Diagnostic Algorithm For Pulmonary Hypertension

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Agenda

• Definitions and Classifications
• Diagnostic Approach
  Clinical
  Imaging
  Hemodynamic assessment
• Risk Assessment
Definitions

- PH is defined as an increase in **mean pulmonary arterial pressure** (PAPm) **≥25 mmHg at rest** as assessed by RHC.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics*</th>
<th>Clinical group(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>PAPm ≥25 mmHg</td>
<td>All</td>
</tr>
</tbody>
</table>
| Pre-capillary PH                  | PAPm ≥25 mmHg, PAWP ≤15 mmHg | 1. Pulmonary arterial hypertension  
2. PH due to lung diseases  
3. PH with unclear and/or multifactorial mechanisms |
| Post-capillary PH                 | PAPm ≥25 mmHg, PAWP >15 mmHg | 2. PH due to left heart disease  
5. PH with unclear and/or multifactorial mechanisms |
| Isolated post-capillary PH (IPc-PH) | DPG <7 mmHg and/or PVR ≤3 WU | 3. Pulmonary arterial hypertension  
4. PH due to left heart diseases  
5. PH with unclear and/or multifactorial mechanisms |
| Combined post-capillary and pre-capillary PH (Cpc-PH) | DPG ≥7 mmHg and/or PVR >3 WU | 3. Pulmonary arterial hypertension  
4. PH due to left heart diseases  
5. PH with unclear and/or multifactorial mechanisms |

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Classification

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic
   - 1.2 Heritable
   - 1.3 Other mutations
   - 1.4 Drugs, toxins and radiation induced
   - 1.5 Associated with:  
     - 1.5.1 Connective tissue disease
     - 1.5.2 Human immunodeficiency virus (HIV) infection
     - 1.5.3 Portal hypertension
     - 1.5.4 Congenital heart disease (Table 6)
     - 1.5.5 Sarcoidosis

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
   - 2.5 Congenital/acquired pulmonary venous stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Acute hypoxia disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases (Table 6)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
   - 4.1 Chronic thromboembolic pulmonary hypertension
   - 4.2 Other pulmonary artery obstructions
   - 4.3 Pulmonary arterial hypeension
   - 4.4 Congenital pulmonary arterial stenoses
   - 4.5 Paroxysmal

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
   - 5.1 Haemodynamic disorders: chronic haemodynamic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Sarcoidosis, sarcoidosis, pulmonary hypertension, sarcoidosis/pulmonary hypertension
   - 5.3 Metabolic disorders: glycogen storage disease, Gusher disease, nephrotic syndrome
   - 5.4 Other: pulmonary temporal thrombotic microangiopathy, Noonan syndrome, chronic renal failures (with/without dysplasia), segmental pulmonary hypertension
Diagnosis

- **Clinical suspicion** based on symptoms and physical examination
- A comprehensive **set of investigations** to
- Haemodynamic criteria are met
  - Etiology
  - Functional and Haemodynamic severity
Clinical presentation

Initial symptoms are typically induced by exertion
- Shortness of breath
- Fatigue
- Syncope
- Angina

Clinical presentation

Less commonly
- Dry cough
- Exercise-induced nausea and vomiting
- Rupture of hypertrophied bronchial arteries
- Compression
  - Left recurrent laryngeal nerve
  - Airway compression
  - LMT compression
Clinical Examination

- Signs PH
- Signs suggestive of the etiology
  - Telangiectases-Sclerodactyly: Scleroderma
  - Inspiratory crackles: interstitial lung disease
  - Digital clubbing: cyanotic CHD-Interstitial
    lung disease-liver disease-PVOD
  - Spider naevi, and palmar erythema: liver
disease.

Chest Radiograph

- Abnormal at the time of diagnosis in 90%
- The degree of PH in any given patient does not correlate with the extent of radiographic abnormalities
Echocardiography Probability for PH

### Table 1: Echocardiographic Probability of PH

<table>
<thead>
<tr>
<th>Peak tricuspid regurgitation velocity (m/s)</th>
<th>Presence of other echo ‘PH signs’</th>
<th>Echocardiographic probability of pulmonary hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.8 or not measurable</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>≤2.8 or not measurable</td>
<td>Yes</td>
<td>Intermediate</td>
</tr>
<tr>
<td>2.9–3.4</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>2.9–3.4</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>&gt;3.4</td>
<td>Not required</td>
<td>High</td>
</tr>
</tbody>
</table>

### Table 2: Additional Factors

- **A: The ventricles**
  - Right ventricle/ left ventricle basal diameter ratio >1.0
  - Right ventricular outflow Doppler acceleration time <105 ms and/or mitral systolic notch
- **B: Pulmonary artery**
  - Early diastolic pulmonary regurgitation velocity >2.2 m/s
  - Right atrial area (end-systole) >18 cm²
- **C: Inferior vena cava and right atrium**
  - Inferior vena cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
  - PA diameter >25 mm.

### Table 3: Management of PH

<table>
<thead>
<tr>
<th>Echocardiographic probability of PH</th>
<th>Without risk factors or associated condition for PAH or CTEPH</th>
<th>Class</th>
<th>Level</th>
<th>With risk factors or associated conditions for PAH or CTEPH</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Alternative diagnosis should be considered</td>
<td>IIa</td>
<td>C</td>
<td>Echo follow-up should be considered</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Alternative diagnosis, echo follow-up, should be considered</td>
<td>IIa</td>
<td>C</td>
<td>Further assessment of PH including RHC should be considered</td>
<td>IIa</td>
<td>B</td>
<td>45, 46</td>
</tr>
<tr>
<td>High</td>
<td>Further investigation of PH (including RHC) is recommended</td>
<td>I</td>
<td>C</td>
<td>Further investigation of PH including RHC is recommended</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
Echocardiography

- Left heart disease
- Congenital heart disease (TTE-TEE)

**Limitations:**
- Underestimate: severe tricuspid regurgitation, TRV may be significantly underestimated and **cannot be used to exclude PH**
- Overestimation: not suitable for screening for mild, asymptomatic PH
- Repeat ECHO measurements alone are **not sufficient to monitor** change in PASP or progression of PAH.
High-Resolution CT

- Chest diseases
- **Ground-glass** abnormalities are also present in PAH (>1/3 of cases)
- PVOD
- Pulmonary capillary haemangiomatosis

Pulmonary function tests and arterial blood gases

- **Lung Volumes**
  1. Chest diseases
  2. PAH: mild to moderate reduction of lung volumes

- **Lung diffusion capacity**
  1. Parenchymal lung disease
  2. Usually normal in PAH – Abnormal: PVOD, Scleroderma
After ruling out Group 2 and 3

Ventilation/perfusion lung scan

- **Screening** method of choice for CTEPH because of its higher sensitivity compared with CT pulmonary angiogram (CTPA), especially in inexperienced centers
- A normal- or low-probability V/Q scan *excludes* CTEPH with a sensitivity of 90 – 100% specificity of 94 – 100%
- Caveat:
  PVOD: Small peripheral unmatched non-segmental defects in perfusion
CT Pulmonary Angiography

- Diagnosis (less sensitive than V/Q)
- Surgical accessibility

Right Heart Catheterization
Right Heart Catheterization

1. Confirm
2. Vasoreactivity (only for IPAH, HPAH and PAH associated with drugs)
3. Stratification
4. Follow Up

• At expert centers, these procedures have
  Low morbidity (1.1%)
  Very mortality (0.055%)

Vasoreactivity Testing

Vasoreactivity testing is recommended in patients with IPAH, HPAH and PAH associated with drugs use to detect patients who can be treated with high doses of a CCB

A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥ 10 mmHg to reach an absolute value of mean PAP ≤ 40 mmHg with an increased or unchanged cardiac output

Nitric oxide is recommended for performing vasoreactivity testing

Intravenous epoprostenol is recommended for performing vasoreactivity testing as an alternative

Adenosine should be considered for performing vasoreactivity testing as an alternative

Inhaled iloprost may be considered for performing vasoreactivity testing as an alternative
Vasoreactivity (Adenosine 500 u/kg/min)

Mean PAP dropped to 30 mmHg
PVR dropped from 12 wood units to 3 woods units
Cardiac index increased from 2.18 L/min/m² 3.6 L/min
Blood tests and immunology

- Routine biochemistry (liver, kidney)
- CBC
- Thyroid function
- NT-proBNP
- Thrombophilia screening in CTEPH

Serology for
- CTD: Scleroderma antinuclear antibodies, including anti-centromere, dsDNA, anti-Ro, U3-RNP, B23, Th/To and U1-RNP
- hepatitis and HIV

Caveat: 40% of patients with IPAH have ANA usually in a low titre (1:80)
Evaluation of severity

- Clinical parameters
- Imaging
- Hemodynamics
- Biochemical markers

Risk Assessment In PAH

<table>
<thead>
<tr>
<th>Determinants of prognosis</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5-18%</th>
<th>High risk &gt;18%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope</td>
<td>Repeated syncope</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440 m</td>
<td>165-440 m</td>
<td>&lt;165 m</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO₂ &gt;15 ml/min/kg (≥80% pred.) V̇E/V̇CO₂ slope &lt;36</td>
<td>Peak VO₂ 11-15 ml/min/kg (35-65% pred.) V̇E/V̇CO₂ slope 36-44.9</td>
<td>Peak VO₂ &lt;11 ml/min/kg (&lt;35% pred.) V̇E/V̇CO₂ &gt;45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/l</td>
<td>BNP 50-300 ng/l</td>
<td>BNP &gt;300 ng/l</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm²</td>
<td>No pericardial effusion</td>
<td>RA area 18-24 cm²</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP &lt;8 mmHg CI &gt;2.5 l/min/m² SvO₂ &gt;65%</td>
<td>RAP 8-14 mmHg CI 2.0-2.4 l/min/m² SvO₂ 60-65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m² SvO₂ &lt;60%</td>
</tr>
</tbody>
</table>
Risk Assessment In PAH

• **WHO-functional class** despite its interobserver variability, remains one of the most powerful predictors of survival

• **RV function** is a key determinant of exercise capacity and outcome in patients with PH

• Estimated PASP at rest is usually **not prognostic** and **not relevant** for therapeutic decision making

• An increase in PAPs does not necessarily reflect disease progression and a decrease in PAPs does not necessarily signal improvement

Conclusions

• The diagnostic process starts with **clinical suspension** and **echocardiographic probabilities**

• Identify the more common clinical groups of PH (2, 3 then group 4 and finally makes the diagnosis and recognizes the different types in group 1 and the rarer conditions in group 5.

• **V/Q scan** is the screening method of choice for CTEPH

• **RHC** is an essential tool for diagnosis, risk stratification and follow up

• **Vasoreactivity** testing is mandatory before CCBs

• Use a multidimensional approach for **severity evaluation**
Thank You