Screening and diagnosing PH – still a challenge

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## Haemodynamic definition of PH

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PWP $\leq$ 15 mmHg
CO normal or reduced   | 1. PAH
3. PH due to lung disease
4. CTEPH
5. PH with unclear and/or multifactorial mechanism |
| Post-capillary PH       | Mean PAP $\geq$ 25 mmHg
PWP $>$ 15 mmHg
CO normal or reduced   | 2. PH due to LHD                                                                  |
| Passive                 | TPG $\leq$ 12 mmHg                                                              |                                                                                  |
| Reactive (out of proportion) | TPG $>$ 12mmHg                                                                   |                                                                                  |

PAP: pulmonary arterial pressure
PCWP: pulmonary capillary wedge pressure

1. Pulmonary Arterial Hypertension
   - Idiopathic PAH
   - Heritable PAH
     - BMPR-2 mutations
     - Alk-1/endoglin
     - undefined
   - Drug/toxin induced
   - Related to:
     - Connective tissue diseases
     - Schistosomiasis
     - HIV
     - Portal hypertension
     - Systemic - to - pulmonary shunts
     - Hemolysis (SCD, thalassemia, PNH, spherocytosis, stomatocytosis)
   - PPHN

1’. PVOD-PCH

2. PH with Left Heart Disease
   - Systolic
   - Diastolic
   - Valvular

3. PH with Lung Diseases/Hypoxemia
   - COPD
   - Interstitial Lung Diseases
   - Sleep-disordered breathing
   - Hypoxia

4. CTEPH

5. Unclear or multifactorial mechanisms
   - Hematologic
   - Systemic
   - Metabolic
   - CHD other than systemic-to-pulmonary shunt
   - Others
Increased awareness of unexplained symptoms

Detect early screening in high-risk populations

Treat early treatment in WHO-FC II recommended

Treat-to-target goal-orientated approach

Potential to improve long-term outcomes
Screening
(early detection of PH)
Who to screen?

- Prevalence of PAH in the general population
  15–50 cases per million (0.0015–0.0050%)
- Prevalence of PAH in at risk populations
  CHD: 4–15%
  Systemic sclerosis: 8–10%
  Portal hypertension: 0.5–10%
  HIV: 0.5%
  Sickle cell disease: 2%
  BMPR2 mutation carriers: 20%
  Prior appetite suppressant use (9.5%)
Who to screen?-2

- Prevalence of CTEPH in the general population
  3–30 cases per million (0.0003–0.0030%)
- Prevalence of CTEPH in at risk populations
  after major symptomatic PE: 0.1–9.1%
  after splenectomy: ~2.0%
  in carriers of APL/LAK: ~2.0%
Screened patients are different from diagnosed patients

Early identification confers a benefit

Survival rate (%)

Years of follow-up

P=0.0037
HR = 4.15
(95% CI 1.47–11.71)


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Histopathology of PAH (PPH): plexogenic arteriopathy

Early

Late
Pulmonary artery pressure rise is a late event

## Exercise-induced pulmonary hypertension

<table>
<thead>
<tr>
<th></th>
<th>EI PH n=78</th>
<th>PAH n=15</th>
<th>normals n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{VO}_2\text{max, }%\text{pred}$</td>
<td>$67 \pm 16$</td>
<td>$56 \pm 20$</td>
<td>$92 \pm 14$</td>
</tr>
<tr>
<td>$\text{PAP, mmHg}$</td>
<td>$37 \pm 6$</td>
<td>$48 \pm 11$</td>
<td>$27 \pm 4$</td>
</tr>
<tr>
<td>$\text{PVR, d.s.cm}^{-5}$</td>
<td>$161 \pm 60$</td>
<td>$294 \pm 258$</td>
<td>$62 \pm 20$</td>
</tr>
</tbody>
</table>

Levels of exercise in normal subjects

Pulmonary blood flow, l.min⁻¹

Pressure, mmHg

P_{ap} > 30 \text{ mmHg}

P_{w} > 15 \text{ mmHg}

Exercise haemodynamics in PAH

Mean PAP (mmHg) vs Cardiac Index (L/min/m²)

- Exercise before epoprostenol therapy
- Exercise after 6 weeks of epoprostenol therapy

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Ideal screening test

– Sensitive
– Specific
– Non-invasive
– Widely available
– Inexpensive
– Able to detect disease at an early stage

Established screening tools

- Resting echocardiography
- Pulmonary Function test
- Biomarkers
- V/Q

Neural networks
CART
Arbitrary criteria for detecting the presence of PH based on tricuspid regurgitation peak velocity and Doppler-calculated PA systolic pressure at rest*

- **Echocardiographic diagnosis: PH unlikely**
  - Tricuspid regurgitation velocity ≤ 2.8 m/sec, PA systolic pressure ≤ 36 mmHg and no additional echocardiographic variables suggestive of PH.

- **Echocardiographic diagnosis: PH possible**
  - Tricuspid regurgitation velocity ≤ 2.8 m/sec, PA systolic pressure ≤ 36 mmHg but presence of additional echocardiographic variables suggestive of PH.
  - Tricuspid regurgitation velocity 2.9-3.4 m/sec, PA systolic pressure 37-50 mmHg with/without additional echocardiographic variables suggestive of PH.

- **Echocardiographic diagnosis: PH likely**
  - Tricuspid regurgitation velocity >3.4 m/sec, PA systolic pressure > 50 mmHg with/without additional echocardiographic variables suggestive of PH.

- **Exercise Doppler echocardiography is not recommended for screening of PH**

*Assuming a normal right atrial pressure of 5 mmHg and on additional echocardiographic variables suggestive of PH*
Maximum TRV values during hypoxia vs exercise in relatives (yellow) and control subjects (blue)

Exercise

During exercise, 32% of relatives but only 10% of controls had TRV values >3.08 m/s; and during hypoxia, 26% of relatives had TRV values >3.08 m/s compared with 10% of controls.
Exercise echocardiography data represented as multipoint pressure–flow relationship

A

![Graph showing systolic PAP vs. cardiac output]

- Severe PAH
- Hypertensive response with normal resting $P_{PA}$
- Well-trained athlete

B

<table>
<thead>
<tr>
<th>TR (m/s)</th>
<th>VTI/LVOT (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9</td>
<td>21.9</td>
</tr>
<tr>
<td>1.98</td>
<td>22.9</td>
</tr>
<tr>
<td>2.11</td>
<td>24.8</td>
</tr>
<tr>
<td>2.2</td>
<td>25.92</td>
</tr>
<tr>
<td>2.24</td>
<td>26.2</td>
</tr>
<tr>
<td>2.33</td>
<td>28.0</td>
</tr>
<tr>
<td>2.4</td>
<td>29.1</td>
</tr>
<tr>
<td>2.78</td>
<td>30.6</td>
</tr>
<tr>
<td>2.8</td>
<td>31.0</td>
</tr>
<tr>
<td>3.0</td>
<td>31.6</td>
</tr>
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The relationship between DLCO and the development of SSc-associated PAH

Clinical suspicion

Echo: TR >2.8m/s and >3 months of effective anticoagulation

V/Q scan

- negative
  - CTEPH ruled out

- Indeterminate
  - CTEPH uncertain

- at least 1-2 segmental larger-sized defects
  - CTEPH likely
    - Right Heart Catheterization and Pulmonary Angiography
      - plus
        - Multidetector CT

ClassificAtion and Regression Tree

63 patients with a TRV ≥2.5 m·s⁻¹ who underwent 6MWT and NT-proBNP plasma level

TRV

2.5≤TRV<2.9 m·s⁻¹ (n=51)

NT-proBNP

NT-proBNP <164.5 pg·mL⁻¹ (n=43)

6MWD

6MWD ≥333 m (n=42)

NT-proBNP ≥164.5 pg·mL⁻¹ (n=8)

6MWD <333 m (n=1)

TRV ≥2.9 m·s⁻¹ (n=12)

RHC (PH confirmed in seven patients)

RHC (PH confirmed in five patients)

RHC (PH confirmed in this patient)

No RHC (PH missed in one patient)
Cross-sectional phase
- To evaluate different screening tests (individually and combined) vs RHC for PAH (primary objective) and PH in SSc patients

Longitudinal cohort (follow-up)
- To evaluate the incidence of PAH and PH in a cohort of SSc patients
- To determine the association of potential prognostic or risk factors (eg, biomarkers, 6MWD, PFTs etc) and the development of PAH/PH
Performance of an optimal screening tool
(96% sensitivity, 80% specificity)

To detect one case of PAH-SCD: number needed to cath: 2.5
To detect one case of PAH-SLE: number needed to cath: 41
To detect one case of iPAH: number needed to cath: 101
To detect one case of CTEPH: number needed to cath: 50-500
Diagnosis
Continue’d

Segmental perfusion defects

No

Consider other uncommon causes

Yes

Perform RHC (PAH probability)

Specific tests

Yes

Search for other causes

No

mPAP ≥ 25 mmHg
PWP ≤ 15 mmHg

PVOD/PCH

Consider Group 4 CTEPH

Consider PVOD/PCH

PVOD PCH

CDT

Clinical signs HRCT, ANA

History

HIV test

HIV

TTE, TEE, CMR

Physical US, LFT

Physical Laboratory Analysis

Schistosomiasis Other group 5

Chronic Haemolysis

Porto Pulmonary

BMPR2, ALK1, Endoglin (HHT)
Family history

CHD
• L-S, 73-year old female
• SA: married, 1 daughter, retired,
• 162cm, 84kg
• Medical Hx: surgically corrected large ASD 1993 ablation of atrial fibrillation, pacemaker implantation for Sick-Sinus-Syndrome, systemic hypertension, hyperlipidemia, coronary disease
• Current medication: Phenprocoumon, Nicorandil 10mg bid, Bisoprolol 5mg, Allopurinol 100mg, Escitalopram 10mg
• NYHA III
• NT-BNP 3097pg/mL
• Echo sPAP 95mmHg
## Hemodynamic parameters

<table>
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<tr>
<th>Parameter</th>
<th>Value</th>
<th>Precapillary PH?</th>
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<tr>
<td>RAP, mm Hg</td>
<td>32</td>
<td>110/44-73</td>
</tr>
<tr>
<td>PAPs/d-m, mmHg</td>
<td>40</td>
<td>110/44-73</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>TPG, mmHg</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>CO, L.min</td>
<td>6.1</td>
<td></td>
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<tr>
<td>CI, L.min.m²</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>PVR, WU (dyn.s.cm⁻⁵)</td>
<td>5.9 (472)</td>
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<tr>
<td>SvO₂, %</td>
<td>53</td>
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Patients with a clinical suspicion of precapillary PH and TRV>2.8m/s

ECG

No RVS

NT-proBNP

≤ 80pg/mL

Precapillary PH unlikely

>80pg/mL

Precapillary PH likely

RVS

Precapillary PH likely

Factors increasing the likelihood of HF with preserved EF (diastolic HF)

Clinical features
- Age >65
- Elevated systolic blood pressure
- Elevated pulse pressure
- Obesity, metabolic syndrome
- Hypertension
- Coronary artery disease
- Diabetes mellitus
- Atrial fibrillation

Echocardiography
- Left atrial enlargement
- Concentric remodelling of the LV (relative wall thickness >0.45)
- LV hypertrophy
- Presence of echocardiographic indicators of elevated LV filling pressure

Interim evaluation (after echocardiography)
- Symptomatic response to diuretics
- Exaggerated increase in systolic blood pressure with exercise
- Re-evaluation of chest radiograph consistent with heart failure

• L-S, 73-year old female
• SA: married, 1 daughter, retired,
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<td>Reactive (out of proportion)</td>
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PAP: pulmonary arterial pressure  
PCWP: pulmonary capillary wedge pressure  
CO: cardiac output
Diastolic Pressure Gradient

- DPG = dPAP - mPCWP

Normal values ≤5mmHg

DPG >5mmHg denotes pulmonary vascular disease

Buchbinder N and Ganz W. *Anesthesiology* 1976; 45(2): 146-55

DPG AND SURVIVAL

Cumulative survival vs. Time to last contact (months)

- **Non-PH**
- **PH due to LHD** (excluding TPG >12 & PVG ≥7mmHg)
- **PH due to LHD with TPG >12 & PVG ≥7mmHg**
- **Pre-capillary PH**

Gerges C et al. *CHEST* 2013; in press
A low DPG is a marker for a favorable prognosis

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[Image]

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Screening and diagnosing PH

- Rise of resting PA pressures (and symptoms) are late sequelae of the pathobiological processes that begin in the distal pulmonary arteries.

- Resting echocardiography is currently the recommended screening modality for high-risk population groups.

- Exercise stress may unmask early pulmonary vascular dysfunction but the definition, clinical significance, and natural history of ‘exercise PAH’ remain undefined.
Screening and diagnosing PH – still a challenge

- Early diagnosis of PAH is currently not possible
- A major contemporary diagnostic challenge is the distinction between pre- and postcapillary PH
Thank you for your attention