Pulmonary Hypertension for the Pulmonologist

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Educational Objectives:

1. Understand the definition and categorization of pulmonary hypertension
2. Develop a framework for preliminary categorization of disease etiology based on clinical parameters and non-invasive diagnostic testing
3. Understand the differences in echocardiographic and hemodynamic profiles of pulmonary hypertension vs. pulmonary arterial hypertension
4. Begin to appreciate the general approach to treatment, initial therapy selection, and when to refer to a PH specialty center.

Scenario:
A 58-year-old male Veteran is referred to you for evaluation of dyspnea. He has a 40-pack-year smoking history, HTN, peripheral arterial disease, prior alcohol abuse, and hepatitis C infection (not treated and without complication, of which he is aware). He reports a dry cough for "years" and some dyspnea only with yardwork or higher physical activity levels. However, over the past 6-12 months, his dyspnea has progressed to the point where he notices it while doing light chores, along with swelling of his legs and some vague chest pressure. He remembers being told a while ago that his oxygen levels might be "a little low," more recently, his primary care physician started him on oxygen at 2 L/min. He was also told that he had COPD and was initiated on fluticasone/salmeterol, which may have slightly improved his dyspnea. He has no history of DVT or PE.

On exam, his lungs demonstrate fine bibasilar rales. His JVP is estimated at 9 cmH2O with mild hepatojugular reflux. His P2 is accentuated, with 1+ lower extremity edema without clubbing. He has tattoos. On his 2 L/min, his resting saturation is 92%; with ambulation, he nadirs at 80%. He comes with a chest radiograph showing some increased interstitial markings at the bases and the following PFTs:

FEV1/FVC: 0.80	TLC: 4.65 (90%)
FEV1: 2.94 (83%)	DLCO: 7.6 (35%)
FVC: 3.66 (79%)	

A diagnosis of pulmonary hypertension is considered.

Question 1: What is the definition of pulmonary hypertension (PH)? What types of PH are most common in general pulmonary practice?

Pulmonary hypertension (PH) is a mean pulmonary artery pressure of > 20mmHg and is categorized into five groups(1).

- WHO Group 1 PH - PAH (pulmonary arterial hypertension)
- WHO Group 2 PH - PH due to left heart disease
- WHO Group 3 PH - PH due to lung diseases (sarcoidosis is now included in this group)
- WHO Group 4 PH - PH due to pulmonary artery obstructions
- WHO Group 5 PH - PH with unclear and/or multifactorial mechanisms (e.g., Sickle cell disease, CKD, etc.)

All types of PH may eventually result in right ventricular (RV) dysfunction and failure. While echocardiography, cardiac MRI, and other testing may suggest PH, an accurate characterization of PH requires invasive hemodynamic confirmation. The newest PH definition includes three hemodynamic subtypes of PH:

Definition	**Hemodynamic Characteristics**	**Clinical Groups**
Pre-capillary PH	mPAP > 20 mmHg PCWP ≤ 15 mmHg PVR ≥ 2 Wood Units	Groups 1, 3, 4, 5
Isolated Post-capillary PH	mPAP > 20 mmHg PCWP > 15 mmHg PVR < 2 Wood Units	Group 2
Combined pre- and post-capillary PH	mPAP > 20 mmHg PCWP > 15 mmHg PVR ≥ 2 Wood Units	Groups 2, 3, 5

Table adapted from Ref 1

PH is a relatively common finding among patients with various primary heart (WHO Group 2) and lung (WHO Group 3) diseases. In the context of a general pulmonology practice, the finding of PH is statistically more likely to be related to common underlying heart or lung conditions as opposed to a primary pulmonary vasculopathy (2). Pulmonologists commonly see WHO Group 3 PH associated with COPD, ILD, and other restrictive lung diseases. Pulmonary vasoactive therapy is seldom recommended for chronic lung disease with mild to moderate PH (i.e., mPAP <35, PVR < 4-5 Wood Units, normal or mildly reduced cardiac index). However, some patients with chronic lung disease have a more severe pulmonary vascular phenotype, and these patients may benefit from a further evaluation at a PH center for clinical trial enrollment or monitored trials of pulmonary vasodilators (3).

In patients with pre-capillary PH without chronic lung or heart disease (i.e., WHO Group 1 PH or PAH), pulmonary vasoactive therapy is generally warranted due to the poor prognosis in this group when left untreated. Currently, 12 approved therapies exist for treating PAH, supported by studies showing a benefit related to improvements in functional class, six-minute walk distance, disease progression, hospitalization, and survival. Despite increased awareness of PH, there continues to be a delay in diagnosis for many patients. As a pulmonologist, it is important for you to recognize PH, identify the likely cause, and know when to refer a patient to a specialty center.

Question 2: Based on the information provided in the initial vignette, what features support a diagnosis of pulmonary hypertension? If PH is present, what might be the underlying etiology?

The symptoms of PH are relatively non-specific and include dyspnea, exertional chest pain, syncope, lower extremity edema, and cardiac arrhythmias. The examination suggests elevated right heart pressures and parenchymal lung disease. This patient's progressive exertional dyspnea could suggest PH. Here is a framework for your initial differential diagnosis for PH in this patient:

WHO Subgroup	**Potential pathophysiologic substrate in case patient**	**Clinical clues**
Group 1 PAH (pulmonary arterial hypertension)	Portopulmonary hypertension, HIV-associated PAH	History of alcohol, Hep C infection, Risk factors for HIV infection
Group 2 PH	Diastolic dysfunction, Systolic dysfunction	HTN, peripheral arterial disease
Group 3 PH	COPD, ILD, combined pulmonary fibrosis / emphysema (CPFE)	Rales, hypoxemia, abnormal CXR
Group 4 PH	Pulmonary vascular obstruction	Hypoxemia
Group 5 PH	Sarcoidosis	Rales, hypoxemia abnormal CXR

The patient does not appear to have other risk factors for PAH. However, a careful history should be obtained to exclude findings of connective tissue disease, methamphetamine or stimulant use, and family history of PH.

Question 3: Do the low DLCO and hypoxemia make a particular type of PH more likely?

The PFTs and exam/CXR are particularly suspicious for combined pulmonary fibrosis and emphysema (CPFE). The classic PFT pattern in CPFE is severely reduced DLCO with "pseudonormalized" flows and volumes due to co-existing obstruction and restriction. This population has a particularly high prevalence (30-50%) of PH (4).

The resting hypoxemia and desaturation despite O_2 are important. This degree of hypoxemia is *atypical* for PAH and should be a clue to something else. In the seminal idiopathic pulmonary arterial hypertension (IPAH) registry, the mean PO_2 in these patients was around 70 torr (5). Severe hypoxemia in PH is seen in advanced parenchymal lung disease but also in the setting of right to left shunt via PFO or congenital heart disease with Eisenmenger physiology.

Question 4: What workup should you order for an initial PH evaluation?

Practically, this somewhat depends on your pre-test probability that the patient has a significant intrinsic pulmonary vascular disease that might require disease-directed therapy (e.g., PAH, CTEPH, etc.). A multitude of tests are recommended by guidelines (6), and the workup should be tailored to each individual patient. Reasonable minimum testing at the outset includes ECG, CXR, PFTs, 6-minute walk testing, and echocardiogram (with bubble study if shunt suspected). A chest CT is often useful to determine the severity of chronic lung disease contributing to PH. In intermediate to high probability for PH, a V/Q scan should be performed to rule-out chronic thromboembolic PH (CTEPH). The history and/or exam typically direct the remaining non-invasive

workup, including appropriate serologies for rheumatologic disease evaluation. Right heart catheterization continues to be required to confirm PH and its appropriate hemodynamic classification with certainty.

Scenario continued:
<u>You order some additional tests… highlights are below:</u>
CT chest: Apical-predominant emphysema with basilar/peripheral subpleural reticulation and mild honeycombing.
ANA, Scl-70, RNP, ACE, HIV: All negative/normal
CBC: Hgb 17, Plt 225
BMP: Na+ 133, otherwise WNL
proBNP: 2,450
Abdominal ultrasound: Shrunken liver with nodular surface contours, increased pulsatile venous flow, normal spleen, no evidence of portal hypertension
V/Q: No perfusion defects
Six-minute walk distance: 305 meters
Transthoracic Echocardiogram (TTE):
LV -- Normal size and function; mild diastolic dysfunction. LA normal size.
RV -- Moderately dilated with moderately reduced function, septal flattening, TAPSE 1.6 cm, with a mid-systolic "notch" in flow velocity envelope in RVOT. PASP ~65. RA moderately dilated.
Negative bubble study.

Question 5: How do these results change your differential for the underlying cause of pulmonary hypertension and your overall assessment of disease severity?

These findings suggest significant PH with elevated PVR and RV strain are present (based on elevated proBNP and echo findings). The VQ scan shows no findings to suggest CTEPH. TTE can reveal findings of left heart disease and assess the likelihood of pre-capillary PH, with the features below helpful in categorizing patients with features of PAH or post-capillary PH (7). Please refer to the table in the supplementary material section reviewing these features.

Scenario continued:
You proceed with right heart catheterization (RHC, the gold standard) and obtain the following hemodynamics:

RA 12, RV 78/10, PA 78/32 (mean 47), wedge 12, CO 2.7, CI 1.6, PA sat 62%, Ao sat 95%, PVR ~13 WU

Free hepatic venous pressure = 13, wedged hepatic venous pressure = 14

Question 6: How do you interpret the RHC findings above? How does this change your differential?

These hemodynamics and echo findings suggest precapillary PH with significant RV dysfunction (high RAP, normal wedge, low CO/CI, high PVR). With the findings of significant parenchymal lung disease, WHO Group 3 PH is this patient's most likely cause of PH. Without other diagnoses to support lung disease or CTEPH, *these values would be entirely consistent with Group 1 PAH.*

The hepatic venous pressure gradient (HVPG)indicates no significant portal hypertension (wedged-free hepatic venous pressure = normal <5). This means the patient *cannot* have portopulmonary

hypertension, as portal hypertension is a prerequisite for developing this pulmonary vascular complication of chronic liver disease.

Question 7: How does PH affect clinical outcomes in parenchymal lung disease?

Pulmonary hypertension accompanying intrinsic lung disease is associated with worse outcomes. This has been shown in both COPD and IPF, for example (8,9). Specifically, poor RV function is a harbinger of worse survival. The prognosis of fibrosing lung disease with PH is worse than idiopathic PAH (10). Similarly, in CPFE, reduced CI or elevated PVR is associated with worse survival (11).

Question 8: What is the general approach to therapy for patients with PH-associated lung disease?

1. Treatment/optimization of the underlying lung disease. This includes guideline-based therapy for COPD, ILD, and long-term oxygen treatment for hypoxemic patients.
2. Management of RV dysfunction. This includes the use of diuretics and salt/fluid restriction.
3. Other therapies like digoxin for inotropic effect and anticoagulation are not strongly recommended in the WHO group 3 PH setting.
4. Consideration of pulmonary vasodilator therapy +/- referral to PH center (see discussion following Question 9).

Question 9: What drugs are available to treat PH, and is there evidence of benefit in Group 3 PH?

Current approved "targeted" therapies for PAH include:

1. *Prostanoids and Prostacyclin Receptor Agonists*
    a. Parenteral (IV/s.c.): epoprostenol (IV only), treprostinil (IV and s.c.)
    b. Inhaled: iloprost, treprostinil
    c. Oral: treprostinil, selexipag
2. *Endothelin receptor antagonists (ERAs)*
    a. Oral: bosentan, ambrisentan, macitentan
3. *Phosphodiesterase-5 inhibitors (PDE5-I)*
    a. Oral: sildenafil, tadalafil
4. *Soluble guanylate cyclase stimulators*
    a. Oral: riociguat

Of critical importance is that these drugs have been predominantly studied in Group 1 PAH. Riociguat is also approved for the treatment of inoperable CTEPH. ***There is a paucity of data demonstrating the benefit of these agents in WHO group 3 PH, and only inhaled treprostinil is presently approved for the treatment of WHO group 3 PH related to ILD.***

Patients with severe PH and/or RV dysfunction, especially when out of proportion to airway or parenchymal abnormalities, should be referred to a PH specialty center, and for some patients, cautious use of pulmonary vasodilator therapy may be recommended (3). In Group 3 PH, a major concern with PH therapy is the potential to worsen hypoxemia due to drug-induced vasodilation, worsening V/Q mismatch. This is less so a concern, however, with the inhalational route. In a recent study of 326 patients with ILD and PH, treatment with inhaled treprostinil resulted in a slightly improved 6-minute walk distance compared to a placebo after 16 weeks of therapy (12). In addition, inhaled treprostinil led to a greater reduction in NT-BNP, and fewer patients experienced clinical worsening during the trial in the inhaled treprostinil group. Inhaled treprostinil was not associated with worsening oxygenation in this study. In this small study, patients with

CPFE seemed to benefit less than other subtypes of ILD. Additional studies are needed to confirm the benefit of this therapy and guide which subgroup(s) might benefit most. (12). In this context, it is worth recalling a key physiologic principle: total oxygen delivery to tissues is dictated both by arterial oxygen content (influenced by SpO2) *and* cardiac output. Therefore, in some cases of Group 3 PH where pulmonary hemodynamics are very deranged it is plausible that pulmonary vasodilation may improve overall oxygen delivery, *if* its net effect is to predominantly increase cardiac output (even if there is a relatively smaller concomitant decrement in SpO2 stemming from V/Q mismatch). Unfortunately, predicting how PAH therapies may influence the balance of these competing factors in any individual patient represents a significant knowledge gap. This same principle explains why a lesser-utilized historical treatment for PAH, atrial septostomy (intentional creation of an atrial R>L shunt which predictably results in arterial hypoxemia but improves systemic cardiac output), can actually improve right heart failure and symptoms in selected patients with Group 1 PAH.

In our patient's case, some PH experts might conclude it reasonable to try the patient on inhaled treprostinil and monitor closely for either improvement or worsening; a frank discussion with the patient regarding the many uncertainties with this approach is crucial, including potential harms. This patient's referral for lung transplantation evaluation at diagnosis would be very appropriate.

Question 10: Should we consider a calcium-channel blocker as a treatment for our patient?

Calcium channel blockers should only be used after demonstrating a positive invasive hemodynamic response that recapitulates acute vasoreactivity to a short-acting pulmonary vasodilator (eg., inhaled NO, inhaled or intravenous epoprostenol). A positive response is defined as a fall in mPAP by at least 10 mmHg to an absolute value <40 with no decrease in cardiac output. Patients who demonstrate this likely have a different type of pulmonary vascular disease that exhibits excellent long-term survival with CCB therapy; however, this is mainly observed in idiopathic PAH (and in only ~10-15% of cases) and is virtually non-existent in other PH subtypes (13). Thus, there is no reason to pursue this for our case patient.

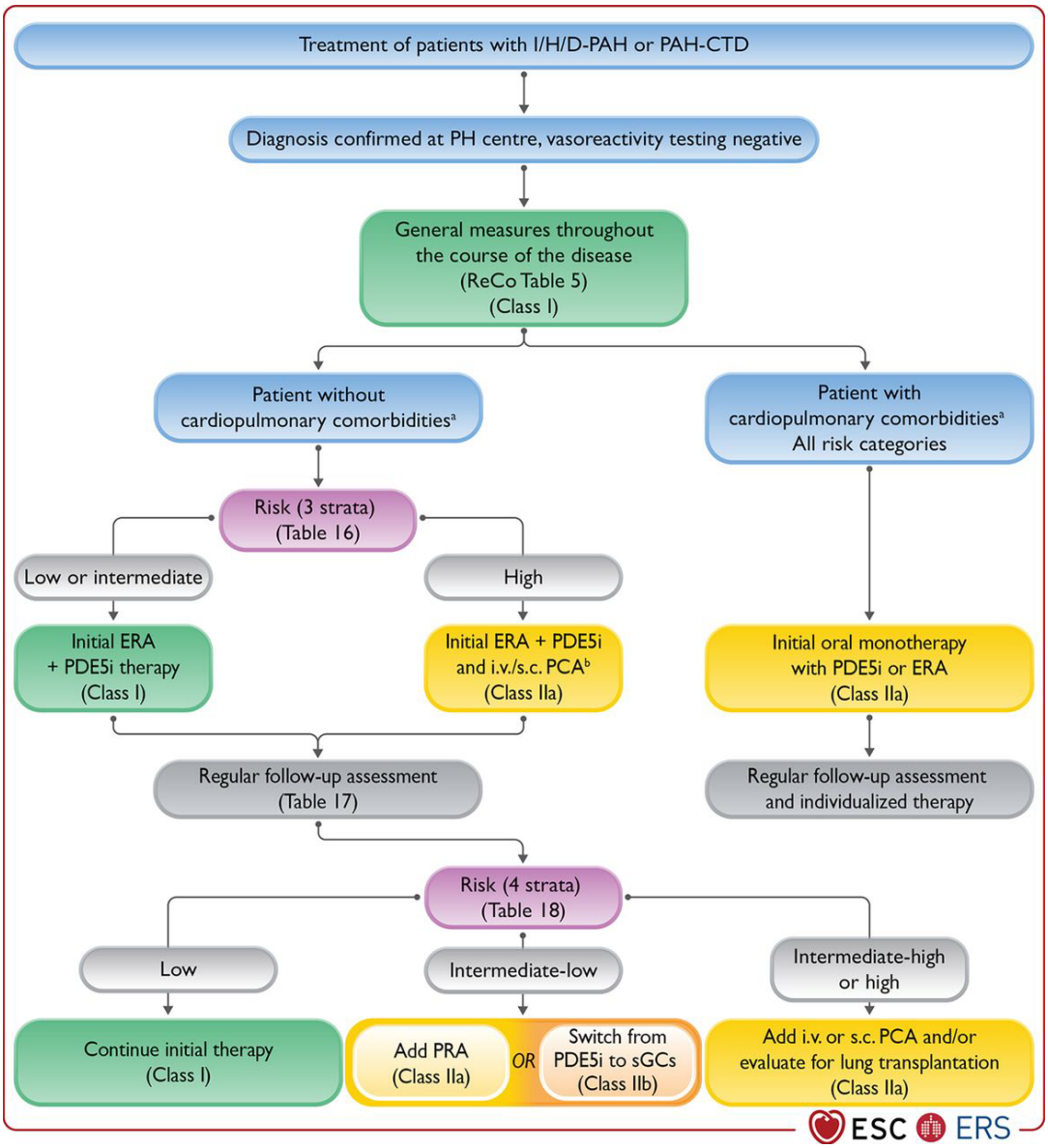
Question 11: Let's say this patient instead had Group 1 PH (PAH)? What therapy would you choose, and how do you follow them?

Head-to-head RCTs compare currently approved pulmonary vasodilators. It is also important to mention that while the threshold for defining PH has been lowered to mPAP > 20mmHg (and PVR >2 for PAH), the inclusion criteria for the majority of RCTs with these agents was an mPAP ≥ 25mmHg and PVR >3- it is not yet clear whether these drugs will have the same efficacy/benefit in patients with mPAP > 20 but < 25mmHg and PVR <3. The choice of therapy in PAH is determined based on risk, so the first step in determining treatment is assessing risk, which can be done using one of several risk calculators (the ESC/ERS risk assessment is shown below, ref 14):

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

A risk calculator derived from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) has also recently been revised, and online calculators are available to facilitate the usage of this tool in clinic settings (15).

For low-risk patients, an initial combination of oral therapy with an ERA and a PDE5-inhibitor is recommended (1, 16). Upfront combination therapy (PDE5 inhibitor + ERA) is superior to monotherapy with respect to clinical outcomes (17). For high-risk patients, initial combination therapy using a parenteral prostacyclin is recommended. Intermediate-risk patients are often managed with triple combination therapy, and patients failing maximal medical therapy should be considered for lung transplantation. The following figure summarizes current guidelines on treatment (1):



Treatment Algorithm for PAH (from reference 1).

Treatment endpoints are not precisely well-defined and tend to be an amalgam of various factors that have been shown to associate with better outcomes. A general goal is for patients to meet low-risk criteria on risk assessment, though it is worth noting a recent analysis which suggests that treatment-induced changes in risk scores (eg, REVEAL) only mediate a small percentage (7-13%) of medications' effect on clinical outcomes, calling into question the validity of current risk scoring systems as appropriate surrogate endpoints in this disease (19).

Question 12: When should I refer to a PH specialty center?

Similar to a transplant population, patients with pulmonary hypertension can benefit from the infrastructure of a dedicated PH program or at least a consultation to define optimal treatment and diagnosis. Data from a single-center study suggest improved survival in PAH patients treated at a PH specialty center (18). Referral to a PH specialty center can clarify PH diagnosis and allow the timely introduction of appropriate therapy (as well as withholding of therapy when it is inappropriate). Most PH centers have dedicated nurses and pharmacists, as much effort is frequently required to get costly PH drugs approved. One needs to be prepared to advance

therapies if the patient is not responding, and parenteral prostacyclins should be at-the-ready for this purpose, where appropriate. Multidisciplinary review at CTEPH centers ensures appropriate therapy for this disease (endarterectomy or balloon pulmonary angioplasty) is considered. For PAH patients failing maximal therapy that includes prostacyclins, and patients with severe PH associated with lung disease, referral for transplant evaluation is indicated. And for some patients with advanced PH who are unsuitable for transplant, consideration of palliative strategies, including atrial septostomy, may be warranted.

References

1. Humbert M, Kovacs G, Hoeper M et al. 2022 ERS/ESC Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2023, 61:2200879.
2. Strange G, Playford D, Stewart S, et al. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. *Heart.* 2012;98(24):1805-1811.
3. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J* 2019; 53: 1801914.
4. Cottin V, Le Pavec J, Prévot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. *Eur Respir J* 2010; 35: 105–111
5. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. *Ann Int Med.* 1987;107(2):216-223.
6. Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801904.
7. Roberts JD, Forfia PR. Diagnosis and assessment of pulmonary vascular disease by Doppler echocardiography. *Pulm Circ.* 2011;1(2):160-181.
8. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Resp Crit Care Med* 1999;159(1):158-164.
9. Nadrous HF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Chest.* 2005;128(4):2393-2399.
10. Hoeper MM, Behr J, Held M, et al. Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias. *PLoS One* 2015; 10;e0141911.
11. Cottin V, Le Pavec J, Prevot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. *Eur Respir J* 2010;35(1):105-111.
12. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled Treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021;384(4):325-334.
13. Montani D, Savale L, Natali D, et al. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. *Eur Heart J.* 2010;31(15):1898-1907.
14. Galiè N, Humbert M, Vachiery JL et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015;46:903-975.
15. Benza R, Gomberg-Maitland M, Elliott C, et al. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. *Chest* 2019;156(2):323-337.
16. Galiè N, Channick R, Frantz R et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J* 2019; 53: 1801889.
17. Galiè N, Barbera JA, Frost A, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373(9):834-44.
18. Pi H, Kosanovich CM, Handen A, et al. Outcomes of pulmonary arterial hypertension are improved in a specialty care center. *Chest* 2020;158(1):330-340.
19. Blette BB, Moutchia J, Al-Naamani et al. Is low risk status a surrogate outcome in pulmonary arterial hypertension? An analysis of three randomized trials. *Lancet Respir Med* 2023 May 22;S2213-2600(23)00155-8.

Supplementary Material

Table 1. Echocardiographic features of pulmonary venous and arterial hypertension

Pulmonary arterial hypertension	Pulmonary venous hypertension
2-D imaging	
Normal LV ejection fraction	Reduced LV ejection fraction
Normal size or small (underfilled) LV	Dilated LV
Dilated RA / Normal LA	Normal RA / Dilated LA
No LVH	LVH
RV:LV size ratio > 1	RV:LV size ratio < 1
RV apex-forming	RV not apex-forming
Reduced RV function/TAPSE	Normal RV function/TAPSE
Doppler imaging	
Grade I or no diastolic dysfunction	Grade II-III diastolic dysfunction
Minimal or no mitral/aortic valve disease	≥ Moderate mitral/aortic valve disease
Systolic notching of FVE in RVOT	No systolic notching of FVE in RVOT
AcT of FVE in RVOT < 70 msec	AcT of FVE in RVOT > 95 msec

Table adapted from reference 7.

Pre/Post-Test Questions:

1. Which of the following is characteristic of pulmonary venous rather than pulmonary arterial hypertension on 2-D echocardiography?

    a. Normal right ventricular function
    b. Normal left ventricular function
    c. No evidence of left ventricular hypertrophy
    d. Right ventricle is apex forming

2. You see a 40-year-old female in your office for evaluation of possible pulmonary hypertension. Her workup so far has included an echocardiogram showing a dilated right ventricle with moderately reduced function and a normal EF with normal left ventricular function. Her spirometry is normal. She has had some negative basic serologies, including ANA, HIV, RNP, ACE, and anti-SCL-70. Her CT scan was largely unremarkable as was a VQ scan. You ultimately decide to refer her for right heart catheterization, and the report shows the following hemodynamics:

    RA 14, PA 55/19 (mean 31), PCWP 8, CO 3.6, CI 1.9, PVR 6.4

    Which is the most likely WHO category of this patient's pulmonary hypertension?

    a. WHO Group 1
    b. WHO Group 2
    c. WHO Group 3
    d. WHO Group 4
    e. Either A or B
    f. All of the above remain significant possible etiologies

3. Which of the following WHO PH classification groups does randomized trial data exist supporting the therapeutic efficacy of at least one pulmonary vasoactive medication?
    a. Group 1 only
    b. Group 3 only
    c. Groups 1 and 3
    d. Groups 1, 3, and4