# Pulmonary Hypertension for the Pulmonologist

## Case related questions.

**Scenario:**
A 58-year-old male Veteran is referred to you for evaluation of dyspnea. He has a 40-pack-year smoking history, hypertension, peripheral arterial disease, prior alcohol abuse, and hepatitis C infection (not treated and without complications). 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 and occurs 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," and his primary care physician prescribed home oxygen at 2 L/min at that time. He was also diagnosed with chronic obstructive pulmonary disease (COPD) and was prescribed fluticasone/salmeterol, which may have slightly improved his dyspnea. He has no history of deep venous thrombosis (DVT) or pulmonary embolism (PE).

On exam, his lungs demonstrate fine bibasilar rales. Jugular venous pressure (JVP) is estimated at 9cmH2O with mild hepatojugular reflux. P2 is accentuated, with 1+ lower extremity edema and no clubbing. He has tattoos. With 2 L/min continuous flow oxygen via nasal cannula, his resting SpO2 is 92%; with ambulation, this decreases to 80%. Previous chest radiograph showed some increased interstitial markings at the bases. Pulmonary function tests (PFT) reveal:

Forced Expiratory Volume in 1 second (FEV1): 2.94 (Z-score -0.45, 83% predicted)
Forced Vital Capacity (FVC): 3.66 (Z-score -1.55, 79%% predicted)
FEV1/FVC:0.80 (Lower limit of normal (LLN) 0.69)
Total Lung Capacity (TLC): 4.65 (Z-score -0.22, 90%% predicted)
Diffusing Capacity of the Lungs for Carbon Monoxide (LCO): 7.6 (Z-score -4.01, 35%% predicted)

A diagnosis of pulmonary hypertension is considered.

**Question 1:** What is the definition of pulmonary hypertension (PH)? How are possible causes of PH classified? What types of PH are most commonly encountered in general pulmonary practice?

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

**Question 3:** What workup should you order for an initial PH evaluation?

**Scenario cont.:**
**You order some additional tests. Results are below.**

**Transthoracic Echocardiogram (TTE)**:
Left Ventricle (LV)- Normal size and function; mild diastolic dysfunction. LA normal size. Right Ventricle (RV) - Moderately dilated with moderately reduced function, septal flattening, and tricuspid annular plane systolic excursion (TAPSE) 1.6 cm. Mid. Mid-systolic "notch" in flow velocity envelope in Right Ventricular Outflow tract (RVOT). Estimated pulmonary arterial systolic pressure (PASP)65mmHg. Right Atrium (RA) moderately dilated. Negative bubble study.
**CT chest:** Apical-predominant emphysema with basilar/peripheral subpleural reticulation and mild honeycombing.
**Anti-nuclear antibody (ANA), Human immunodeficiency virus (HIV), Ribo Nucleoprotein (RNP) antibody, Angiotensin Converting enzyme (ACE) anti-Scl-**70, All negative/normal
**Complete Blood Count (CBC)**: Hemoglobin 17, Platelet 225
**Basic Metabolic Profile (BMP)**: $Na^+$ 133, otherwise normalnormal
**N-Terminal Pro-Brain Natriuretic Peptide** (**NT-proBNP)**: 1,250 (normal is < 300)
**Abdominal ultrasound**: Nodular liver, increased pulsatile venous flow, normal spleen, no evidence of portal hypertension
**V/Q scan**: No perfusion defects
**Six-minute walk distance**: 305 meters (51% predicted)

**Question 4:** How do these results change your differential for the underlying cause of pulmonary hypertension and your overall assessment of disease severity?

**Scenario cont.:**
**You proceed with right heart catheterization (RHC) and obtain the following hemodynamics:**

*RA 12 mmHg, RV 78/10, PA 78/32 (mean 47 mmHg), PCWP 12 mmHg, CO 2.7 L/min, CI 1.6 L/min/$m^2$, PA sat 62%, Ao sat 95%, PVR ~13 Wood units*

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

**Question 5:** How do you interpret the RHC findings above? How does this change your differential?

**Question 6:** What is the general approach to therapy for patients with WHO Group 3 PH?

**Question 7:** What drugs are available to treat PH, and is there evidence of benefit in Group 3 PH?

**Question 8:** Should we prescribe a calcium-channel blocker as a treatment for our patient?

**Question 9:** Imagine this patient instead had Group 1 PH (PAH)? What therapy would you choose, and how do you follow them?

**Question 10:** When should I refer to a PH specialty center?

# Pulmonary Hypertension for the Pulmonologist

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**Educational Objectives:**

1. Understand the definition of pulmonary hypertension (PH) and World Health Organization (WHO) groups of etiologies
2. Understand the differences in echocardiographic and hemodynamic profiles of pre-capillary, post-capillary, and combined PH
3. Assign one or more preliminary WHO Groups for PH based on clinical parameters and non-invasive diagnostic testing
4. Describe the general approach to treatment of PH, 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, hypertension, peripheral arterial disease, prior alcohol abuse, and hepatitis C infection (not treated and without complications). 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 and occurs 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," and his primary care physician prescribed home oxygen at 2 L/min at that time. He was also diagnosed with chronic obstructive pulmonary disease (COPD) and was prescribed fluticasone/salmeterol, which may have slightly improved his dyspnea. He has no history of deep venous thrombosis (DVT) or pulmonary embolism (PE).

On exam, his lungs demonstrate fine bibasilar rales. Jugular venous pressure (JVP) is estimated at 9cmH2O with mild hepatojugular reflux. P2 is accentuated, with 1+ lower extremity edema and no clubbing. He has tattoos. With 2 L/min continuous flow oxygen via nasal cannula, his resting SpO2 is 92%; with ambulation, this decreases to 80%. Previous

chest radiograph showed some increased interstitial markings at the bases. Pulmonary function tests (PFT) reveal:

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A diagnosis of pulmonary hypertension is considered.

**Question 1: What is the definition of pulmonary hypertension (PH)? How are possible causes of PH classified? What types of PH are most commonly encountered in general pulmonary practice?**

Pulmonary hypertension (PH) is defined as a resting mean pulmonary artery pressure of more than 20mmHg and is categorized into five groups by the World Health Organization (WHO).[1]

- WHO Group 1 – Pulmonary Arterial Hypertension (PAH)
- WHO Group 2- PH associated with left heart disease
- WHO Group 3- PH associated with lung disease and/or hypoxia
- WHO Group 4 - PH due to pulmonary artery obstructions
- WHO Group 5 - PH with unclear and/or multifactorial mechanisms

All types of PH can result in right ventricular (RV) dysfunction and failure. While echocardiography, cardiac Magnetic Resonance Imaging (MRI), and other testing may suggest PH, an accurate characterization of PH requires invasive hemodynamic confirmation with a right heart catheterization (RHC). The newest PH definition includes three hemodynamic subtypes of PH, as shown in Table 1.

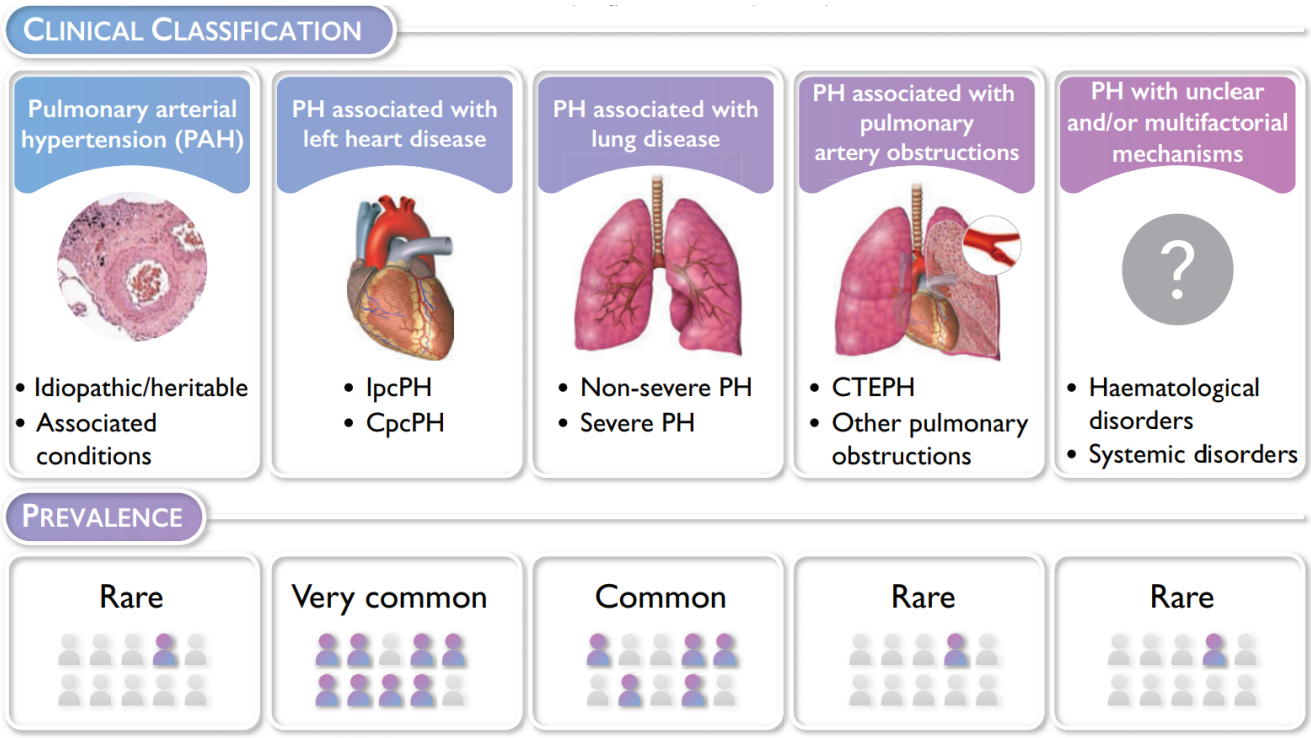
**Table 1.** Types of PH as Defined by RHC and WHO Group Association

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

*Abbreviations: mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.*

Table derived from 2022 European Respiratory Society Guidelines for Diagnosis and Treatment of PH, Hemodynamic Definitions of PH.[1]

**Figure 1.** Clinical Classification and Prevalence of Pulmonary Hypertension by WHO group




*Abbreviations: Ipc, isolated post-capillary hypotension; Cpc, combined post-capillary and pre-capillary; CTEPH, chronic thromboembolic pulmonary hypertension.*

Figure reproduced from 2022 European Respiratory Society Guidelines for Diagnosis and Treatment of PH.[1]

As shown in Figure 1, PH is most frequently attributable to primary heart (WHO Group 2) and lung (WHO Group 3) diseases. Therefore, in general pulmonology practice, PH is statistically more likely to be from common underlying heart or lung conditions than a primary pulmonary vasculopathy.[2]

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

Symptoms of PH are non-specific. Early symptoms include dyspnea, fatigue, and palpitations. As the disease progresses, patients can have hemoptysis and signs of elevated right heart pressures resulting in elevated Jugular Venous Pressure (JVP), lower extremity edema, abdominal distention, and cardiac arrhythmias. This patient's progressive exertional dyspnea could be from PH. As detailed in Table 2, key features of the vignette are listed, along with the etiology and subgroup they may reflect. Table S1 lists each WHO group along with examples of etiologies and clinical features (see supplementary material).

**Table 2.** Vignette Key Features and Potential WHO Groups

| Key feature | Example etiologies | WHO Group |
|---|---|---|
| Smoking history | Chronic Obstructive Pulmonary Disease (COPD), Interstitial Lung Disease (ILD) | 3 |
| Prior alcohol abuse and current hepatitis C infection | Porto-pulmonary hypertension, drug-induced PAH | 1 |
| Dry cough with basilar rales and CXR interstitial markings | ILD, Combined pulmonary fibrosis and emphysema | 3 |
| Resting hypoxemia | Multiple (see below) | Any group |
| Elevated JVP, hepatojugular reflux, Prominent P2, extremity edema | Left heart failure, valvular heart disease (also could be due to any cause of PH resulting in right heart failure) | 2 |
| PFTs: normal spirometry and TLC, with severely reduced DLCO | Pulmonary vascular disease | 1 |

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.

Resting hypoxemia with exertional desaturation despite $O_2$ therapy deserves special attention. This degree of hypoxemia is *atypical* for PAH and should be a clue to something else. In a large PAH registry, the mean $P_aO_2$ was around 70 mmHg.[3] Severe hypoxemia in PH can be seen in advanced parenchymal lung disease, worsening right heart failure, right to left shunt via patent foramen ovale (PFO), or congenital heart disease with Eisenmenger physiology.

**Question 3: What workup should you order for an initial PH evaluation?**

Several tests are recommended by guidelines, and the workup should be tailored to each individual patient.[4] Reasonable minimum diagnostic testing at the outset includes Electrocardiogram (ECG), Chest X-Ray (CXR), PFTs, and echocardiogram (with bubble study if shunt suspected). Six-minute walk distance provides an objective measure of exercise limitation. Chest Computed Tomography scan (CT) is often useful to determine the severity of chronic lung disease contributing to PH. In intermediate to high probability for PH, a Ventilation-Perfusion (V/Q) scan should be performed to rule-out chronic thromboembolic PH (CTEPH). The history and/or exam typically directs the remaining non-invasive workup, including appropriate serologies for rheumatologic disease evaluation and/or sleep study for suspected sleep apnea. Right heart catheterization (RHC) continues to be required to confirm PH and its appropriate hemodynamic classification with certainty.

**Scenario cont.:**

**You order some additional tests. Results are below.**

**Transthoracic Echocardiogram (TTE)**:
Left Ventricle (LV)- Normal size and function; mild diastolic dysfunction. LA normal size. Right Ventricle (RV) - Moderately dilated with moderately reduced function, septal flattening, and tricuspid annular plane systolic excursion (TAPSE) 1.6 cm. Mid. Mid-systolic "notch" in flow velocity envelope in Right Ventricular Outflow tract (RVOT). Estimated pulmonary arterial systolic pressure (PASP)65mmHg. Right Atrium (RA) moderately dilated. Negative bubble study.

**CT chest:** Apical-predominant emphysema with basilar/peripheral subpleural reticulation and mild honeycombing.
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**Abdominal ultrasound**: Nodular liver, increased pulsatile venous flow, normal spleen, no evidence of portal hypertension
**V/Q scan**: No perfusion defects
**Six-minute walk distance**: 305 meters (51% predicted)

**Question 4: How do these results change your differential for the underlying cause of pulmonary hypertension and your overall assessment of disease severity?**

Echocardiogram findings strongly suggest PH. PASP) is elevated, and right ventricular (RV) failure is present as evidenced by dilated RV with systolic dysfunction (decreased TAPSE measurement) and evidence of septal flattening. Left heart function is normal, making Group 2 etiologies less likely. Table S2 (see supplementary material) reviews echo features that can suggest pre- vs post-capillary hypertension.[1,5,7] CT Chest shows substantial abnormalities, making Group 3 etiologies more likely. Lab studies are mostly normal, apart from an expected elevation in NT-proBNP that is frequently seen in PH. Though not exhaustive, this makes some Group 1 and Group 5 etiologies less likely. Abdominal ultrasound has no evidence of portal hypertension, making this cause of Group 1 PAH less likely. The V/Q scan shows no findings to suggest CTEPH, making Group 4 less likely. Definitive confirmation and classification still requires right heart catheterization.

**Scenario cont.:**

**You proceed with right heart catheterization (RHC) and obtain the following hemodynamics:**

*RA 12 mmHg, RV 78/10, PA 78/32 (mean 47 mmHg), PCWP 12 mmHg, CO 2.7 L/min, CI 1.6 L/min/$m^2$, PA sat 62%, Ao sat 95%, PVR ~13 Wood units*

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

**Question 5: How do you interpret the RHC findings above? How does this change your differential?**

These hemodynamics and echo findings suggest precapillary PH with reduced cardiac function (high right atrial [RA] pressure, normal pulmonary capillary wedge pressure [PCWP], low cardiac output [CO]/cardiac index [CI],], and high pulmonary vascular resistance [PVR]). The hepatic venous pressure gradient (HVPG) indicates no significant portal hypertension (wedged minus free hepatic venous pressure = normal [<5]). In light of the findings of significant parenchymal lung disease, WHO Group 3 PH is the most appropriate classification.

Unfortunately, pulmonary hypertension accompanying intrinsic lung disease is associated with poor outcomes.[6-9]

**Question 6: What is the general approach to therapy for patients with WHO Group 3 PH?**

Pulmonologists commonly manage WHO Group 3 PH by treating the underlying condition (such as COPD, interstitial lung disease, and other restrictive lung diseases). In these patients, although pulmonary vasoactive therapy is seldom recommended, a referral to a PH center should be considered if symptoms or RHC findings are out of proportion to expected clinical presentation or fail to improve with usual treatment.

Vasoactive therapy is generally recommended only for patients in WHO Group 1. Currently, 13 approved therapies exist for treating PAH, supported by studies showing benefits 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.

Treatment for WHO Group 3 PH:

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.
    a. Other therapies like digoxin for inotropic effect and anticoagulation are not strongly recommended in the WHO group 3 PH setting.
3. Consideration of pulmonary vasodilator therapy +/- referral to PH center.

**Question 7: What drugs are available to treat PH, and is there evidence of benefit in Group 3 PH?**

Current approved therapies for PAH include:

1. *Prostanoids and Prostacyclin Receptor Agonists: Prostacyclin Pathway Agents (PPA)*
    a. Parenteral: epoprostenol (Intravenous only (IV)only), treprostinil (IV and subcutaneous (SC)
    b. Inhaled: iloprost, treprostinil, epoprostenol
    c. Oral: treprostinil, selexipag
2. *Endothelin receptor antagonists (ERAs)*
    a. Oral: bosentan, ambrisentan, macitentan
3. *Phosphodiesterase-5 inhibitors (PDE-5i)*
    a. Oral: sildenafil, tadalafil
4. *Soluble guanylate cyclase stimulators*
    a. Oral: riociguat
5. *Activin signaling inhibitors*
    a. Parenteral: sotatercept (SC)

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.

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 (such as worsening RV failure and worsening hypoxemia).[10,11]

**Question 8: Should we prescribe a calcium-channel blocker as a treatment for our patient?**

No. Calcium channel blockers (CCB) should only be used for patients with WHO Group 1 disease after demonstrating a positive invasive hemodynamic response to a short-acting pulmonary vasodilator (eg., inhaled NO, inhaled or intravenous epoprostenol). A positive response is defined as a fall in mean PA pressure (mPAP) by at least 10 mmHg to an absolute value <40 with no decrease in cardiac output. Patients who demonstrate this are likely have a different type of pulmonary vascular disease that exhibits excellent long-term survival with CCB therapy; however, this is only ~10-15% of cases of idiopathic PAH and is virtually non-existent in other PH subtypes.[12] Thus, there is no reason to pursue this for the patient in our vignette.

**Question 9: Imagine this patient instead had Group 1 PH (PAH)? What therapy would you choose, and how do you follow them?**

The choice of therapy in PAH is determined based on risk. Therefore, the first step in determining treatment is assessing risk, using a calculator such as in Table 3.

**Table 3.** European Respiratory Society Risk Calculator (Comprehensive risk assessment in pulmonary arterial hypertension – three strata model)

| Determinants of prognosis (estimated 1-year mortality) | Low risk (<5%) | Intermediate risk (5–20%) | High risk (>20%) |
|---|---|---|---|
| **Clinical observations and modifiable variables** | | | |
| Signs of right HF | Absent | Absent | Present |
| Progression of symptoms and clinical manifestations | No | Slow | Rapid |
| Syncope | No | Occasional syncope[a] | Repeated syncope[b] |
| WHO-FC | I, II | III | IV |
| 6MWD[c] | >440 m | 165–440 m | <165 m |
| CPET | Peak $VO_2$ >15 mL/min/kg (>65% pred.)<br>$VE/VCO_2$ slope <36 | Peak $VO_2$ 11–15 mL/min/kg (35–65% pred.)<br>$VE/VCO_2$ slope 36–44 | Peak $VO_2$ <11 mL/min/kg (<35% pred.)<br>$VE/VCO_2$ slope >44 |
| Biomarkers: BNP or NT-proBNP[d] | BNP <50 ng/L<br>NT-proBNP <300 ng/L | BNP 50–800 ng/L<br>NT-proBNP 300–1100 ng/L | BNP >800 ng/L<br>NT-proBNP >1100 ng/L |
| Echocardiography | RA area <18 $cm^2$<br>TAPSE/sPAP >0.32 mm/mmHg<br>No pericardial effusion | RA area 18–26 $cm^2$<br>TAPSE/sPAP 0.19–0.32 mm/mmHg<br>Minimal pericardial effusion | RA area >26 $cm^2$<br>TAPSE/sPAP <0.19 mm/mmHg<br>Moderate or large pericardial effusion |
| cMRI[e] | RVEF >54%<br>SVI >40 $mL/m^2$<br>RVESVI <42 $mL/m^2$ | RVEF 37–54%<br>SVI 26–40 $mL/m^2$<br>RVESVI<br>42–54 $mL/m^2$ | RVEF <37%<br>SVI <26 $mL/m^2$<br>RVESVI >54 $mL/m^2$ |
| Haemodynamics | RAP <8 mmHg<br>CI ≥2.5 $L/min/m^2$<br>SVI >38 $mL/m^2$<br>$SvO_2$ >65% | RAP 8–14 mmHg<br>CI 2.0–2.4 $L/min/m^2$<br>SVI 31–38 $mL/m^2$<br>$SvO_2$ 60–65% | RAP >14 mmHg<br>CI <2.0 $L/min/m^2$<br>SVI <31 $mL/m^2$<br>$SvO_2$ <60% |



6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; $SvO_2$, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; $VE/VCO_2$, ventilatory equivalents for carbon dioxide; $VO_2$, oxygen uptake; WHO-FC, World Health Organization functional class.
[a]Occasional syncope during heavy exercise or occasional orthostatic syncope in a stable patient.
[b]Repeated episodes of syncope even with little or regular physical activity.
[c]Observe that 6MWD is dependent upon age, height, and burden of comorbidities.
[d]To harmonize with the four-strata model shown in *Table 18*, the BNP and NT-proBNP cut-off levels have been updated from the 2015 version based on data from the REVEAL registry, acknowledging that the European validation studies have used the original cut-off levels.[274,292,293,295,296,302]
[e]cMRI parameters adapted from *Section 6.2.2.2*.

Table 3 reproduced from Table 16 of 2022 European Respiratory Society Guidelines for Diagnosis and Treatment of PH.[1]

A risk calculator derived from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) has also recently been revised and is available online for ease of use in the clinic.[13] Notice that WHO Functional class is distinct from WHO Groups and is summarized in Table S3 (see supplementary material). The patient in our vignette fits best in the intermediate risk group.

In 2024, a new treatment algorithm for PAH (Figure S1, see supplementary material) was published incorporating the recently approved activin signaling inhibitor sotatercept.[14] Initial therapy is selected based upon the patient's initial risk assessment, with future changes based upon risk reassessments at 3-4 months and repeated thereafter. For low or intermediate-risk patients, an initial combination of therapy with an ERA and a PDE-5i is recommended.[1,14-15] For high-risk patients, adding a PPA upfront is recommended. The patient in our vignette is not high-risk, therefore if he had WHO Group 1 PAH, initial therapy with ERA + PDE-5i should be prescribed.

Upon risk reassessment, medications are added unless risk remains low, and patients with any high-risk features should be referred for lung transplant evaluation.

There is no expert consensus regarding treatment endpoints. Generally, one could aim for patients to meet low-risk criteria on repeat assessment. However, a recent analysis suggests that treatment-induced changes in risk scores (e.g., REVEAL) only explain 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.[16]

**Question 10: When should I refer to a PH specialty center?**

Like 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.[17] 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 providers should have the ability to rapidly provide parenteral prostacyclin therapy if needed. Multidisciplinary review at CTEPH centers ensures appropriate therapies for this disease (endarterectomy or balloon pulmonary angioplasty) are considered. For PAH patients failing maximal therapy (that includes a PPA) and patients with severe PH associated with lung disease, referral for transplant evaluation is indicated. For some patients with advanced PH who are unsuitable for transplant, consideration of palliative strategies, including atrial septostomy, may be warranted.

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## Supplementary Material

**Table S1.** WHO Groups, Disease Etiologies, and Clinical clues

| WHO Subgroup | Etiology or Associated Condition | History or Clinical Clues |
|---|---|---|
| Group 1 PAH (pulmonary arterial hypertension) | Idiopathic or hereditary<br><br>Drugs/toxins (ex. methamphetamines)<br><br>Connective tissue disease (CTD: scleroderma, systemic lupus erythematosus [SLE], mixed connective tissue disease [MCTD], dermatomyositis, Sjögren's syndrome)<br><br>HIV-associated<br>Porto-pulmonary hypertension due to cirrhosis<br>Schistosomiasis<br><br>Pulmonary venous occlusive disease (PVOD)* | Family history of PAH<br><br>Substance abuse history<br><br>Fevers, skin/nail changes or rashes, Raynaud's syndrome, muscle weakness, joint pains, etc<br><br>High-risk sexual history<br>Alcohol use, hepatitis C infection<br>Travel history (Africa, Asia, South America)<br><br>Family history of PVOD |
| Group 2 PH | Left-sided heart disease (diastolic or systolic dysfunction) | History of hypertension, coronary artery disease, aortic or mitral valve disease |
| Group 3 PH | COPD, ILD, combined pulmonary fibrosis / emphysema (CPFE) | History of smoking, occupational exposures, radiation, family history of lung disease, history of CTD |
| Group 4 PH | Pulmonary vascular thrombo-embolic obstruction | History of pulmonary embolism, hypercoagulability |
| Group 5 PH | Sarcoidosis<br>Pulmonary Langerhans Cell Histiocytosis (PLCH)<br><br>Hematologic disorders<br>Chronic kidney disease (CKD)<br>Metabolic storage disorders | Erythema nodosum, hilar lymphadenopathy, cystic lung disease, history of smoking<br><br>Sickle cell disease<br>History of Gaucher's or glycogen storage diseases |

**PVOD is a rare diagnosis and has its own associated diseases such as a variety of CTDs, chemotherapy, and hematopoietic stem cell transplants.*

Table derived from Reference 18.

**Table S2.** 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 |

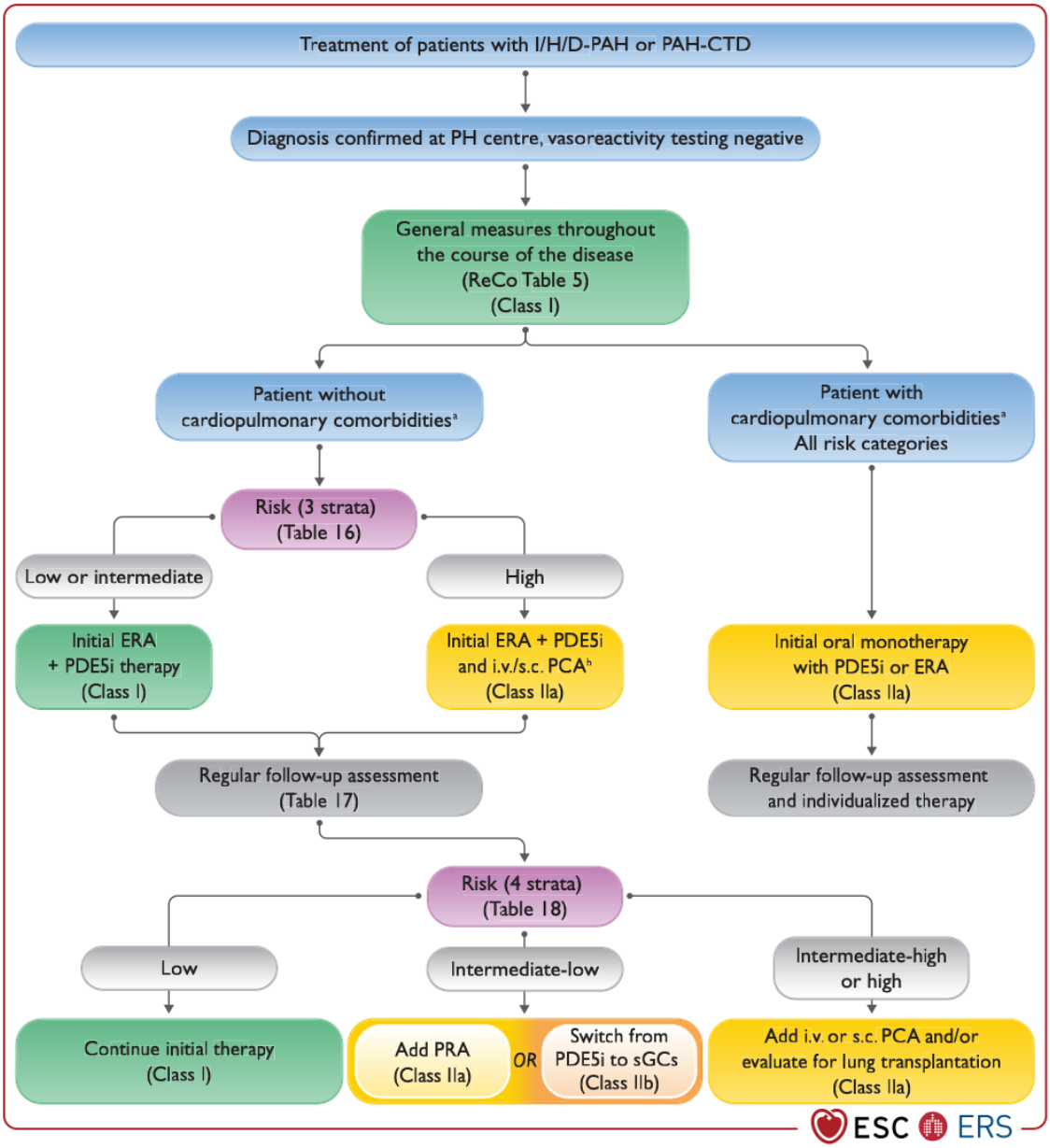
Adapted from reference 7.

**Table S3.** WHO Functional Class

| Class | Description |
|---|---|
| I | Patients with Pulmonary Hypertension but **without any resulting limitation of physical activity**. Ordinary physical activity does not cause; breathlessness, fatigue (tiredness), or activities that can cause chest pain, dizziness or even black outs. |
| II | Patients with Pulmonary Hypertension resulting in **slight limitation of physical activity**. They are comfortable at rest. Ordinary physical activity causes undue breathlessness, fatigue (tiredness), or activities that can cause chest pain, dizziness or even black outs. |
| III | Patients with Pulmonary Hypertension resulting in **marked limitation of physical activity**. They are comfortable at rest. Less than ordinary activity causes undue breathlessness, fatigue (tiredness), or activities that can cause chest pain, dizziness or even black outs. |
| IV | Patients with pulmonary hypertension with **inability to carry out any physical activity without symptoms**. These patients manifest signs of right heart failure, breathlessness and /or fatigue, which may even be present at rest. Discomfort is increased by any physical activity. |

Derived from Reference 1. Figure reproduced from 2022 European Respiratory Society Guidelines for Diagnosis and Treatment of PH.[1]

**Figure S1.** ERS PAH Treatment Pathway




Evidence-based pulmonary arterial hypertension treatment algorithm for patients with idiopathic, heritable, drug-associated, and connective tissue disease-associated pulmonary arterial hypertension. DLCO, Lung diffusion capacity for carbon monoxide; ERA, endothelin receptor antagonist; I/H/D-PAH, idiopathic, heritable, or drug-associated pulmonary arterial hypertension; i.v., intravenous; PAH-CTD, PAH associated with connective tissue disease; PCA, prostacyclin analogue; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension; PRA, prostacyclin receptor agonist; ReCo, recommendation; s.c., subcutaneous; sGCs, soluble guanylate cyclase stimulator. [a]Cardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction, and include obesity, hypertension, diabetes mellitus, and coronary heart disease; pulmonary comorbidities may include signs of mild parenchymal lung disease and are often associated with a low DLCO (<45% of the predicted value). [b]Intravenous epoprostenol or i.v./s.c. treprostinil.

Figure reproduced from 2022 European Respiratory Society Guidelines for Diagnosis and Treatment of PH.[1]

# Pulmonary Hypertension for the Pulmonologist

## Post-Test Case Related Questions

1. Which of these echocardiography findings is more likely in post-capillary pulmonary hypertension than in pre-capillary pulmonary hypertension?
    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 antibody, ACE, and anti-SCL-70. Her CT scan was largely unremarkable as was a V/Q 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, and 4

# Pulmonary Hypertension for the Pulmonologist

## Post Case Related Questions with Answer Key

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