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**Objectives:**

1. Apply diagnostic criteria for pulmonary hypertension (PH) and identify its subgroups (WHO groups)
2. Screen for PH using history and exam and identify high risk patients requiring further evaluation
3. Explain the role of right heart catheterization in diagnosing PH and interpret hemodynamic results to differentiate between groups
4. Provide general and group specific therapies for PH

**Teaching Instructions:**

Plan to spend approximately 30 minutes reviewing this talk including the Interactive Board, Teaching Handout, and Cases. Familiarize yourself with the interactive graphics within the Interactive Board as well as with the overall content and flow of this talk. All clickable elements within the Interactive Board will be denoted by a shaded rounded rectangle and a mouse cursor.

Begin with reviewing the objectives for the session. For the purposes of overall flow and alignment with the Teaching Handout, it is recommended that you progress through the Interactive Board in order however the clickable features within the Interactive Board allow for flexibility to adapt to your audience.

This can be presented in one of two ways:

1. Project the Interactive Board
2. Recreate the diagram within the Teaching Handout for presentation on a whiteboard

**The anticipated time for the content of this talk is approximately 25-30 minutes without cases and 35-40 minutes with cases**.

**Objective 1:** **Apply diagnostic criteria pulmonary hypertension (PH) and identify its subgroups. *(Definitions – Hemodynamic, WHO groups)***

It is critical to understand the hemodynamic definition of PH as well as to have a general concept of pulmonary vasculature.

Definitions – Hemodynamic:

*Briefly review the schematic of the heart and pulmonary vasculature. Blood flows from the right atrium (RA) to right ventricle (RV) to the pulmonary artery (PA) through pulmonary arterioles, then capillary beds, pulmonary venules, pulmonary vein where it then enters the left heart circulation.*

The most recent hemodynamic definition of PH is a mean arterial pressure (mPAP) of 20 mmHg. The mean pulmonary arterial pressure is analogous to mean arterial pressure (MAP) in the systemic circulation. This can only be derived during right heart catheterization.

*Bonus Learning:* This is distinct from pulmonary hemodynamic measurements derived from transthoracic echocardiogram (TTE) which make estimations of right ventricular systolic pressure (RVSP). It is important to understand that these are distinct hemodynamic entities.

Definitions – WHO Groups:

There are 5 main groups (determined by the World Health Organization) of pulmonary hypertension, which have distinct mechanisms, etiologies, and treatments.

*Teach a shorthand for remembering the classes is by taking the number and drawing a mirror image to the left, which gives a clue to each etiology. Ask learners specific causes of PH in each group and to describe the basic pathophysiology of each group. Click on each button to reveal the underlying causes in each group. Have learners fill out their handout as you go through each WHO group.*

|  |  |  |
| --- | --- | --- |
| **Group** | **Pathophysiology** | **Etiologies** |
| **I**  **Pulmonary arterial hypertension**  (pulmonary artery) | Pulmonary arterial vasoconstriction and vascular hypertrophy | Idiopathic PAH  Drug and toxin-induced (methamphetamine, some possible agents include cocaine)  Connective tissue diseases  HIV infection  Porto pulmonary hypertension  Congenital heart disease  Schistosomiasis |
| **II**  **From left heart disease**  (heart) | Elevated left atrial pressure | Heart failure with preserved EF  Heart failure with reduced EF  Valvular heart disease  Congenital heart disease leading to post-capillary pulmonary hypertension |
| **III**  **From lung diseases or hypoxia**  (lungs) | Hypoxic vasoconstriction and capillary destruction | Obstructive lung disease (COPD)  Restrictive lung disease  OSA/OHS  Interstitial lung disease |
| **IV**  **Chronic thromboembolic pulmonary hypertension**  (legs) | Chronic pulmonary arterial obstruction from unresolved or large clot or tumor | PE (recurrent, submassive/massive PE)  Other pulmonary artery obstruction (cancer, pulmonary artery stenosis, parasites, sarcoma) |
| **V**  (grab bag) | Unclear or multifactorial mechanism | Hematological disorders (hemolysis, sickle cell disease, myeloproliferative disorders)  Other systemic disorders (sarcoidosis, chronic renal failure)\* |

Information from Simonneau et al, Haemodynamic definitions and updated clinical classification of pulmonary hypertension, World Symposium on Pulmonary Hypertension, 2019.

\*Historically thyroid disorders were included in group V PH as a etiology of PH. While there is strong rationale for concurrent thyroid disease and PH and potentially some prognostic implications depending on the level of thyroid dysfunction, the consensus was to withdraw thyroid disorders from this list in 2019 until further evidence.

**Objective 2: Screen for PH using history and exam and identify high risk patients requiring further evaluation (*Screening*)**

*Ask the learners what clinical features, including symptoms and physical exam findings, would prompt screening for pulmonary hypertension. Click on “Who should be screened?” and then “Symptoms?” and “Exam Findings?” to reveal a brief list of clinical features which would prompt screening.*

Patients with suspicion symptoms and exam findings should be screened for PH. Symptoms largely depend on the presence of RV failure. Symptoms include new or progressive exertional dyspnea or fatigue, orthostasis or syncope, and weight gain. Exam may reveal increased JVP, hepatojugular reflex, lower extremity edema, abdominal distention from ascites in the presence of severe RV dysfunction. A loud and split S2 may be observed or a systolic murmur if there is tricuspid regurgitation (with RV dilation).

*Discuss with learners how to approach the initial screening of patients for whom there is a clinical suspicion for pulmonary hypertension. Click “How do we screen?” to reveal an ultrasound machine.*

The initial screening test for PH is a TTE, which estimates RV systolic pressure (RVSP), which is the single most useful measurement in determining risk of PH. It is calculated using the velocity of the tricuspid regurgitant jet. In some patients without a tricuspid regurgitant jet, the RVSP cannot be assessed, but RV size and systolic function can provide clues to potential underlying PH.

It is important to highlight that the RVSP and mPAP are different hemodynamic measurements. In the absence of RV outflow tract or pulmonic valve pathology, RVSP is reflective of the PA systolic pressure PASP (because during systole, the pulmonic valve is open and the RV and PA pressures equalize). RVSP will be definitionally higher than mPAP (in the same way that systolic BP is higher than MAP) and the cut offs for elevated RVSP and mPAP are different.

Patients who have a RVSP <40 are lower risk for PH and can be observed and clinically followed. Patients with RVSP of >40 are high risk and should be referred for right heart catheterization (RHC) which is the gold standard for diagnosis.

*Bonus learning*: RVSP is calculated based on the peak velocity of the tricuspid regurgitant jet and the right atrial pressure using the equation; RVSP = 4 V2 + RAP

**Objective 3*:* Explain the role of right heart catheterization in diagnosing PH and interpret hemodynamic results to differentiate between groups (*Diagnosis – RHC, Work-up*)**

Once a patient is identified as high risk for PH on TTE, definitive diagnosis is obtained via RHC.

Diagnosis – RHC:

Mechanics of RHC are outlined below. A RHC can broadly provide 3 pieces of information:

1. Measure pressures –
   1. Some pressures are measured directly (the RA, RV, PA)
   2. Some pressures are inferred (pulmonary capillary wedge pressure, PCWP)
2. Indirectly measure cardiac output (CO)
3. Calculate pulmonary vascular resistance (PVR)

*Measures Pressures: Click “Measures pressures” to reveal the normal values and characteristic pressure tracings within each compartment.* *To assist in remembering these values, you may use the “nickel, dime, quarter, dollar” mnemonic.*

* RA pressure is usually 0-5 mmHg. (nickel)
* RVSP is typically 25 mmHg, RV diastolic pressure is 0-5 (same as RA-P because during diastole, the tricuspid valve is open). (quarter)
* PASP is generally the same as RVSP in the absence of any significant pulmonic valve or RV outflow tract pathology.
* PCWP, sometimes also called pulmonary artery occlusion pressure, is obtained by wedging the catheter in the pulmonary capillary bed. The PCWP infers LA pressure which is an inference of the LV filling pressure. This pressure is typically 5-10 mmHg. (dime)
* LV pressures are not measured, but LV systolic pressures mimic systemic systolic pressure and is ~ at least 100 mmHg. (dollar)

*Measures CO:* *Click “Measures CO” to reveal the two methods for measuring cardiac output.*

In thermodilution, cold saline is injected through a proximal port in the catheter and then temperature changes are measured in a distal port. The area under the curve in the associated temperature change is used to calculate CO.

Using “Fick’s equation,” the equation for cardiac output is derived from arterial oxygen saturation (measured in arterial blood), mixed venous oxygen saturation (measured in the pulmonary artery), and VO2 (which is generally assumed based on patients height, weight, etc).

*Bonus learning*: each method of measuring cardiac output is prone to error. As VO2 is estimated, rather than calculated, it can be misleading, especially in those with obesity and severe pulmonary hypertension. Structural heart disease including tricuspid regurgitation and intracardiac shunts can confound thermodilution.

*Calculates PVR*: *Click to reveal the equation to calculate PVR.*

Lastly, two distinct patterns of PH are evident on RHC.

* **Post-capillary PH** occurs in Group II PH. This means the pulmonary hypertension occurs in the pulmonary venous system. PCWP and PA diastolic pressures are elevated in addition to elevated mPAP and PA systolic pressures. Often, PVR is normal (>3 Woods units) in these patients.
* **Pre-capillary pulmonary hypertension** is seen in all other WHO groups. PA systolic pressures and mPAP are elevated without elevation in PCWP.

Of note, many patients do not undergo RHC for definitive evaluation of their PH. If the elevation is mildly elevated and can be reasonably attributed to WHO II or III etiologies, patients often will not obtain further testing. This decision is generally the discretion of a pulmonary hypertension specialist.

Diagnosis – Work-up:

*Ask learners to identify testing to evaluate for underlying etiologies in each WHO group. Click on each WHO group to reveal the answer.*

Because PH is a heterogenous disease with a variety of causes, further evaluation is needed to elucidate the underlying etiology. Though generally, the specific evaluation is tailored to patient history and risk factors.

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| **Group** | **Etiologies** | **Evaluation** |
| **I**  **Pulmonary arterial hypertension**  (pulmonary artery) | Idiopathic PAH  Drug and toxin-induced (methamphetamine, some possible agents include cocaine)  Connective tissue diseases  HIV infection  Porto pulmonary hypertension | Family and past medical history  Urine toxicology  HIV Ab  ANA  LFTs |
| **II**  **From left heart disease**  (heart) | Heart failure with preserved EF  Heart failure with reduced EF  Valvular heart disease  Congenital heart disease | TTE |
| **III**  **From lung diseases or hypoxia**  (lungs) | Obstructive lung disease (COPD)  Restrictive lung disease  OSA/OHS  Interstitial lung disease | PFTs  Polysomnogram  CXR/ Chest CT |
| **IV**  **CTEPH**  (legs) | PE | V/Q scan |
| **V**  (grab bag) | Hematological disorders  Other systemic disorders (sarcoidosis, chronic renal failure) | BMP  CBC  TSH |

**Objective 4: Provide general and group specific therapies for PH (*Treatment*)**

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| **Group** | **General Treatment** | **Treatments** |
| **I**  **Pulmonary arterial hypertension**  (pulmonary artery) | All patients with PH should be managed:   * Salt and fluid restriction * Volume management with diuretics. * Patients who have SpO2 <88% should receive O2 therapy to avoid hypoxemia. * Ideally patients should be referred to a PH center of excellence and managed by a PH specialist. | Patients with Group 1 PH should undergo vasoreactivity testing (during RHC) to determine response to CCB. Roughly 10-20% of patients with group 1 PH will respond to CCB.  Other agents include:   * Endothelin receptor antagonists (ambrisentan, bosentan, macitentan) * Prostacyclin receptor agonists (selexipag, trepostinil, epoprostenol) * PDE5 inhibitors (tadalfil, sildenafil) * Guanylate cyclase agonists (riociguat) |
| **II**  **From left heart disease**  (heart) | Treat underlying heart disease |
| **III**  **From lung diseases or hypoxia**  (lungs) | Treat underlying lung disease  Lung transplant  Inhaled prostacyclin agonist |
| **IV**  **CTEPH**  (legs) | Clot removal (thrombolysis, thromboendarectomy)  Anticoagulation  Guanylate cyclase agonists |
| **V**  (grab bag) | Treat underlying disease |

**Take Home Points**

1. Patients with signs of volume overload, exertional dyspnea or presyncope should be screened for PH with a TTE. Patients with RVSP > 40 on TTE should undergo a RHC right heart and diagnostic testing specific to each WHO subgroup.
2. PH is defined as mPAP ≥20 mmHg on RHC. Group II PH can be distinguished with elevated PCWP and low-normal PVR, where as other Groups of PH have normal PCWP and elevated PVR.
3. The mainstay of all PH management is diuretic therapy, salt and fluid restriction, and oxygen therapy for patients with hypoxemia SpO­2<88%. Further group specific therapies for WHO group I, III, IV, and V should be prescribed under the direction of a pulmonary hypertension specialist.

**References**

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2. Galie, N., et al., *An overview of the 6th World Symposium on Pulmonary Hypertension.* Eur Respir J, 2019. **53**(1).
3. Simonneau, G. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. *2019*; 53: 1801913