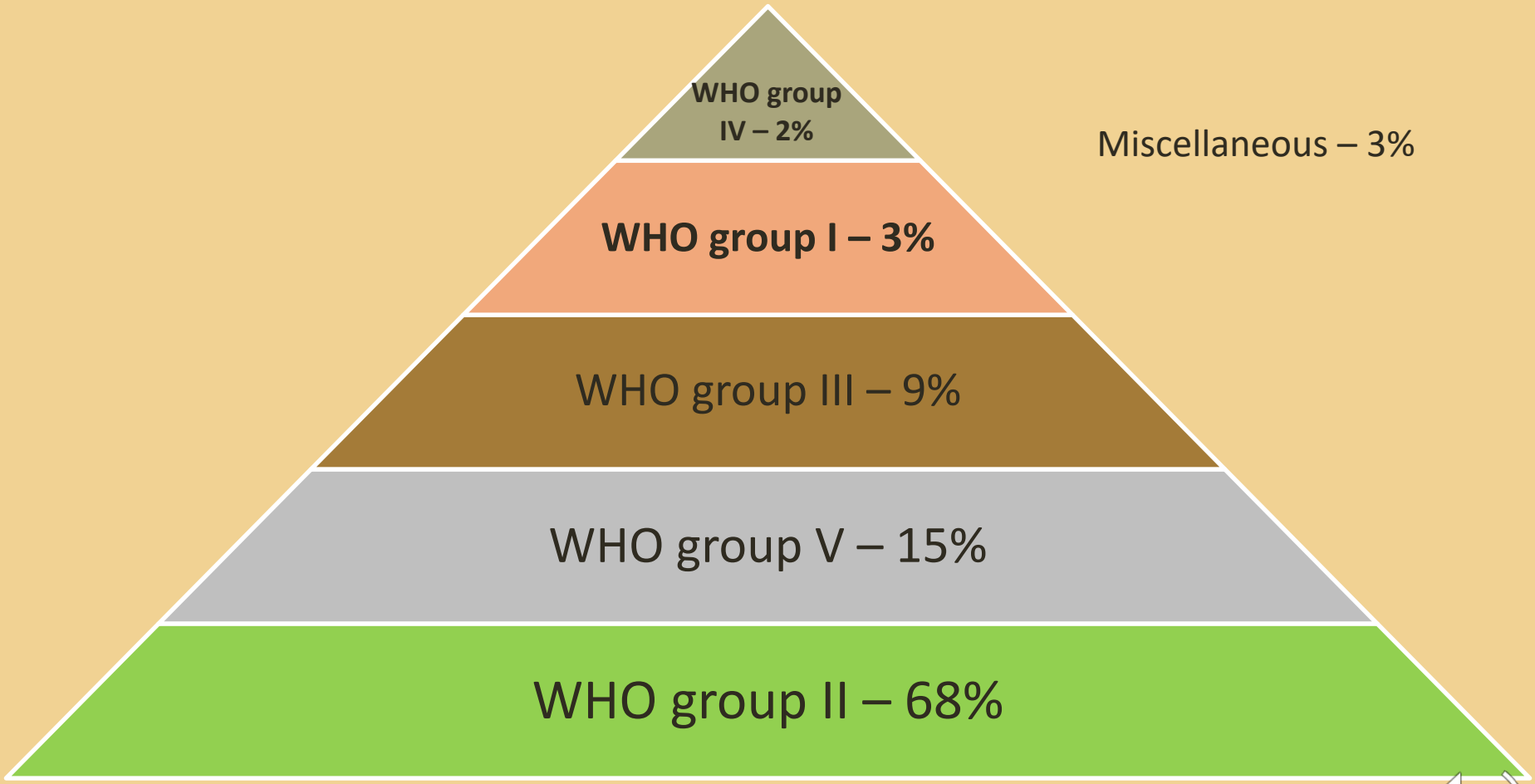
Pulmonary arterial hypertension (PAH)

CTEPH

Left heart disease

Lung disease

World Health Organization (WHO) classifications of pulmonary hypertension



Adapted from Strange G, et al. Heart. 2012;98(24):1805-11.

WHO group I pulmonary hypertension

- Also known as pulmonary arterial hypertension (PAH)
- Accounts for only 3% of total PH cases
- Strong predilection for (younger) women
- Etiologies include congenital heart disease, connective tissue disease, liver disease, HIV, hepatitis, drug induced (pharmaceutical and recreational, heritable (BMPR2 gene strongly implicated)
- Characterized by excess proliferation, apoptosis-resistance, inflammation, fibrosis, and vasoconstriction[7]

7. Ryan, JJ et al. Can J Cardiol. 2015;31(4):391-406.

Pathways of disease in PAH

- Prostacyclin
- Endothelin
- Nitric oxide

WHO group II pulmonary hypertension

- Encompasses the overwhelming majority of PH cases (nearly 70%)
- Structural heart disease (left heart failure, valvular disease)
- Risk factors include old age, female sex, untreated or severe obstructive sleep apnea (OSA), atrial fibrillation, obesity, long-standing hypertension, renal insufficiency

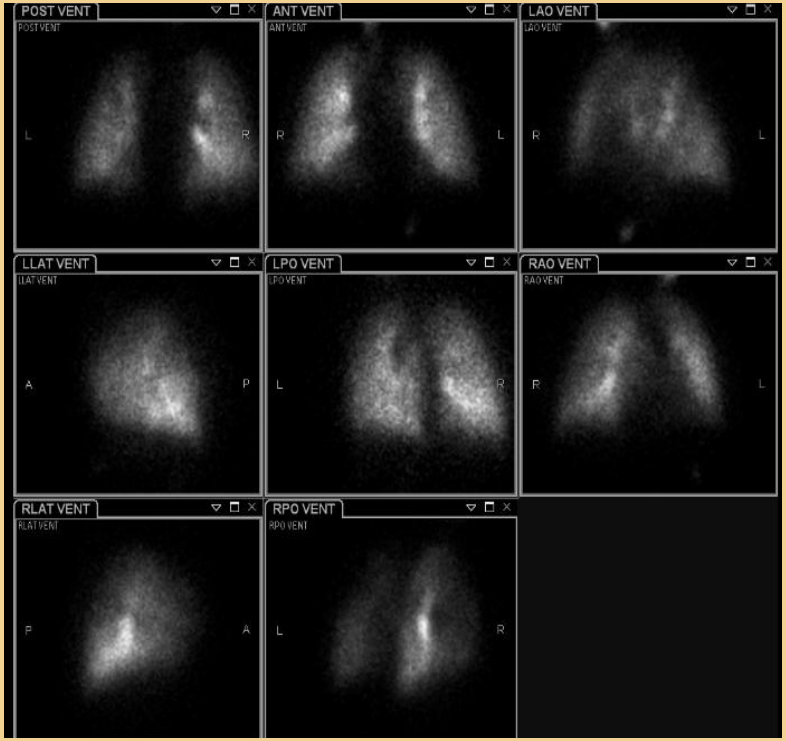
WHO group III pulmonary hypertension

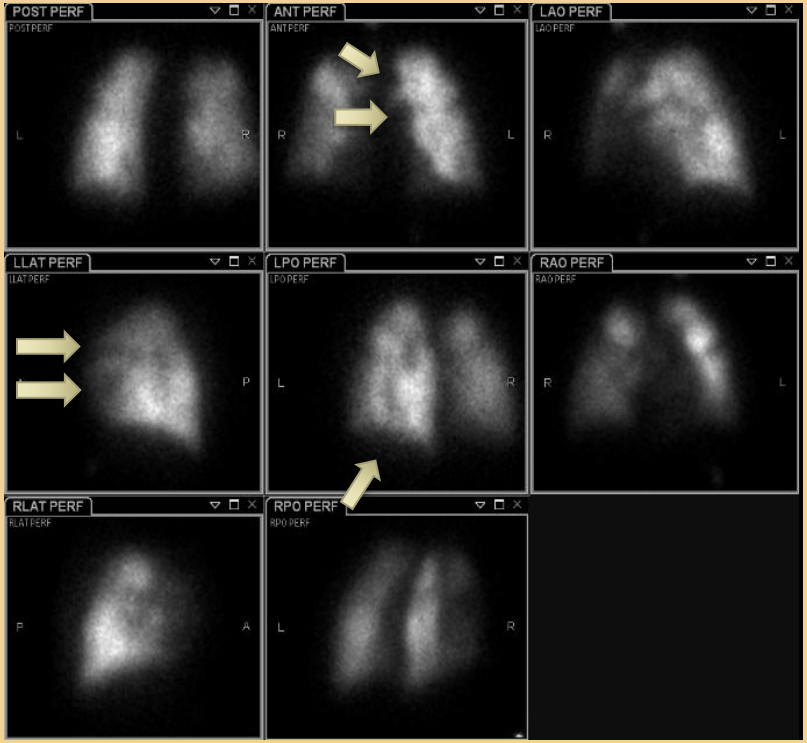
- Accounts for approximately 25% of PH cases
- COPD, emphysema, untreated or severe OSA, prolonged high altitude exposure, interstitial lung disease, pulmonary fibrosis

WHO group IV pulmonary hypertension

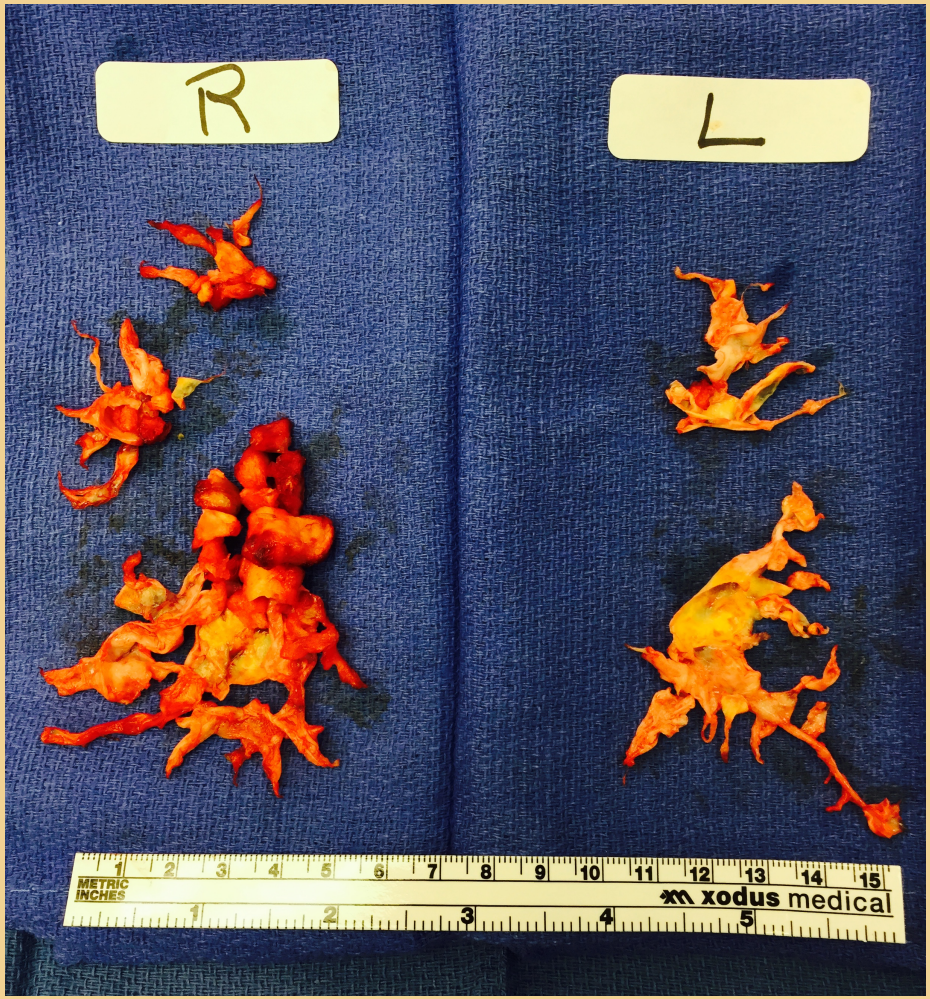
- Chronic thromboembolic pulmonary hypertension (CTEPH)
- Rare – accounts for only 1% of PH cases
- Risk factors include history of DVT/PE, hypercoagulable disorder, thyroid replacement therapy, malignancy, or splenectomy
- Pulmonary thromboembolectomy can be **curative** in the appropriately selected patient

Ventilation perfusion scintigraphy (V/Q)

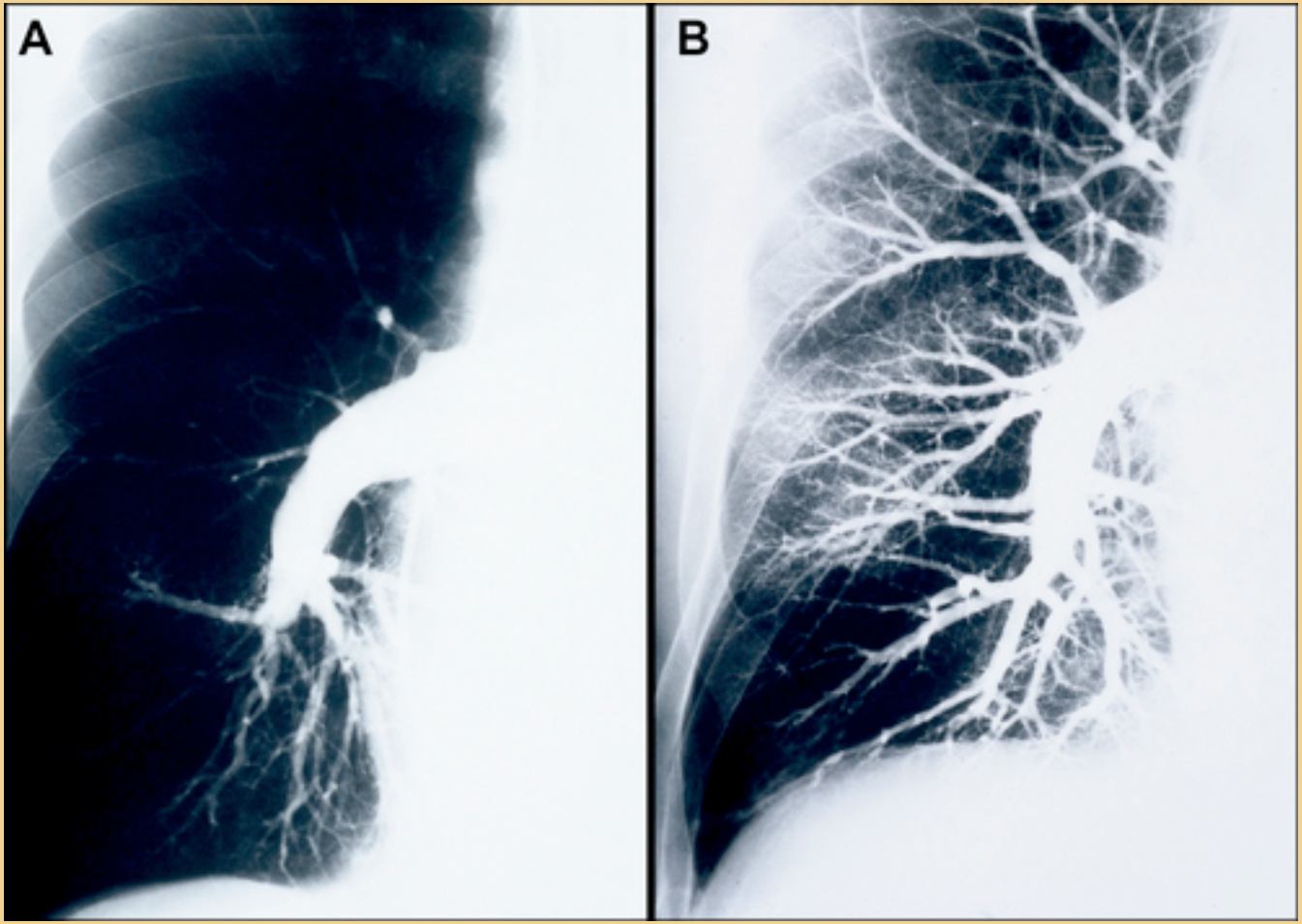




Pulmonary thromboembolectomy (PTE)



Pulmonary angiogram: before and after



WHO group V pulmonary hypertension

- Encompasses all other etiologies, <1% of patients
- Sarcoidosis, myeloproliferative disorders, hemolytic anemias, vasculitis, langerhans cell histiocytosis, neurofibromatosis, and glycogen storage diseases - - to name a few

Differentiating between WHO group I and WHO group II PH

- Most misdiagnoses occur when trying to delineate a PAH patient from a WHO group II patient
  - PAH → female, fertile, previously functional
  - WHO group II → older, obese, OSA

Vocabulary review!

- WHO group I pulmonary hypertension = pre-capillary pulmonary hypertension = pulmonary arterial hypertension (PAH)
- WHO group II pulmonary hypertension = post-capillary hypertension
- It is also possible to have combined pre and post-capillary pulmonary hypertension

Case presentation – “Jean”

A 75y/o female presents to your office for a yearly evaluation. Her past medical history is significant for atrial fibrillation, OSA, and obesity. She endorses worsening shortness of breath with exertion over the past 6 months, mild lower extremity swelling, and difficulty breathing at night prompting you to order a 12-lead EKG, CXR, and TTE. She has no history of coronary artery disease or COPD.

The patient’s EKG does not demonstrate any evidence of recent ischemia or infarction. CXR is largely unremarkable without an enlarged cardiac silhouette.

TTE reveals a left ventricular ejection fraction (LVEF) of 65-69% with concentric left ventricular hypertrophy and a dilated left atrium. There is mild to moderate mitral regurgitation. The patient’s right ventricular size and systolic function are normal – however, the echo report reveals pulmonary hypertension with an estimated right ventricular systolic pressure of 60mmHg.

How do we approach this patient’s evaluation?

History taking is a crucial diagnostic tool!

- There is nothing less expensive, less invasive, or more comprehensively helpful when painting the picture of a new PH patient
- Inquire about the various risk factors for each WHO group
- Most commonly reported symptoms amongst PH patients are shortness of breath, fatigue, chest pain, edema, lightheadedness/pre-syncope/syncope, and palpitations

Obtaining a relevant history cont.

- Symptoms of left heart failure
  - Shortness of breath, cough, early satiety, lower extremity edema
  - Orthopnea and paroxysmal nocturnal dyspnea are highly specific with a strong negative predictive value[8]
- Symptoms of right heart failure
  - **Pre-syncope or syncope**, abdominal distention and early satiety, ascites

8. Ekundayo OJ et al. 2009;104(2):259-264.

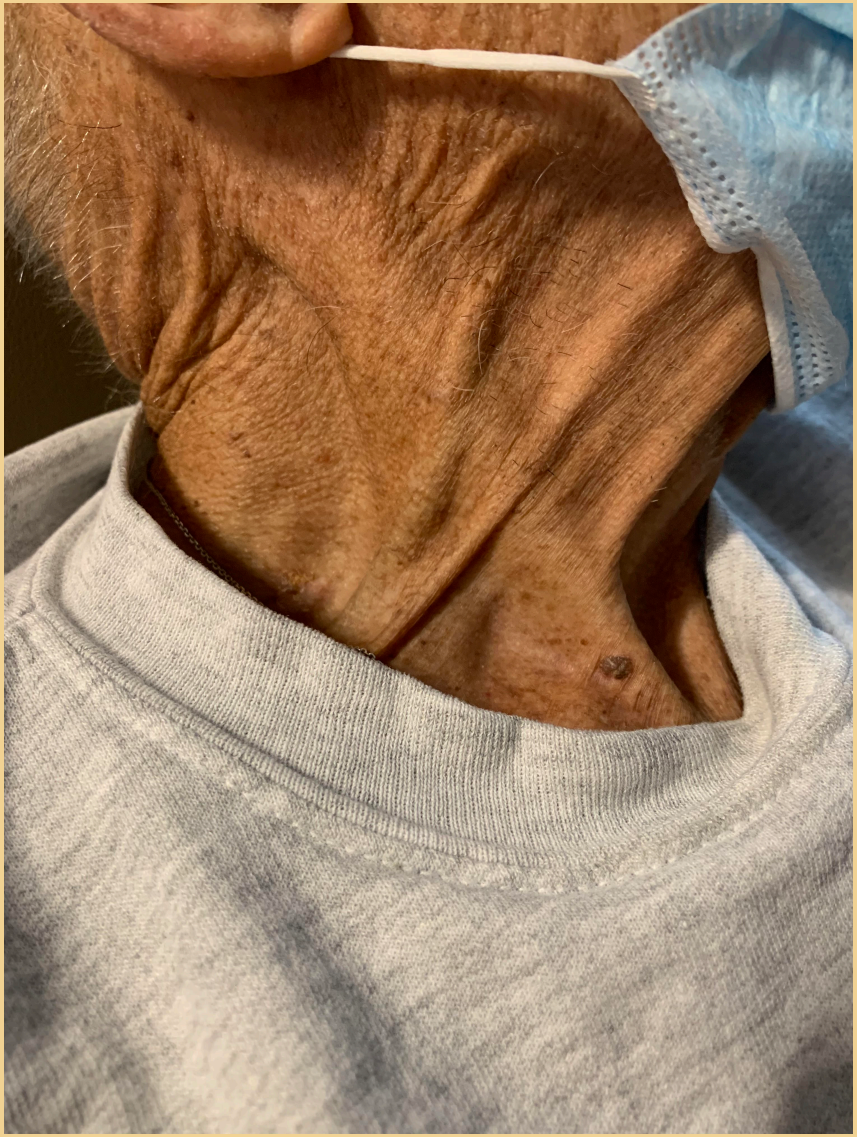
Using the medical history to phenotype PH

- History of atrial fibrillation
  - Atrial fibrillation can induce an acute exacerbation of heart failure
  - Heart failure can also induce atrial fibrillation by increasing left atrial pressure and causing left atrial dilation
- History of obesity and OSA
  - High rate of comorbid OSA and heart failure with preserved ejection fration (HFpEF)
  - Untreated OSA causes hypoxia, elevation in systemic BP, hypoxemia, and neurohormonal/sympathetic nervous system stimulation

Physical Exam

- Detailed skin exam – assess for skin changes (particularly on the hands, fingers, and fingernails as well as the lips and face), assess for rashes
- Pulmonary – pleural effusion, crackles
- Cardiac – edema, JVD, murmurs, accessory sounds **(pulmonary S2)**
- Abdominal exam - hepatosplenomegaly
- Peripherally – **cool extremities, diminished pulses**

Jugular venous distention



Focused diagnostics

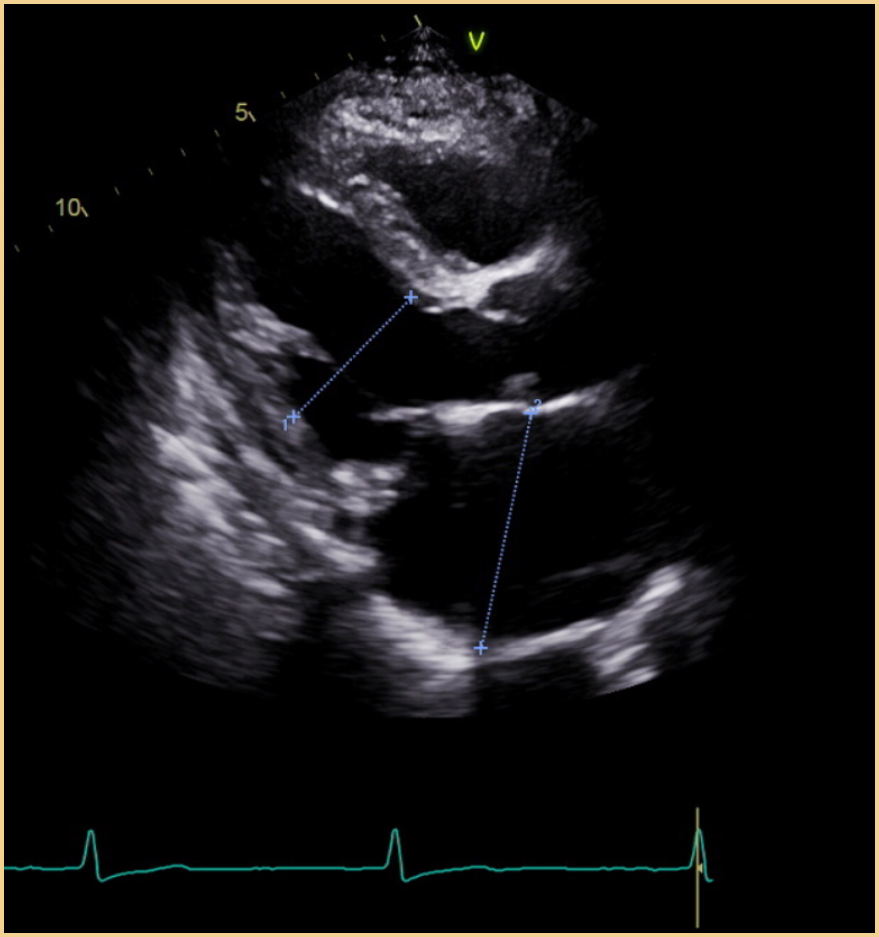
- Your history and physical exam should inform diagnostics
  - All patients need a baseline EKG and CXR
  - Serologies to rule out CTD
  - Pulmonary function testing +/- high resolution CT
  - Ventilation perfusion scintigraphy (V/Q scan)
    - If ordered – this MUST be interpreted by an experienced operator

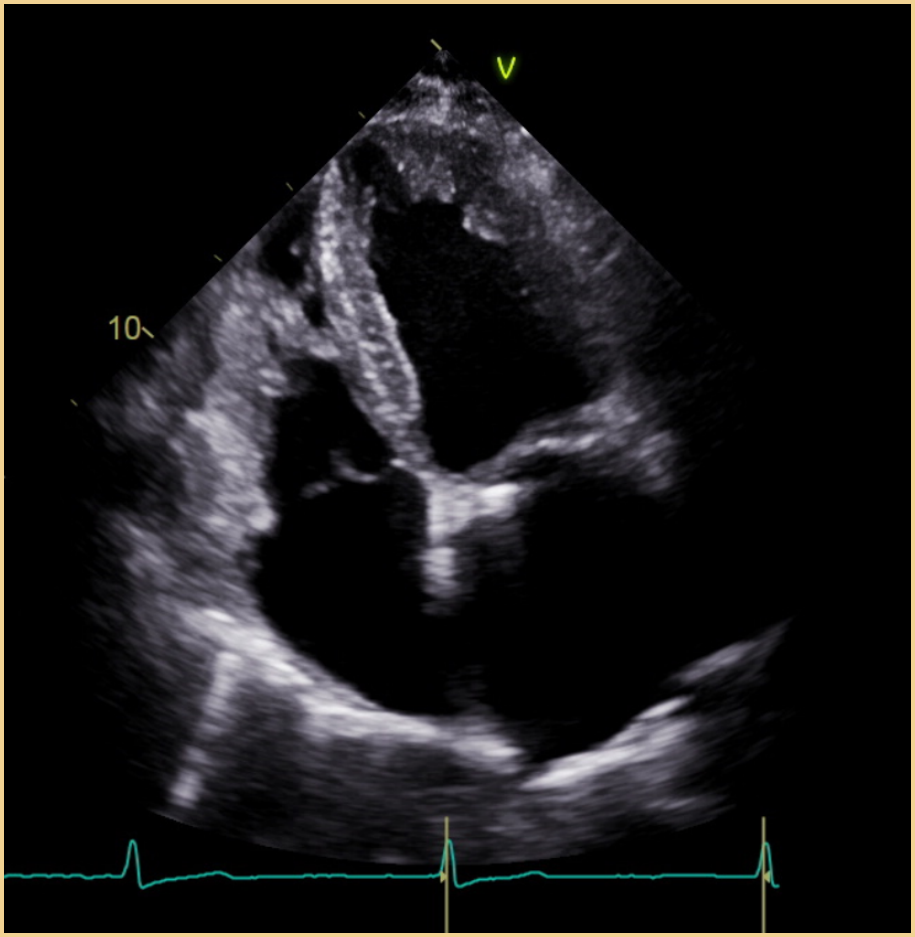
What can be learned from the patient's Echo?

- Concentric left ventricular hypertrophy (LVH)
  - Often results from long-standing hypertension, major risk factor for HFpEF
- Left atrial enlargement (LAE)
  - Commonly referred to as the HgbA1C of heart failure
  - LAVI >43ml/m2 has been shown to differentiate pre-capillary PH from post-capillary PH with 97% sensitivity and 100% specificity[9]

9. Crawley SF et al. 2013;6(10):1120-1.

Left atrial enlargement





What can be learned from the patient's Echo?

- Mitral regurgitation (MR)
  - Severe, ongoing MR leads to chronically elevated left atrial pressure and passive transmission of pressure into the pulmonary circulation[10]

10. Patel H et al. J Am Heart Assoc. 2014;3(4)

Question: This patient almost certainly carries a diagnosis of heart failure with preserved ejection fraction (HFpEF)

A. Yes, I'm pretty sure
B. I think so but I'm not confident
C. No, the patient's Echo report didn't mention anything about heart failure

A. Yes, we're pretty sure!

- Female of advanced age
- Multiple risk factors including atrial fibrillation, MR, OSA, and obesity
- Symptoms of left heart failure
- Echo report with reported concentric LVH and a dilated left atrium

Other considerations when reviewing an Echo of a potential PH patient

- Right ventricular dilation and dysfunction
  - Right ventricular end diastolic diameter (RVEDd)
    - Normal ~35mm
  - Tricuspid annular plane systolic excursion (TAPSE)
    - Normal ~22-25mmHg
  - Right ventricular fractional area change (RVFAC)
    - Abnormal if <35%
    - In small observational studies, RVFAC has been shown to be an independent predictor of reduced cardiac index in PAH patients[10]

10. Julien HM et al. 2015;65(10).

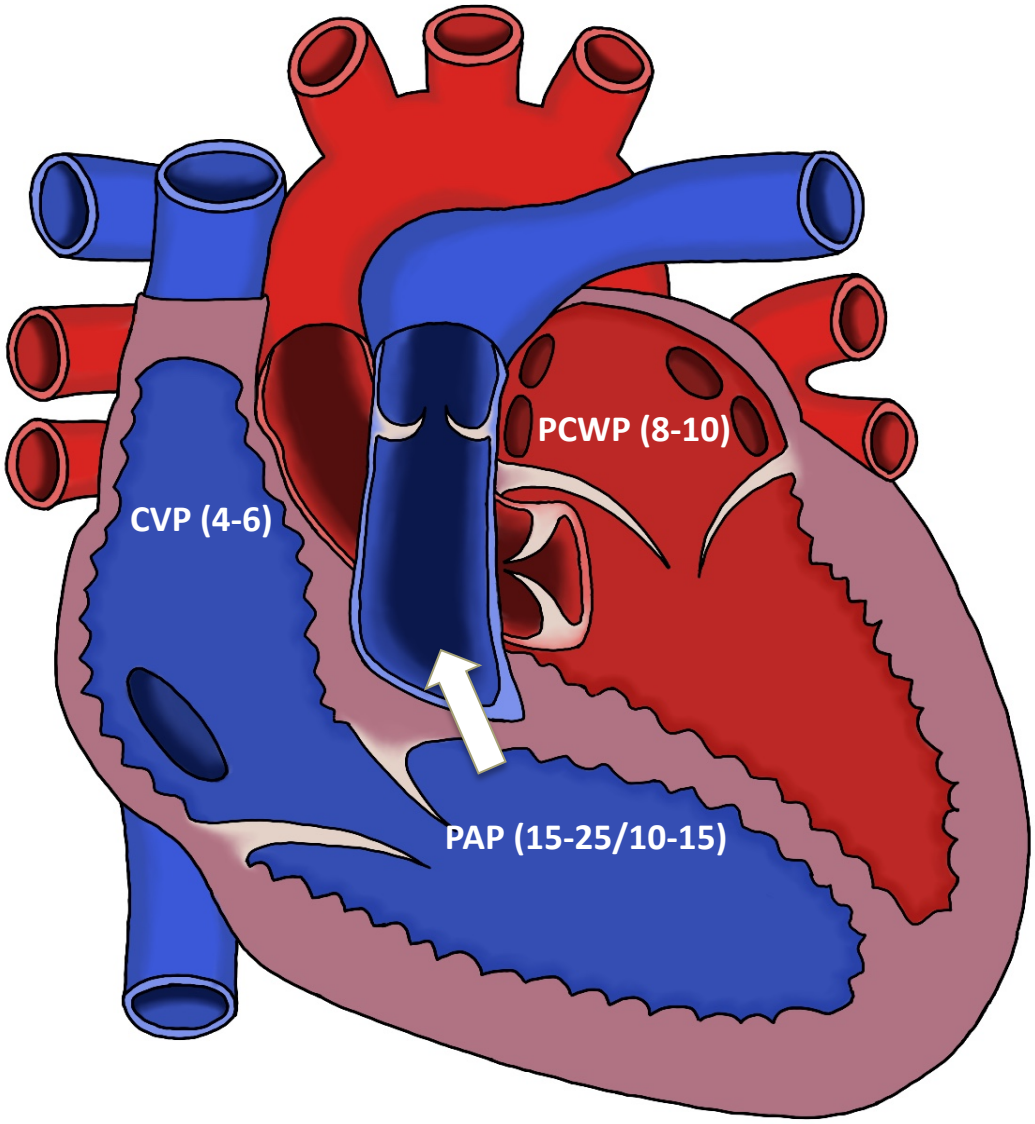
Which WHO group does our patient most likely fall into?

A. WHO group I
B. WHO group II
C. WHO group III
D. WHO group IV
E. I don’t have enough information to decide

Based on what we know – which WHO group does our patient fall into?

B. WHO group II

Right Heart Catheterization



Digital artwork by Jessie Alyward

Pre or post-capillary?

- PAH i.e. pre-capillary disease
  - Mean pulmonary artery pressure ≥20mmHg **AND** end-expiratory left atrial pressure (PCWP) ≤15mmHg **AND** pulmonary vascular resistance (PVR) >3 wood units (WU)
    - PVR in WU = (mean PA – PCWP) / cardiac output

Who needs a RHC in PH?

- WHO group I
- WHO group II – failure to improve with appropriate risk factor mitigation

Our patient presents to the cath lab

- Right atrial pressure/central venous pressure (CVP): 6mmHg
- Pulmonary artery pressure (PAP): 36/18mmHg (mean PAP 27mmHg)
- Left atrial pressure/pulmonary capillary wedge pressure (PCWP): 8mmHg
- Cardiac output: 6.0L/min (normal 5-6L/min)
- Cardiac index: 2.7L/min/m2 (normal 2.5-4L/min/m2)
- PVR: 3.1 wood units

Now that we've dried our patient out, let's water them!

- Fluid challenge
  - 500cc bolus of fluid over a period of 5 minutes to see if we can induce a change in PCWP to confirm the diagnosis of WHO group II PH
  - If PCWP ≥18mmHg, the diagnosis is confirmed
- Our patient's PCWP rises to 20mmHg with a fluid challenge
- This patient has confirmed WHO group II (post-capillary) pulmonary hypertension

Wrapping up this case study

- What do we do for this patient?
  - Ongoing, aggressive risk factor modification
    - Tightly controlled volume status
    - Rate and rhythm control
    - CPAP/BiPAP compliance
    - Blood pressure control
    - Frequent outpatient touch points
    - Consider clinical trial enrollment

Case Study #2 – “Susan”

A healthy, 24y/o caucasian female without any known PMH presents to your office with complaints of exertional dyspnea and decreased exercise capacity over the past two months. She was previously a track athlete. Now, she finds that she is becoming lightheaded and dyspneic with more than moderate exertion. She has never carried a diagnosis of asthma. She does not smoke or vape. No history of DVT/PE and she is not using oral contraceptives. She also complains of joint pains and states that her fingers become painful and appear cyanotic in the cold weather.

You gather an extensive history from the patient which is otherwise non-contributory.

What relevant diagnostics should be completed?

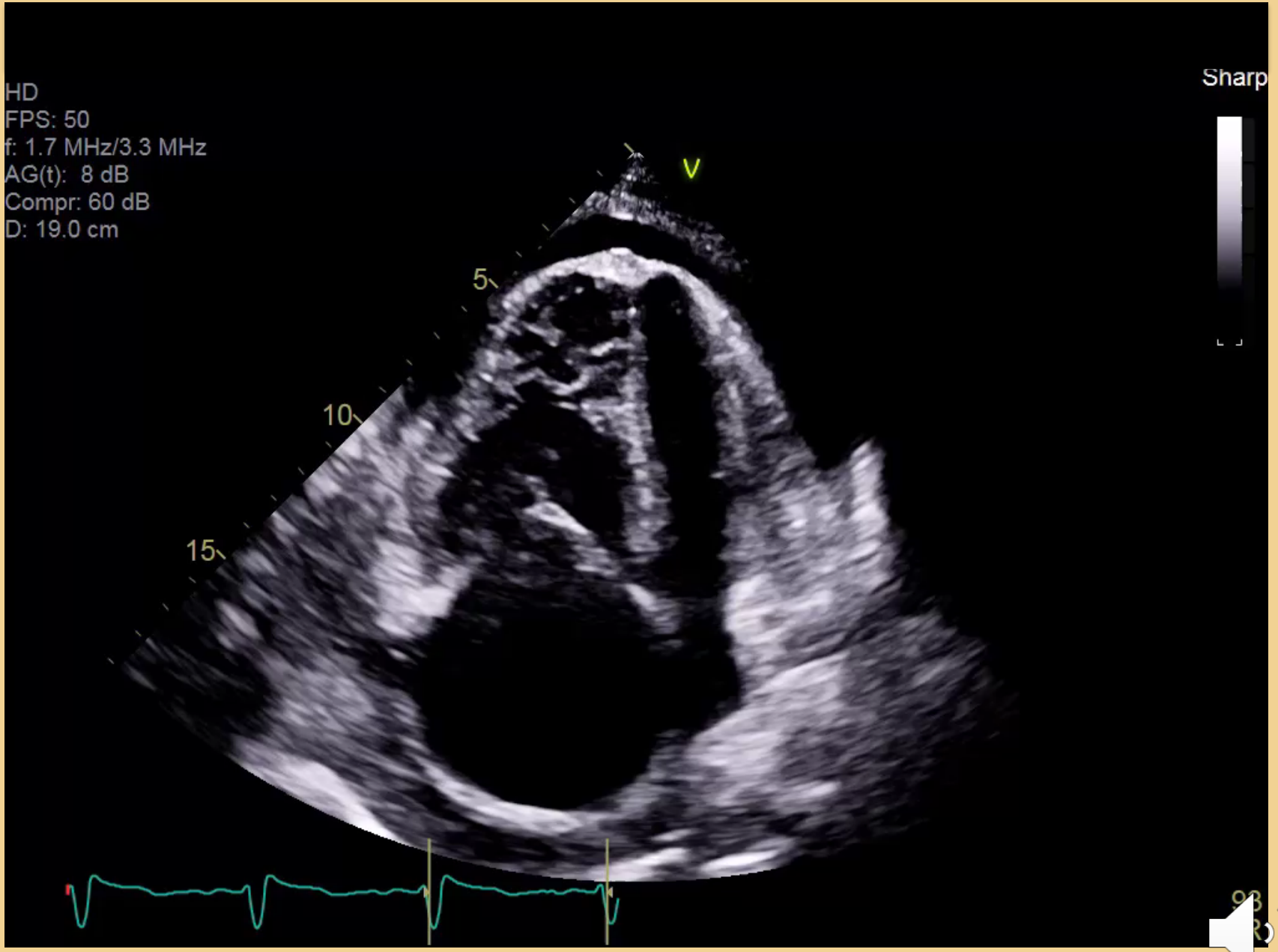
A. TTE, stress test, PFTs
B. TTE, stress test, rheumatologic studies
C. TTE, rheumatologic studies, PFTs

What relevant diagnostics should be completed?

C. TTE, rheumatologic studies, PFTs

Diagnostics

- Serologies: SCL-70 is positive, ANA is positive
- PFTs: No evidence of reactive airway disease
- TTE
  - Normal LAVI, normal LVEF
  - No mitral or aortic valve pathology
  - However …..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Findings that warrant urgent referral to a PH center

- Estimated RVSP >70 in the absence of any apparent left heart disease
- Moderate to severe RV dysfunction on TTE, or evidence of right ventricular failure on exam
- Hypotension
- Cool extremities/concern for low output state
- Syncope
- Pregnant patients with echocardiographic PH

Our young patient presents to the cath lab at a PH center

- CVP: 14mmHg
- PAP: 102/60mmHg (mean 81mmHg)
- PCWP: 8mmHg
- CO: 4.67L/min
- CI: 2.9L/min/m2
- PVR: 15 wood units

- Vasodilator/iNO challenge
  - Roughly 5% of those with PAH respond to calcium channel blocker therapy, and this portends a more favorable prognosis[11]

11. Julien HM et al. Journal Am Coll Cardiol. 2015;65(10).

What about combined pre-capillary and post-capillary PH?

- Ongoing, passive elevation of pulmonary venous pressure from elevated left atrial pressure induces irreversible changes in the pulmonary vasculature
  - Intimal hypertrophy
  - Endothelial injury

REVEAL

- Assigns a score up to 16, with higher scores representing increased morbidity and mortality
  - “Low” risk ≤6
  - “Intermediate” risk 7-8
  - “High” risk ≥9
- REVEAL assigns point values for PAH subgroup, biological sex, renal insufficiency, NYHA WHO FC, HR/BP, all-cause hospitalization, 6MWT, BNP, presence or absence of pericardial effusion, measured DLCO, PAP/PVR by RHC

Pulmonary vasodilator therapy

- Prostacyclin
  - Prostacyclin analogs: oral, inhaled, or IV treprostinil
- Endothelin
  - Endothelin receptor antagonists: ambrisentan, bosentan, macitentan
- Nitric oxide
  - Phosphdiesterase-5 (PDE-5) inhibitors: sildenafil, tadalafil

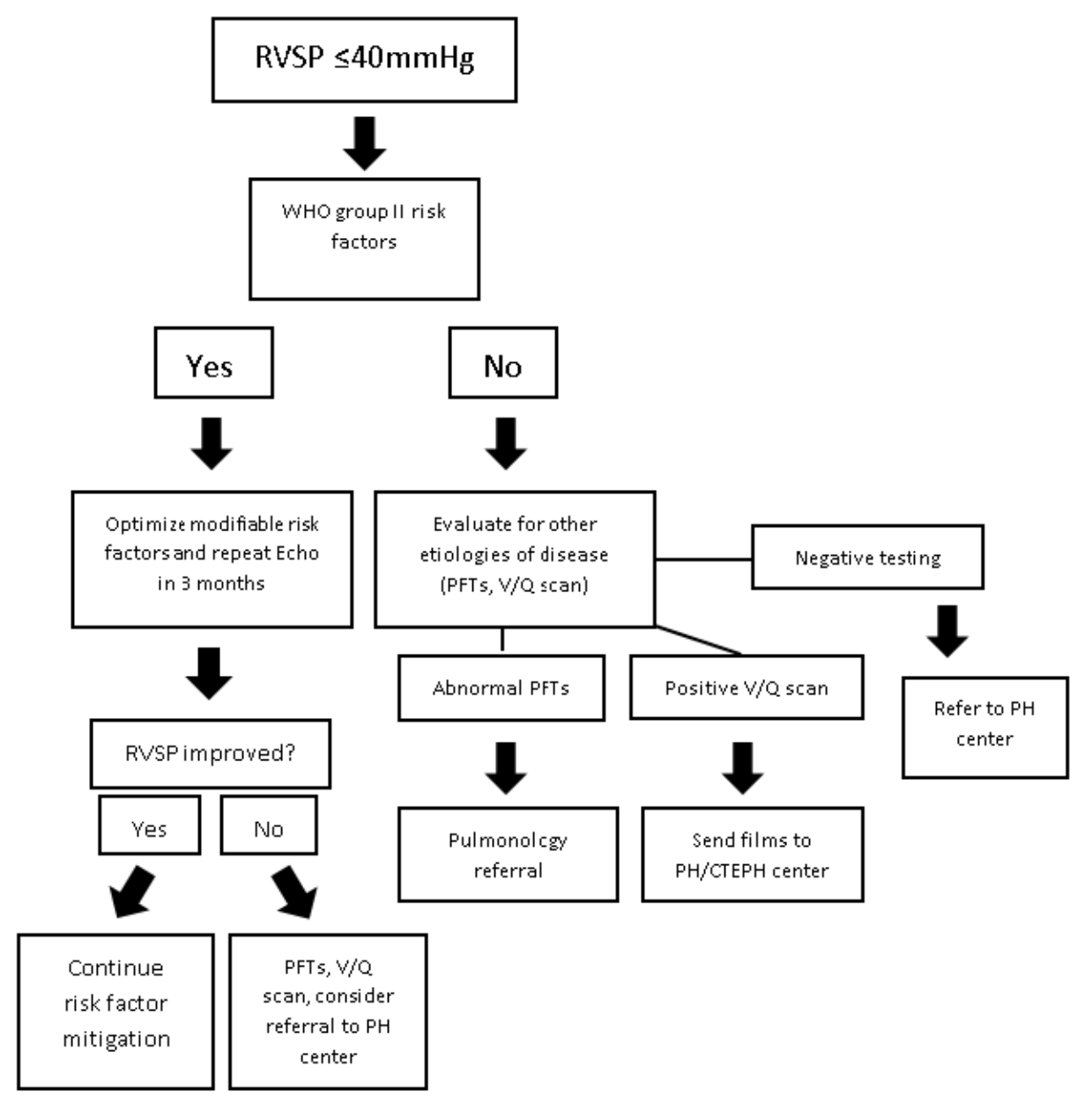
In a WHO group II (post-capillary PH) patient started on pulmonary vasodilator therapy, we would expect to see:

A. No clinical change
B. Clinical improvement
C. Clinical worsening

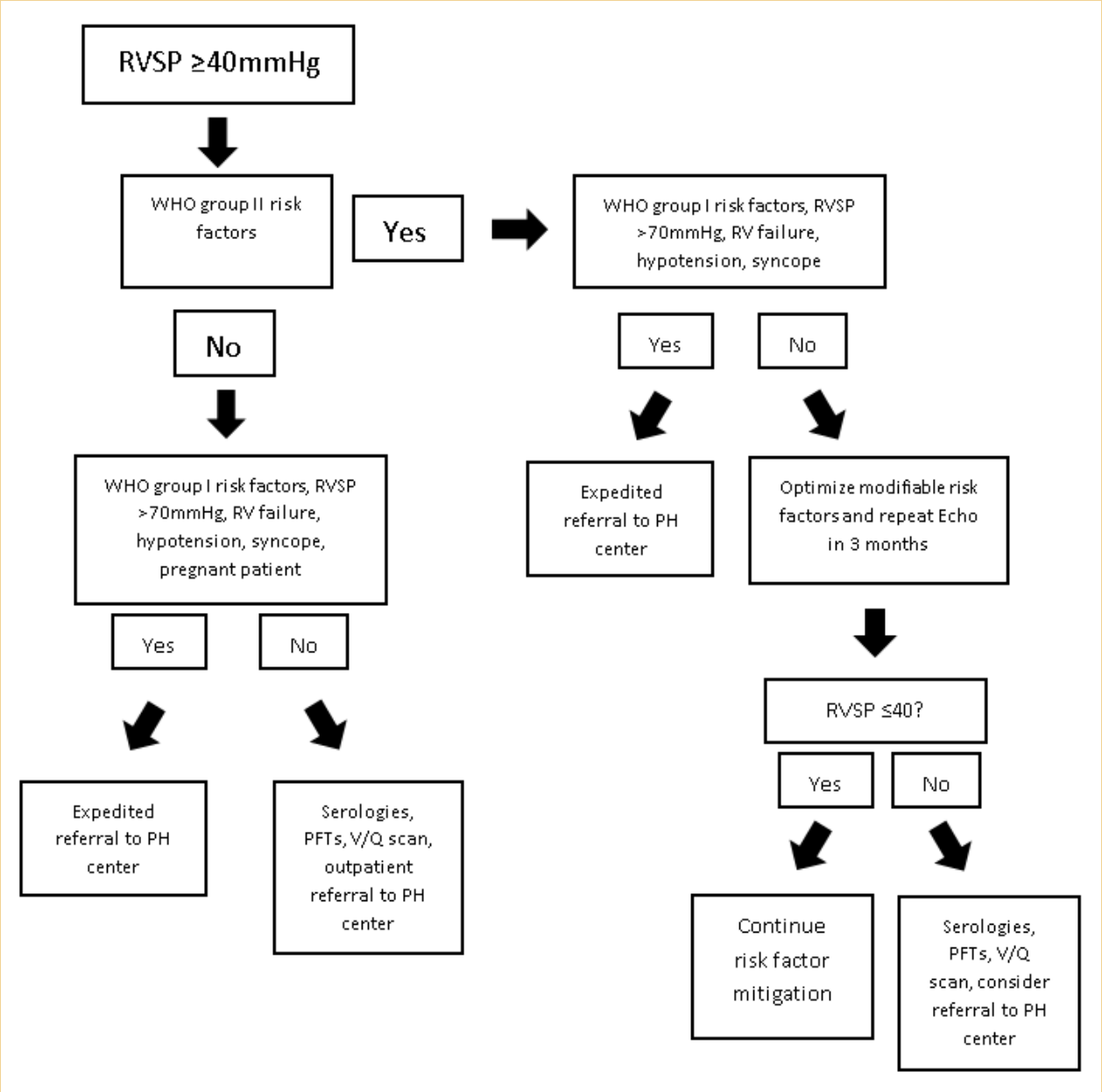
In a WHO group II (post-capillary PH) patient started on pulmonary vasodilator therapy, we would expect to see:

C. Clinical worsening

Suggested triage algorithms



Suggested triage algorithms



Conclusion

- Pulmonary hypertension is an all encompassing term for a wide variety of unique disease processes
- Patients suspected to have pulmonary hypertension warrant a focused and individualized evaluation tailored to their risk factors and symptomatology
- Therapy for the overwhelming majority of PH patients revolves around aggressive risk factor mitigation

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Questions?

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