Definitions and Diagnosis: Evolution in our Definitions and Diagnosis

Pre-1998 World Symposium Evian, France

'PPH'

'Secondary' Pulmonary Hypertension
Guidelines build on our evolution of knowledge and by constructive comments and proposals over time.

*Increasing understanding of PAH from 2015-2020*

- Basic science
- Clinical Trials
- Registries
- Consensus

**EVOLUTION OF KNOWLEDGE**
Pulmonary Hypertension is continuing to evolve: The burden of PH is growing as awareness increases.

The UK National Registry

Over 30 causes of pulmonary hypertension are described in 5 major groups\(^1,2\)

(Groups 1-5) National Audit of Pulmonary Hypertension 2013, NHS Information Centre.
IPAH is diagnosed increasingly in older patients and raises questions about Definitions and Diagnosis

<table>
<thead>
<tr>
<th>Registry</th>
<th>Time period</th>
<th>Age, years (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH registry</td>
<td>1981–1985</td>
<td>36 ± 15</td>
</tr>
<tr>
<td>French registry</td>
<td>2002–2003</td>
<td>50 ± 15</td>
</tr>
<tr>
<td>US REVEAL 3-5</td>
<td>2006–2009</td>
<td>50 ± 14</td>
</tr>
<tr>
<td>UK and Ireland registry</td>
<td>2001–2009</td>
<td>50 ± 17</td>
</tr>
<tr>
<td>UK National Audit 7</td>
<td>2012–2013</td>
<td>57*</td>
</tr>
<tr>
<td>COMPERA 8</td>
<td>2007–2011</td>
<td>65 ± 15</td>
</tr>
</tbody>
</table>

Certain essential and recommended diagnostic tests appear to be underused

The PAH-Quality Enhancement Research Initiative (PAH-QuERI)

10% Did not perform RHC, required for a diagnosis of PAH

71% Did not screen for CTD

43% Did not conduct a V/Q scan to exclude CTEPH


CTD, connective tissue disease; HIV, human immune deficiency virus; RHC, right heart catheterization; V/Q, ventilation/perfusion.
Definitions and Diagnosis: Comments

• 1: Who are the Guidelines intended for?
  – Expert Centres or the broader medical public?

• 2: The face of PH is changing: How does that reflect on the current Definitions and Diagnosis approach in the guidelines?
  – Do we want to err on the side of under diagnosis or over diagnosis?

• 3: Does the Classification of PH need to be changed in light of the evolving phenotype and treatment responses?

• 4: Is the ‘Gold Standard’ RHC is in need of some polishing?
The Guidelines are for Practicing Clinicians and PH Expert Centres

Galie, N et al Eur Heart J 2016: 37;67-119
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Older patients experience more comorbidities compared with younger patients

<table>
<thead>
<tr>
<th>Comorbidities (n=455)</th>
<th>Age ≤50 years</th>
<th>Age &gt;50 years</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>1%</td>
<td>24%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0%</td>
<td>11%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5%</td>
<td>23%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8%</td>
<td>16%</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Older patients have a worse outcome compared with younger patients

Patients with Group 1 PAH and Group 2 PVH have distinct clinical phenotypes.

Bar graph demonstrating the percentage of patients with PAH and PVH with each of the four clinical features of the MS, p = 0.004 for hypertension, p = 0.002 for obesity, p = 0.005 for diabetes mellitus, and p = 0.023 for hyperlipidemia. The odds ratio with 95% CI for PVH with each factor is presented below the graph. DM = diabetes mellitus; HL = hyperlipidemia; HTN = hypertension.

PVH due to HFrEF was a frequent cause of PH evaluated at a larger referral centre. > 90% of these pts have multiple features of the Metabolic Syndrome.
The diffusion capacity and PAH: Distinct phenotypes

Survival

<table>
<thead>
<tr>
<th></th>
<th>DLCO &lt;45%</th>
<th>DLCO &gt;45%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1yr</td>
<td>87%</td>
<td>95%</td>
</tr>
<tr>
<td>3yr</td>
<td>54%</td>
<td>86%</td>
</tr>
<tr>
<td>5yr</td>
<td>38%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Perhaps we need to give more directions on how to ‘Consider’ left heart and lung diseases?

Consider left heart disease and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, Arterial blood gases (Table 9)

Galie, N et al Eur Heart J 2016: 37;67-119
The Inclusion and Exclusion Criteria as per the Revised Criteria Amendment in AMBITION. A good place to start?

**Inclusion criteria:**

- Confirmed diagnosis of PAH with:*
  - mPAP $\geq$ 25 mm Hg
  - PVR $\geq$ 300 dyne·sec/cm$^5$ *(up from 240)*
  - PCWP or LVEDP $\leq$ 12 mm Hg if PVR $\geq$ 300 to <500 dyne·sec/cm$^5$
  - or PCWP or LVEDP $\leq$ 15 mm Hg if PVR $\geq$ 500 dyne·sec/cm$^5$

**Exclusion criteria:**

- Participants must not have $\geq$ 3 of the following HFpEF risk factors:
  - BMI $\geq$ 30 kg/m2
  - History of essential hypertension
  - Diabetes mellitus (any type)
  - Historical evidence of significant CAD established by any of the following:
    - History of MI, History of PCI
    - Angiographic evidence of CAD
    - (>50% stenosis in $\geq$ 1 vessel)
    - Positive ST
    - Previous CABG
    - Stable angina

Simple diagnostics remain very helpful

- **Group 2**
  - Upper lobe diversion, Kerely B lines, effusions, pulmonary oedema

- **Group 3**:
  - Fibrosis, hyperinflation, increased bronchial wall markings, bullae
LA volume by CMR distinguishes idiopathic from pulmonary hypertension due to HFpEF


CMR, cardiovascular magnetic resonance imaging; HFpEF, heart failure with preserved ejection fraction; IPAH, idiopathic PAH; LA, left atrial.
Diagnostic algorithm for PAH: Improving the Pre-test Probability of PAH

1. Symptoms, signs, history suggestive of PH
   - Metabolic Syndrome?
     - No
     - Yes
     - No
     - Yes
     - Echocardiography enlarged Left Atrium?
       - No
       - Yes
       - No
       - Yes
       - Chest X-Ray upper lobe diversion?
         - No
         - Yes
         - No
         - Yes
         - Abnormal lung function and DLCO <50%
           - No
           - Yes
           - V/Q Scan Mismatched perfusion defects?
             - No
             - Yes
             - Group 1 (PAH) High Probability
               Proceed with dedicated RHC
             - Yes
               - Group 2 (PVH)
               - Group 3 (Lungs)
               - Group 4 (CTEPH)

First consider
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Comments

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Pulmonary hypertension is a severe manifestation of many connective tissue diseases

- Systemic sclerosis (SSc)\(^1\)
- Systemic lupus erythematosus (SLE)\(^2\)
- SSc-SLE overlap syndrome\(^3\)
- Mixed connective tissue disease (MCTD)\(^4\)
- Inflammatory myositis (dermatomyositis and polymyositis)\(^5\)
- Sjögren's syndrome\(^6\)
- Rheumatoid arthritis\(^7\)

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3-yr survival rate in the UK
- 75% SLE-PAH
- 47% SSc-PAH (p=0.01).


Heterogeneous conditions under the heading of Group I PAH

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1. Idiopathic</td>
</tr>
<tr>
<td>1.1.1. Acute vasodilator responsive</td>
</tr>
<tr>
<td>1.1.2. Classical IPAH</td>
</tr>
<tr>
<td>1.1.3. Atypical IPAH</td>
</tr>
<tr>
<td>1.4.1. CTD</td>
</tr>
<tr>
<td>1.4.1.1. Scleroderma</td>
</tr>
<tr>
<td>1.4.1.2 SLE</td>
</tr>
<tr>
<td>1.4.1.3. CTD Other</td>
</tr>
</tbody>
</table>

Towards a molecular classification of PAH*

*Stefan Graf and Nicholas Morrell: Eur Respir J 2016 48:987-989
Definitions and Diagnosis: Comments

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   - Is the increase in age a reflection of a failure in our guidelines?
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The ESC Guidelines allow for Expert Centres to complete the PAH work up with the RHC

Galie, N et al Eur Heart J 2016: 37;67-119
Limitations and controversies in right heart catheterization

• Data acquisition during RHC requires resting and supine patients.
  – There is no standard operating procedure for capturing hemodynamic changes with an upright posture or with physical activity¹.

• Ongoing debate about definitions surrounding PH and Left Heart Disease and the DPG²,⁵
  – Ipc-PH (Isolated) DPG < 7mmHg
  – Cpc-PH (Combined) DPG >7mmHg

• Proposed role for DPG and a PVR of >3 WU³,⁴
  – Review if large database⁴

4. Gerges M et al Eur Respir J 2016; 48; 553-555
5. PROGNOSIS: Tampakakis E et al JACC Heart Fail 2015;3;424
Time to look at ‘Borderline PAH’ again?

Maron et al.; Borderline pulmonary hypertension increases mortality Circulation 2016

Torbicki A Nature Reviews Cardiol 2016
Should fluid or exercise challenge distinguish PAH from Group 2 PH?

- Fluid challenge and exercise testing may be useful in identifying patients with occult HFpEF.

- ‘However, these technique remain investigational and require meticulous evaluation and standardization before its use in clinical practice can be recommended’.

- Will this still be the case by the time of the next guidelines?

HFpEF, heart failure with preserved ejection fraction; LV, left ventricular. Hoeper MM et al. J Am Coll Cardiol 2013
The role for fluid challenging at right heart catheterisation?

- Used to detect latent pulmonary venous hypertension (Group 2)\(^1\)
- Emerging consensus to infuse 500ml of pre-warmed 0.9% saline solution over 5 - 10 minutes\(^1,2,3,4\)
- Debate about how to standardise and what cut-offs of PAWP to consider but 20mmHg seems like best option\(^3,4\)
- Exercise may be more sensitive way to detect HFpEF\(^5\)

53 out of 107 patients had PH. Based on the PAWP-based definition, 29 out of 53 had PAH and 24 out of 53 had PVH. After considering the resting and post-fluid-challenge LVEDP, 11 PAH patients were reclassified as occult PVH.

Can we agree on criteria for diagnosis of exercise pulmonary hypertension?

The previous definition of exercise PH (mPA pressure >30mmHg) was abandoned because healthy individuals can exceed the threshold at high cardiac output (CO).

- Sensitivity 0.99 but Specificity 0.77
- Combining mPA >30mmHg and TPR >3mmHg.min.L\(^{-1}\)
- Sensitivity 0.93 and Specificity 1.0
Relationship between exercise mean pulmonary artery pressure (mPAP) and cardiac output (CO).
Prognostic Relevance of Right Ventricular Contractile Reserve in Patients With Severe Pulmonary Hypertension

A low PASP

Right ventricular function and pulmonary arterial pressure (PAP)

Pulmonary arterial pressure at rest (straight line) and during exercise (dotted line) as seen in echocardiography

A (red) only small increase of PAP
B (green) higher increase of PAP

During exercise
A is not able to increase pulmonary arterial pressure (PAP) while B shows an increase in sPAP >30mmHg = suggesting a better right ventricular reserve

B high PASP

Time to ‘Pimp the Right Heart Cath in PH’?

• Given that the it is recommended that the RHC only be done at the expert centre-can we ‘Pimp’ the test?
• We already do ‘Provocation’ testing with the NO vasodilator trial
  – Should we exercise for diagnosis and/or prognosis?
  – Should we fluid load when ‘atypical’ PAH phenotype?
• Perhaps we should relook at the test as a battery of tests?
  – Fluid challenge– Liver wedge- Exercise - Vasoreactivity - Saturation
  – The ‘FLEVS’ RHC test for PH?
Diagnostic algorithm 2015-2020….
Definitions and Diagnosis: Proposals and Summary

• 1: Expand the algorithm for clinical evaluation prior to referral to expert centre
  – Increase the role of bedside evaluation
  – Increase the discriminating role of left atrial size and diffusion capacity

• 2: Refresh the Classification of PH
  – Consider dividing IPAH into Classical and atypical...
  – Break up the connective tissue diseases...
  – Review the evidence emerging around ‘Borderline’ PAH

• 3: ‘Pimp’ the Right Heart Catheterisation
  – Provocative Testing (i.e. ‘FLEVS’ testing)…