Pulmonary Arterial Hypertension: Latest Concepts in Evaluation & Treatment

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Disclosures

- None
Overview

- Definition
- Pathology/Pathogenesis
- Classification
- Diagnosis
- Risk assessment
- Treatment Choices

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PH Hemodynamic Definition
PH = Elevated Blood Pressure in the Lungs

- PAH
- CTEPH
- PVH
- Lung Dz
Hemodynamically Defining PAH - OLD

- PH = mPAP \geq 25 \text{ mmHg}
- PAH = mPAP \geq 25 \text{ mmHg}

\[ \text{PAWP} \leq 15 \text{ mmHg} \]
\[ \text{PVR} \geq 3 \text{ Woods Units} \]
\[ (\text{PVR} = (m\text{PAP} - \text{PAWP}) / \text{C.O.}) \]
\[ \text{TPG} > 12 \text{ mmHg} \]

- In theory, this hemodynamically “localizes the lesion”

Vachiery et al, JACC 62: D100-8, 2013
Hemodynamically Defining PAH – a CHANGE

What is actually the upper limit of normal mPAP?

- KOVACS et al. (2009) analyzed all available data obtained by RHC studies in healthy individuals = 1187 normal subjects from 47 studies

- mPAP at rest was $14.0 \pm 3.3$ mmHg (independent of sex & ethnicity & only slightly influenced by age and posture)

- Considering this mPAP of 14 mmHg, two standard deviations would suggest mPAP $>20$ mmHg as above the upper limit of normal (i.e. above the 97.5th percentile)

- “normal” mPAP definition is, therefore, no longer arbitrary, but based on a scientific approach

## Where Do We Stand Now – Hemodynamic Diagnosis

### TABLE 1 Haemodynamic definitions of pulmonary hypertension (PH)

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Characteristics</th>
<th>Clinical groups#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-capillary PH</td>
<td>mPAP &gt;20 mmHg</td>
<td>1, 3, 4 and 5</td>
</tr>
<tr>
<td></td>
<td>PAWP ≤15 mmHg</td>
<td></td>
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<tr>
<td></td>
<td>PVR ≥3 WU</td>
<td></td>
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<tr>
<td>Isolated post-capillary PH (IpcPH)</td>
<td>mPAP &gt;20 mmHg</td>
<td>2 and 5</td>
</tr>
<tr>
<td></td>
<td>PAWP &gt;15 mmHg</td>
<td></td>
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<tr>
<td></td>
<td>PVR &lt;3 WU</td>
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<td>Combined pre- and post-capillary PH (CpcPH)</td>
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</table>

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units. #: group 1: PAH; group 2: PH due to left heart disease; group 3: PH due to lung diseases and/or hypoxia; group 4: PH due to pulmonary artery obstructions; group 5: PH with unclear and/or multifactorial mechanisms.
Pulmonary Hypertension Pathology
Where Do WE Stand Now? Pulmonary Vasculopathy as a Spectrum
Global Pulmonary Vascular Remodeling in Pulmonary Hypertension Associated With Heart Failure and Preserved or Reduced Ejection Fraction

Figure 5. Pulmonary vascular structure in patients with HF-PH and PVOD with elevated TPG.
Examples representative of the mean histomorphometry values for all vessels within the patient in 3 patients with approximately similar degrees of elevation in the TPG are shown. Rows indicate cohort group (top: HFpEF, HFrEF, and PVOD). Columns represent vessel type (from left: arteries, veins, and IV). Top, HFrEF: artery, ED 219 μm (A); vein, ED 122 μm (B); and IV, ED 60 μm (C). Middle, HFpEF: artery, ED 220 μm (D); vein, ED 86 μm (E); and IV, ED 69 μm (F). Bottom, PVOD: artery, ED 151 μm (G); vein, ED 48 μm (H); and IV, ED 86 μm (I). ED indicates external diameter; HFpEF, heart failure with preserved ejection fraction; HF-PH, heart failure–pulmonary hypertension; HFrEF, heart failure with reduced ejection fraction; IV, indeterminate vessels; PVOD, pulmonary veno-occlusive disease; and TPG, transpulmonary gradient.
Spectrum of Pulmonary Vasculopathy

IPAH

Other forms of PAH
(Systemic sclerosis, etc)

Arterial

EIF2AK4+
PVOD

Venous
Capillary

Nossent et al. J Heart Lung Transplant 2017
Arterial versus Venous/Capillary Disease

• The role of the pulmonary veins, microcirculation and bronchial arteries has been underappreciated

• Group 2 and 3 PH exhibits vasculopathy in the whole spectrum of the pulmonary vessels, including pulmonary venous remodeling

• PVOD can be redefined as a pre-capillary phenomenon with a significant venous component

• Variations in clinical phenotype, clinical course and treatment response may be related to these phenomena
PH Classification
# Discussions on Updated Classification of PH

## 1. Pulmonary Arterial Hypertension

1.1 Idiopathic PAH  
1.2 Heritable PAH  
1.3 Drug- and toxin-induced PAH  
1.4 PAH associated with:  
   1.4.1 Connective tissue disease  
   1.4.2 HIV infection  
   1.4.3 Portal hypertension  
   1.4.4 Congenital heart disease  
   1.4.5 Schistosomiasis  
1.5 PAH long-term responders to CCB  
1.6 PAH with overt signs of venous/capillaries (PVOD/PCH) involvement  
1.7 Persistent PH of the Newborn syndrome

## 2. PH due to left heart disease

2.1 PH due to heart failure with preserved EF  
2.2 PH due to heart failure with reduced EF  
2.3 Valvular heart disease  
2.4 Congenital/acquired CV conditions leading to post-capillary PH

## 3. PH due to lung diseases and/or hypoxia

3.1 Obstructive lung disease  
3.2 Restrictive lung disease  
3.3 Other lung disease with mixed restrictive/obstructive pattern  
3.4 Hypoxia without lung disease  
3.5 Developmental lung disorders

## 4. PH due to pulmonary artery obstruction

4.1 Chronic thromboembolic PH  
4.2 Other pulmonary artery obstructions

## 5. PH with unclear mechanisms

5.1 Haematologic disorders  
5.2 Systemic disorders  
5.3 Others  
5.4 Complex congenital heart disease
### Updated Classification

**PAH with long term response to CCB**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Acute pulmonary vasoreactivity</th>
<th>Decrease in mPAP ≥ 10 mmHg to value ≤ 40 mmHg Increased or unchanged CO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Long-term response to CCB</td>
<td>FC 1 or 2 Sustained hemodynamic improvements On CCB only 1+ years</td>
</tr>
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</table>

**Drug and toxin induced PAH** *Update*

<table>
<thead>
<tr>
<th>Definite</th>
<th>Epidemic or epi case-control study; large multicenter series; pathophys. mechanisms</th>
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<tr>
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<td>Aminorex Fenfluramine Dexfenfluramine Methamphetamine Benfluorex Dasatinib Toxic rapeseed oil</td>
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**Possible**

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<td>Cocaine Amphetamines Phenylpropanolamine L-Tryptophan St Johns Wort Interferon alpha and beta Alkylating agents Direct-acting antiviral agents against hepatitis C virus Bosutinib Leflunomide Indirubin (chinese herb)</td>
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**Notes**

- Definite PAH: Epidemic or epi case-control study; large multicenter series; pathophys. mechanisms.
- Possible PAH: Isolated case reports or small series.

- Drug and toxin induced PAH: *Update* Zamanian et al, AJRCCM 2018
Updated Classification

PAH with **overt signs of venous/capillary involvement**

| Pulmonary function tests | Decreased DLCO (usually < 50% predicted)  
<table>
<thead>
<tr>
<th></th>
<th>Severe hypoxemia</th>
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| HRCT of the chest        | Interlobular septal thickening  
|                          | Centrilobular ground-glass opacities/nodules  
|                          | Mediastinal lymph node enlargement |
| Response to PAH therapy  | Possible pulmonary edema |
| Genetic background       | Biallelic *EIF2AK4* mutations |
| Occupational exposure    | Organic solvent (trichloroethylene) |
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Updated Proposed Classification

Group 4—Chronic Thromboembolic Pulmonary Hypertension (Nice 2013)

- Group 4—CTEPH and other pulmonary artery obstructions (Nice 2018)
  - 4.1 CTEPH
  - 4.2 other pulmonary artery obstructions
    - Sarcoma or angiosarcoma
    - Other malignant tumors (RCC, uterine, testicular, other)
    - Non-malignant tumors (uterine leiomyoma)
    - Arteritis without CTD
    - Congenital PA stenosis
    - Parasites
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Diagnostic Work-up and Expert Center Referral

- Recommendation for referral to expert PH center, particularly in the context of high likelihood of complex pulmonary vascular disease:
  
  » Suggestive family history
  » Known associated genetic mutations
  » Risk factors for PAH (CTD, CHD, portal HTN, HIV, schistosomiasis)
  » Suspicion of PVOD/PCH

  » All above considered with low probability of PH being due primarily to left heart disease or lung disease and associated hypoxia and parenchymal distortion/destruction

» V/Q scan to evaluate for CTEPH
Echocardiogram Findings

- Increased sPAP or TR jet
- Right atrial and ventricular dilatation
- Decreased RV contractile function
- Flattening of intraventricular septum
- Small LV dimension
- Dilated main PA
- Plethoric and poorly compressible IVC c/w elevated RA/CVP
- Pericardial effusion
- TAPSE < 18-20 mm
Right Heart Catheterization

- Echocardiography is the screening tool of choice, but diagnosis and indication for treatment with PAH therapy can only be based on right heart catheterization data.

Waveforms by location of the Swan-Ganz catheter tip. Tracings obtained in the right atrium or pulmonary capillary wedge position share similar morphology. The transition from the right ventricle to the pulmonary artery tracing can be identified by the increase in diastolic pressure and the presence of a diastolic notch. The diastolic "step-up" results from the transducer crossing the pulmonic valve; the diastolic notch reflects closing of the pulmonic valve. Redrawn from Marino, P. The ICU Book, Philadelphia, Lea and Febiger, 1991, p. 103.
## Proposed Simplified Risk Assessment in PAH

<table>
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<tr>
<th>Prognostic Criteria</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional class</td>
<td>1 or 2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6 MWD</td>
<td>&gt; 440 m</td>
<td>165 – 440 m</td>
<td>&lt; 165 m</td>
</tr>
<tr>
<td>NT-pro BNP</td>
<td>&lt; 300 ng/ml</td>
<td>300-1400 ng/ml</td>
<td>&gt; 1400 ng/ml</td>
</tr>
<tr>
<td>BNP</td>
<td>&lt; 50 ng/l</td>
<td>50-300 ng/l</td>
<td>&gt; 300 ng/l</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>&lt; 8 mmHg</td>
<td>8-14 mmHg</td>
<td>&gt; 14 mmHg</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>≥ 2.5 l/min/m^2</td>
<td>2.0-2.4 l/min/m^2</td>
<td>&lt; 2.0 l/min/m^2</td>
</tr>
<tr>
<td>Or Svo2</td>
<td>&gt;65%</td>
<td>60-65%</td>
<td>&lt; 60%</td>
</tr>
</tbody>
</table>
Proposed Simplified Risk Assessment in PAH

• **Low Risk:** at least 3 low risk and no high risk criteria
• **Intermediate Risk:** definitions of low or high risk not fulfilled
• **High Risk:** at least 2 high risk criteria, including CI or SVO2

• Much debate regarding employment of this tool, which is largely based on validation in large national registries of PAH versus large REVEAL registry based risk calculation tool.
REVEAL Risk Score

- Updated REVEAL Risk Calculator includes:
  - Hospitalization in the past year
  - eGFR
- New cut points for:
  - BNP
  - Heart rate
  - 6 Min Walk distance
  - PVR
  - DLCO
Evolution of Treatment Approach

Patient presents

Time (months)

Therapy added or switched upon "failure" in FC 3

Upfront triple combo therapy

Initial monotherapy

Add therapy

May buy time but not achieve goals

Treatment Goals Achieved

- FC 1
- FC 2
- FC 3
- FC 4

Initial monotherapy

Upfront combo therapy

Add therapy
Proposed Treatment Algorithm

• Initial therapy in newly diagnosed PAH patients that are not vasoreactive:
  » Low or intermediate risk patient: potential for initial monotherapy vs oral combination therapy
  » High risk patient: initial combination therapy to include parenteral prostacyclin therapy; consider lung transplant referral.

• Algorithm then calls for reassessment at 3-6 months after therapy initiation
  » If intermediate or high risk status develops or persists, then therapy augmentation is indicated

• If after additional cycle of reassessment at 3-6 month interval intermediate or high risk status persists, then maximal multimodality (triple class) PAH therapy is indicated and lung transplant evaluation.
Recommendations

- There is still no multicentre trial that suggests targeting PH-LHD with PAH-specific drugs is beneficial. Therefore, we maintain a strong recommendation against the use of PAH therapies in group 2 PH.

- In addition, a safety signal should be acknowledged: 1) the use of sildenafil in the context of PH post-VHD intervention is associated with an increased risk of clinical deterioration and death, and 2) the use of macitentan in CpcPH due to heart failure is associated with an increased risk of fluid retention.

- Following the MELODY-1 trial, new standards have been proposed to explore the role of PAH-approved therapies in the context of group 2 PH. If pursued, such trials should be limited to PH due to HFpEF with CpcPH. The agent of choice should ideally be a HFpEF disease-modifying drug. Finally, a proof-of-concept study should be performed first, with safety and tolerability, haemodynamic and/or CPET efficacy end-points.

- Vasoreactivity testing is not recommended in patients with PH-LHD, outside of the context of assessment for heart transplantation.
Summary

• New perspective on the types of pulmonary vessels involved in the development of various forms of pre-capillary PH, with particular recognition of the role of pulmonary veins and capillaries.
• The hemodynamic definition of PAH may have changed, but the hemodynamic definition of those appropriate for PAH therapy has not.
• New risk assessment guidelines are tied to new treatment algorithms proposed, but controversy remains as to which risk assessment tool is most robust.
• Strategies for treating PAH have evolved and continue to evolve with new clinical trials investigating various combination therapy approaches.
• Treatment of pulmonary hypertension clinical syndromes in the context of left heart disease and chronic lung disease remains a common and perplexing challenge.