

Definition: Resting mean pulmonary artery pressure (mPAP) >20 mmHg (normal is 8-20 mmHg) and an elevated pulmonary vascular resistance (PVR) ≥ 3 Woods units measured on right heart catheterization. The World Health Organization breaks down pulmonary hypertension into 5 classes.

Group 1: Pulmonary Arterial Hypertension

- **Etiology:** Idiopathic, heritable (BMP2 gene mutation), connective tissue disease, HIV infection, schistosomiasis (common worldwide), drugs/toxins
- **Pathophysiology:** hyperplasia and hypertrophy of all 3 walls of small pulmonary arterioles
- **Imaging:** Chest x-ray can show enlargement of central pulmonary arteries and right heart border prominence. CT Chest: main pulmonary artery/ascending aorta diameter ratio ≥ 1 can suggest PH.
- **Echocardiography:** Tricuspid regurgitant jet velocity (TRV) ≥ 2.8 m/s. Estimated pulmonary artery systolic pressure (PASP) >35 mmHg in young adults or >40 mmHg in older (echo PASP is an estimate and may not correlate with right heart catheterization, see below); Abnormal right ventricular size, wall thickness, or function
- **Right Heart Catheterization:** mPAP ≥ 20 mmHg and PVR ≥ 3 Woods units. Mean pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg
- **Acute Vasoreactivity Testing:** Select patients (idiopathic, heritable, drug-induced) should undergo. Contraindicated if SBP <90, cardiac index <2, or severe symptoms. Can use short acting vasodilators (*inhaled nitric oxide* 10-20 ppm over 5 minutes; *IV epoprostenol* 1-2 ng/kg/min increased by 2 ng/kg every 5-10 minutes until drop in BP, increased HR, or adverse symptoms; *IV adenosine* 50 mcg/kg/min increased every 2 minutes until adverse symptoms) to assess for positive response (\downarrow mPAP by at least 10 mmHg and mPAP <40 mmHg, unchanged or improved cardiac output)
- **Treatment:**
 - **Calcium channel blockers:** In vasoreactive positive, can trial CCB (nifedipine ER 30 mg/day or diltiazem 120 mg/day), can titrate to maximum tolerated dose.
 - **Prostacyclin agonists:** epoprostenol (IV infusion), treprostinil (IV infusion or inhaled), iloprost (inhaled), selexipag (oral).
 - **Endothelin receptor antagonists:** bosentan (oral), ambrisentan (oral), macitentan (oral)
 - **Guanylate cyclase stimulant:** riociguat (oral)
 - **Phosphodiesterase-5 inhibitor:** sildenafil (oral or IV), tadalafil (oral)
 - **Combination therapy (for advanced disease):** ambrisentan+tadalafil (AMBITON trial), macitentan+sildenafil (SERAPHIN trial), tadalafil+bosentan (PHIRST/PHIRST-2 trials), riociguat+bosentan (PATENT/PATENT-2 trials)

Group 2: Pulmonary Hypertension Secondary to Left Heart Disease

- **Pathophysiology:** increased left heart filling pressures can result in elevated mPAP and reduce pulmonary artery compliance
- **Imaging:** CXR can show findings of heart failure (cardiomegaly, pulmonary vascular congestion, pleural effusion), prominent right heart border
- **Echocardiography:** findings similar to Group 1
- **Right heart catheterization:** mPAP >20 mmHg, PCWP ≥ 15 mmHg

- **Treatment:** treatment of underlying heart disease with GDMT, diuretics, device therapy (ICD or CRT) if needed
 - Sildenafil can be considered in select patients with the 20/20/10/5 rule (transpulmonary gradient >20 mmHg, PCWP <20 mmHg, diastolic pulmonary vascular pressure gradient >10 mmHg, PVR > 5 Woods units)

Group 3: Pulmonary Hypertension Secondary to Chronic Lung Disease (CLD)/Hypoxia

- **Pathophysiology:** hypoxic pulmonary vasoconstriction occurs to limit blood flow to hypoxic alveoli and preserve ventilation-perfusion match. Chronic hypoxia leads to vascular remodeling
- **Imaging:** High resolution CT chest shows enlarged pulmonary arteries, attenuation of peripheral pulmonary vasculature, right ventricular enlargement
- **Pulmonary Tests:** Severely decreased diffusing capacity (<30% predicted) on PFT. Nocturnal pulse oximetry and/or polysomnography for OSA, arterial blood gas analysis
- **Echocardiography:** If PASP > 40 mmHg, TRV >3 m/s, RV dilation, then refer for right heart catheterization
- **Right heart catheterization:** CLD and/or hypoxia with pulmonary hypertension noted by mPAP 21-24 mmHg AND PVR \geq 3 Woods units OR mPAP 25-34 mmHg. In severe pulmonary hypertension, mPAP \geq 35 mmHg or mPAP \geq 25 mmHg with cardiac index <2 L/min/m².
- **Treatment:** treat the underlying condition. Supplemental O₂ if hypoxemia with goal SpO₂ 90-96%. Mixed data for PAH therapy in COPD. Prostanoids have shown improvement in parameters in ILD. Lung transplantation should be considered in progression despite therapy

Group 4: Pulmonary Hypertension Secondary to Chronic Thromboembolic Disease

- **Epidemiology:** Occurs in 1-5 percent of patients with history of acute pulmonary embolism
- **Echocardiography:** the TRV and PASP are increased and similar to that of PAH.
- **Pulmonary Function Testing:** Reduction in DLCO. On ABG, there can be an increased A-a gradient and decreased PaO₂ with exercise.
- **Imaging:** CXR similar to other PH groups. V/Q scanning can detect larger mismatched VQ defects (preferred over CTPA initially)
- **Right heart catheterization:** may not be significantly abnormal. Exercise will increase cardiac output with disproportionate increase in mPAP. Pulmonary angiography can be done to look for luminal irregularities.
- **Treatment:** Initiate anticoagulation with unfractionated heparin or low molecular weight heparin and then transition to oral anticoagulation. Surgery is definitive management, pulmonary endarterectomy is procedure of choice. Riociguat is effective in inoperable CTEPH. Small number of studies showed benefit in PVR with bosentan, prostanoids, or endothelin receptor antagonists.

Group 5: Pulmonary Hypertension Secondary to Unclear or Multifactorial Causes

- **Etiology:** Hematological disorders (chronic hemolytic anemia, myeloproliferative disorders), systemic disorders (sarcoidosis, glycogen storage disease, gaucher disease), CKD, fibrosing mediastinitis
- **Work up:** Imaging and right heart catheterization show findings similar to above classes.
- **Treatment:** treat the underlying disorder. PAH treatment has been mixed and inconclusive