The ECHO Suggests Pulmonary Hypertension. What Next?

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Disclosures

I have no conflicts of interest to declare
Objectives

1) Review definition and classification of PH

2) Discuss presentation and diagnostic approach

3) Overview of treatment strategies

(Recently published: 2015 ESC/ERS Guidelines)
Definition
Definition

- PH refers to elevated pulmonary arterial pressure
- Pressure elevation in *pulmonary arterial system* alone (increased resistance or flow) OR 2° to pressure elevation in *pulmonary venous system*
Definition

- PH defined as \( mPAP \geq 25 \text{ mmHg} \) at rest
- Upper limit of normal \( mPAP \) 20 mmHg
- \( mPAP \) 21-24 mmHg considered “borderline”:
  - Unclear clinical significance
  - May progress to significant disease
    (especially idiopathic, family hx, CTD)
  - Warrants monitoring
Importance: The Right Ventricle

- Thin muscular wall chamber
- Designed to deliver venous return to a low pressure/low resistance pulmonary circulation
- Limited contractile reserve to compensate for increased PVR
- Chronic rise managed in part by RVH
- RV dilatation to increase preload
- Ultimately **RV failure**...morbidity/mortality
Classification
WHO Classification

- Categorizes multiple clinical conditions into **five groups** based on pathophysiology, natural hx and response to treatment
  - **Previous:** Primary PH (no identifiable cause)  
    Secondary PH (identifiable cause)
  - **Now** recognized that some types of ‘secondary PH’ have similar pathophysiology and response to Rx as ‘primary PH’ (i.e. familial, CTD, portal HTN, HIV, drug-induced, congenital heart disease)
WHO Classification

- Pulmonary arterial hypertension (Group 1)
  - Diseases with 1° vasculopathy of small PAs
  - Absence of significant:
    Left heart disease (Group 2)
    Lung disease and/or hypoxemia (Group 3)
    Thromboembolic disease (Group 4)
    Rare diseases/unclear mechanism (Group 5)
  - Includes: IPAH, heritable PAH and associated conditions (CTD, portal HTN, HIV, drugs, CHD)
WHO Classification

- **Group 1:** Pulmonary arterial hypertension (PAH)

- **Group 2:** PH owing to left heart disease

- **Group 3:** PH owing to lung disease and/or hypoxemia

- **Group 4:** Chronic thromboembolic PH (CTEPH)

- **Group 5:** PH with unclear/multifactorial mechanisms
WHO Classification

1. Pulmonary arterial hypertension
   - Idiopathic
   - Heritable
   - Drugs
   - Connective tissue disease
   - HIV
   - Portal hypertension
   - Congenital heart disease
   - Schistosomiasis

2. Pulmonary hypertension owing to left heart disease
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular disease

3. Pulmonary hypertension owing to lung disease/hypoxia
   - Chronic obstructive pulmonary disease
   - Interstitial lung disease
   - Sleep disorder
   - Alveolar hypoventilation

4. Chronic thromboembolic pulmonary hypertension
   - Operable
   - Inoperable

5. Multifactorial/unclear mechanisms
   - Haematological
     - Chronic haematolytic anaemia
   - Myeloproliferative disease
   - Splenectomy
   - Systemic disorders
     - Sarcoidosis
     - Langerhans cell histiocytosis
   - Lymphangioleiomyomatosis
   - Neurofibromatosis
   - Vasculitis
   - Metabolic disorders
     - Glycogen storage disease
     - Gaucher’s disease
   - Thyroid disorder
   - Others
     - Tumour obstruction
     - Fibrosing mediastinitis
     - Chronic renal failure
Presentation
Symptoms

- Symptoms of PH nonspecific – often leads to delay in diagnosis
- Mainly related to progressive RV dysfunction
- Initial symptoms typically induced by exertion
- Progressive exertional dyspnea most common
- Chest pain, syncope, fatigue
- With overt RV failure – abdominal distension, ankle edema
Symptoms

- Less common symptoms due to mechanical complications: hemoptysis, wheeze, hoarseness
- Symptoms of associated conditions
Physical Examination

- Often normal in early stages
- Classic signs as RV hypertrophy and failure develop
- **Signs:**
  - left parasternal lift
  - loud P2, right ventricular S3
  - pansystolic murmur of TR
  - elevated JVP
  - pulsatile hepatomegaly
  - ascites, peripheral edema
- Also findings of associated conditions
Electrocardiogram

- Can provide supportive evidence of PH
- Normal EKG does not exclude PH and abnormal does not confirm the diagnosis
- Abnormal EKG more likely in severe PH
- Abnormalities: Right axis deviation
  - Right atrial enlargement
  - RV hypertrophy/strain pattern
  - Right bundle branch block
Pulmonary Hypertension: EKG

RAD, Right atrial enlargement, RV hypertrophy, RV strain
Pulmonary Hypertension: EKG

RAD, Right atrial enlargement, Right bundle branch block
Normal CXR does not exclude the diagnosis

Classic abnormalities:
- central pulmonary artery dilatation
- attenuation of peripheral vessels (‘pruning’)
- RA/RV enlargement
- findings of underlying etiology (eg. ILD, COPD, chest wall deformity, LV failure)
Pulmonary Hypertension: CXR

Prominent main PA, dilated right interlobar PA
Pulmonary Hypertension: CXR

Prominent main PA, RA enlargement, peripheral pruning
Pulmonary Hypertension: CXR

Right ventricular enlargement
PFTs

- Classic finding – isolated reduction in DLCO
- May see mild restrictive defect
- ABGs: hypoxemia, chronic respiratory alkalosis
- Otherwise findings of significant lung disease (WHO Group 3)
ECHO

- Non-invasive screening tool for PH
- **Utilities:**
  1) Estimate pulmonary artery systolic pressure
  2) Assess RV thickness, RA/RV size, RV function
  3) Identify 2° causes: LV systolic/diastolic dysfxn, left sided valvular disease, intracardiac shunt
Pulmonary artery systolic pressure (PASP) or RVSP estimated based on doppler assessment of peak tricuspid regurgitant jet velocity (TRV)

Calculation taking into account right atrial pressure (RAP) with simplified Bernoulli equation:

\[ \text{PASP} = (4 \times \text{TRV}^2) + \text{RAP} \]
ECHO

- **Limitations:**
  1) Cannot measure without significant tricuspid regurg
  2) TRV technically difficult to measure
  3) Can under/overestimate true PA systolic pressure

- **Usual PASP (or RVSP) cut-off = 40 mmHg**
  (correlates with mPAP 25 mmHg)

- **Better:**
  - PASP > 50, associated PH findings: PH likely
  - PASP < 36, no ass’d PH findings: PH unlikely
ECHO

- Associated findings of PH ('the company it keeps'): 
  1) RVH (wall thickness > 5 mm)
  2) RV dilatation (RV/LV > 1.0, septal flattening)
  3) RA enlargement
  4) RV systolic dysfunction (TAPSE < 15 mm)
  5) Functional TR severity
Echocardiography

- Main findings are:
  1. Right ventricular enlargement (RVE).
  2. Right ventricular hypertrophy (RVH).
  3. Right atrial enlargement (RAE).
  4. Functional tricuspid regurgitation (TR) with a high velocity regurgitant jet by Doppler (TR jet), and a mid-systolic notch on the pulmonary artery Doppler flow tracing (PA flow).
  5. The interventricular septum is shifted toward the left ventricular cavity.
Pulmonary Hypertension: ECHO
Right Heart Catheterization

- Gold standard for diagnosis of PH (mPAP ≥ 25)
- Rule out PH due to left heart disease (Group 2):
  - PCWP ≥ 15 mmHg
  - TPG ≤ 12 mmHg, PVR < 3 WU
- Versus Group 1 (PAH) and Groups 3-5
  - PCWP < 15 mmHg
  - TPG > 12 mmHg, PVR > 3 WU
- Low threshold for left heart catheterization with direct measurement of LVEDP
Diagnostic Approach
WHO Group 2 PH: Owing to left Heart Disease (PH-LHD)

- Most common cause of pulmonary hypertension
  
  *Most common cause of RHD is LHD*

- Elevated mPAP occurs as a result of elevated left heart filling pressures

- Important to recognize because:
  
  1) Presence of PH in patients with LHD associated with **reduced survival**
  
  2) Dictates **proper management** = optimal treatment of left heart disease
WHO Group 2 PH: Owing to left Heart Disease (PH-LHD)

- **Etiologies:**
  1) Heart failure with reduced EF (HFrEF)
     - `Systolic Dysfunction`
     - Ischemic vs. nonischemic cardiomyopathy
  2) Heart failure with preserved EF (HFpEF)
     - `Diastolic Dysfunction`
     - Most common cause of PH-LHD, often neglected
     - Difficult to distinguish from PAH
  3) Left sided valvular disease (mitral, aortic)
  4) Other: Constrictive pericarditis, Restrictive CM
WHO Group 2 PH: Owing to left Heart Disease (PH-LHD)

- **Clues:**
  - older age (>60)
  - orthopnea, PND
  - atrial fibrillation (uncommon in PAH)
  - hx of CAD, HTN, DM
  - left sided S3, S4, murmurs
  - **ECHO:** EF<50%, LAE, LVH
    - Diastolic dysfunction (insensitive)
    - Mod-Severe AV, MV dysfunction
WHO Group 2 PH: Owing to left Heart Disease (PH-LHD)

1) **Isolated post-capillary PH**
   - Early in PH-LHD
   - Elevated mPAP only due to elevated LH filling pressures
   - Severity of PH proportional to left sided pressures
   - ‘Pulmonary venous HTN’, ‘Passive PH’
   - Normal PVR (< 3 WU), normal TPG (≤ 12 mmHg)
   - mPAP normalizes with reduction in LH pressures to normal
WHO Group 2 PH: Owing to left Heart Disease (PH-LHD)

2) **Combined Post/Pre-capillary PH**
   - Chronic elevation in LH filling pressures leading to vasculopathy of small pulmonary arteries
   - Vasoconstriction, endothelial dysfunction, remodeling
   - Elevated mPAP disproportionate to left sided pressures
   - ‘Mixed PH’, ‘Out-of-proportion PH’
   - Elevated PVR (> 3 WU), elevated TPG (> 12 mmHg)
   - mPAP doesn’t normalize with normalization of LH pressures
   - ? Role for targeted PAH therapy
WHO Group 3 PH: Owing to lung disease and/or hypoxemia

1) **Chronic Lung Disease**
   - PH is a common complication
   - Most commonly COPD, ILD, and combined pulmonary fibrosis and emphysema (CPFE)
   - Also ‘extraparenchymal restrictive diseases’ with alveolar hypoventilation: chest wall deformity, NM weakness
   - Diagnosis: PFTs +/- ABGs, CT chest
   - PH generally seen only with **severe disease**
   - Should not attribute to lung disease if PFTs only mildly abnormal and absence of respiratory failure
WHO Group 3 PH: Owing to lung disease and/or hypoxemia

1) **Chronic Lung Disease**

- PH usually mild-moderate in severity
- Severe (‘Out-of-proportion’) PH may indicate additional condition (PAH, PH-LHD, CTEPH)
WHO Group 3 PH: Owing to lung disease and/or hypoxemia

2) **Sleep-disordered breathing**
   - PH prevalence in untreated OSA 15-20% - usually **mild**
   - More significant PH if obesity hypoventilation syndrome
   - Overnight **polysomnography** if clinical suspicion
WHO Group 4 PH: Chronic thromboembolic PH (CTEPH)

- PH due to persistent thromboembolic occlusion of proximal or distal vasculature
- Nonresolution of acute embolic masses, become fibrosed leading to chronic mechanical obstruction
- Estimated to complicate 1-9% of symptomatic acute PE within the first 2 years
- Documented VTE history absent in up to 40% CTEPH cases
WHO Group 4 PH: Chronic thromboembolic PH (CTEPH)

- **V/Q scan** is the initial imaging modality of choice
- High sensitivity (96-97%): normal scan excludes dx
- One (usually several) segmental or larger defects

Further work-up for V/Q scans suggesting CTEPH:

1) **Right Heart Cath** – confirm diagnosis, severity
2) **Pulmonary Angiography** – distribution of obstructing thrombi (? accessible to endarterectomy)
* Should investigate after 3 **months** of anticoagulation
WHO Group 1 PH:
Pulmonary arterial hypertension (PAH)

- Diseases in which the primary abnormality is localized to the small pulmonary arteries

- Absence of significant LHD, significant lung disease, and chronic thromboembolic disease

- **Includes**: Idiopathic/Heritable PAH
  Secondary to drugs, CTD, CHD, Portal HTN, HIV
WHO Group 1 PH:
Pulmonary arterial hypertension (PAH)

- Similar pathophysiology:
  1) Endothelial Dysfunction
     - $\uparrow$ Endothelin-1 (vasoconstrictor, proliferation)
     - $\downarrow$ Prostacyclin, NO (vasodilators, antiproliferation)
  2) Vascular remodeling
     - intimal hyperplasia, smooth muscle hypertrophy
  3) In-situ thrombosis
WHO Group 1: Pulmonary Arterial Hypertension
WHO Group 1 PH:
Pulmonary arterial hypertension (PAH)

- **Heritable PAH**: clinically indistinguishable from IPAH
  - up to 80% mutations in BMPR2

- **Drugs/toxins**: appetite suppressants
  - stimulants (amphetamines, cocaine)
  - other

- **CTD**: limited scleroderma most commonly associated
  - can occur with any CTD (SLE, RA, MCTD)
  - serology (ANA, RF, anti-ENA profile)
Congenital Heart Disease:

- atrial septal, ventricular septal, great artery defects
- PAH develops due to left-to-right shunt with increased pulmonary blood flow
- right-to-left shunt once right side pressures exceed left (Eisenmenger syndrome)
- agitated saline contrast ECHO (‘Bubble study’)
WHO Group 1 PH: Pulmonary arterial hypertension (PAH)

- **Portal Hypertension:**
  - PAH can complicate portal HTN
  - ‘portopulmonary HTN’; unclear mechanism
  - up to 2-5% of cirrhosis patients in screening studies
  - **LFTs** +/- abdominal U/S

- **HIV:**
  - PAH develops in 0.5%
  - mechanism unclear
  - HIV testing if risk factors
Symptoms, signs, EKG, CXR suggestive of PH

Echocardiogram suggestive of PH

Yes → Consider other diagnoses RHC if PH still suspected

No → Significant Left Heart Disease?

Yes → Group 2

No → Full PFTs +/- ABGs, HRCT

Sleep Study if clinical suspicion

Significant lung disease and/or hypoxemia

Yes → Group 3

No → V/Q scan - ? Mismatched defects

Group 1 likely

Yes → Confirm with RHC mPAP≥25, PAWP<15

No → LFTs, CTD serology

HIV test if risk factors

R/O drugs/toxins

Secondary Cause

IPAH/HPAP
Treatment Strategies
WHO Group 1 PH: Pulmonary arterial hypertension (PAH)

- Untreated PH in general is progressive and often fatal
- Natural history and prognosis best studied for Group 1 PAH
- Largest data base to date: REVEAL Registry
- Can calculate risk score based on multiple variables:
  - Age, Comorbidities, Secondary conditions
  - WHO Functional Class (I-IV)
  - Vitals (HR, BP), 6MWT, CPET, PFTs
  - ECHO, RHC (focus on RV function, not PAP)
- Useful at baseline as well as therapeutic target
## WHO Functional Classification for PH

<table>
<thead>
<tr>
<th>Class</th>
<th>WHO Functional Classification</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Patients with PH but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain or heart syncope.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain or heart syncope.</td>
</tr>
<tr>
<td>III</td>
<td>Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain or heart syncope.</td>
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<tr>
<td>IV</td>
<td>Patients with PH resulting in inability to carry on any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity.</td>
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Remains one of the most powerful predictors of survival despite inter-observer variability.
Survival according to functional class

Survival (%)

Time (months)

No. at risk

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>WHO FC II</th>
<th>WHO FC III</th>
<th>WHO FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
<td>37</td>
<td>7</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>48</td>
<td>6</td>
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<td>24</td>
<td>19</td>
<td>70</td>
<td>9</td>
</tr>
<tr>
<td>36</td>
<td>23</td>
<td>79</td>
<td>11</td>
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Survival at 36 months:
- WHO FC II: 27%
- WHO FC III: 89%
- WHO FC IV: 17%
WHO Group 1 PH:
Pulmonary arterial hypertension (PAH)

- Treatment of PAH has evolved dramatically over the past two decades
- Corresponding improvement in patient outcomes

<table>
<thead>
<tr>
<th>Survival</th>
<th>Untreated</th>
<th>Current</th>
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<tbody>
<tr>
<td>1 year</td>
<td>68%</td>
<td>92%</td>
</tr>
<tr>
<td>3 year</td>
<td>48%</td>
<td>74%</td>
</tr>
<tr>
<td>5 year</td>
<td>34%</td>
<td>65%</td>
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- Goals: improve exercise capacity, QOL, RV function and survival
WHO Group 1 PH: Pulmonary arterial hypertension (PAH)

1) **General Measures:**
   - Education, Psychosocial support
   - Regular Exercise, Supervised rehabilitation
     (avoid excessive exercise leading to distressing symptoms)
   - Avoidance of pregnancy
   - Infection prevention (influenza, pneumococcal vaccine)

2) **Supportive therapy:**
   - Anticoagulation, Diuretics, Digoxin (limited evidence)
   - Supplemental O₂ if hypoxemic
3) **Advanced Therapy:**
- High dose CCB in small proportion of IPAH with positive response to acute vasodilator challenge

- Other therapies target 1 of 3 specific pathways:
  - Endothelin-1, Nitric oxide, Prostacyclin

- Demonstrated improvement in several outcomes:
  - Symptoms, functional capacity, exercise capacity, hemodynamics, time to deterioration, survival
Targeted PAH Therapies

- Bosentan
- Macitentan
- Ambrisentan
- Sitaxsentan
- Sildenafil
- Tadalafil
- Vardenafil
- Riociguat
- Selexipag
- Epoprostenol
- Iloprost
- Treprostinil
- Beraprost
PAH Treatment Algorithm

Figure 5 – Treatment algorithm. FC: functional class. Adapted from Barst et al. [63]
WHO Group 2 PH: Owing to left Heart Disease (PH-LHD)

- Optimal treatment of left heart disease
  - **Systolic dysfunction**: ACE-I/ARB, β-blockers, Aldactone Na restriction, Diuretics, Devices
  - **Diastolic dysfunction**: BP/HR control, maintain NSR Na restriction, Diuretics

- Treatment of ischemia

- **Aortic/Mitral VHD**: Timing of intervention

- PAH therapy should generally be avoided due to lack of evidence for improved outcomes and potential for harm (increased CHF, mortality)
WHO Group 2 PH: Owing to left Heart Disease (PH-LHD)

- Role for targeted PAH therapy in patients with combined post/pre-capillary PH in whom PH persists despite optimal Rx for LHD and normalization of left sided pressures...Studies underway
WHO Group 3 PH: Owing to lung disease and/or hypoxemia

- Optimal treatment of pulmonary condition:
  - $O_2$ for chronic hypoxemia
  - Medical therapies for COPD, ILD
  - Nocturnal CPAP for OSA, BIPAP for OHS, restrictive diseases
- R/O concomitant CTEPH (Group 4)
- PAH-specific drugs generally not recommended
- Caveat is patients with PH severity ‘out-of-keeping’ with lung disease severity - ? concomitant PAH (Group 1)
WHO Group 4 PH: Chronic thromboembolic PH (CTEPH)

- Lifelong anticoagulation

- Pulmonary endarterectomy (PEA) treatment of choice accessible disease (only PH treatment with potential cure)

- Early evidence for role of PAH-therapy in patients with persistent PH post-PEA or inoperable (Riociguat)
Thank-you