Investigating pulmonary hypertension in the 21st century: heart or lungs?

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Speaker Disclosure

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David is a member of the CRG for Specialist Respiratory Medicine.
Overview

• Overview of the pulmonary hypertension (PH) landscape?
• How common is PH in left heart disease and what is its impact?
• How do I investigate a patient with suspected PH and what are the diagnostic challenges?
Pulmonary Hypertension in 2017

- Worldwide collaboration
  - classification
  - multiple clinical trials
- New drug approvals
  - epoprostenol, iloprost, treprostinil, selixipag
  - bosentan, ambrisentan, macitentan
  - sildenafil, tadalafil
  - riociguat
- Multiple trials on-going
- Established surgical intervention for CTEPH
- Improved survival
Pulmonary Hypertension is highly heterogeneous

1. Pulmonary Arterial Hypertension
   - idiopathic
   - heritable
   - drugs
   - connective tissue disease
   - HIV
   - portal hypertension
   - congenital heart disease
   - schistosomiasis
   - haemolytic anaemia

1’. pulmonary veno-occlusive disease
   - pulmonary capillary haemangiomatosis

4. Chronic Thromboembolic Pulmonary Hypertension
   - operable
   - inoperable

2. PH-Left Heart
   - systolic dysfunction
   - diastolic dysfunction
   - valvular disease

3. PH-Lung Disease/Hypoxia
   - COPD
   - interstitial lung disease
   - sleep disorder
   - alveolar hypoventilation

5. Multifactorial/Unclear
   - Haematological
     - Myeloproliferative
     - 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
PAH: changes in the blood vessels impact on right ventricular function
PAH: therapies target 3 major pathways

Lau EMT et al, *Nature Reviews Cardiology* 2017
PAH: improvement following 1 year of iv prostanoid therapy
Improved survival but changing characteristics of IPAH in the modern era

...older patients have different clinical, physiological and haemodynamic characteristics and more comorbidities\(^1\)....and respond less well to therapy\(^2\)

\(^1\)Ling Y et al. *Am J Respir Crit Care Med* 2012,
\(^2\)Charalampopoulos A, *Pulm Circ* 2012
CTEPH: treatment options

- Surgery can be curative
- Balloon angioplasty

- Medical treatment
  - Anticoagulation
  - PAH therapies

Delcroix M et al, *Circulation* 2016
Overview

• Overview of the pulmonary hypertension (PH) landscape?
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• How do I investigate a patient with suspected PH and what are the diagnostic challenges?
How common is pulmonary hypertension in heart failure?

- >3000 patients studied including HFpEF
- Definitions vary between studies
- Only minority of patients had cardiac catheterisation

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**Table 1**

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>n</th>
<th>Type</th>
<th>Definition of PH</th>
<th>Population</th>
<th>EF</th>
<th>% Measurable TRV</th>
<th>Prevalence of PH</th>
<th>Corrected Prevalence of PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bursi (8)*</td>
<td>1,049</td>
<td>Echocardiography</td>
<td>TTG+RAP ≥35 mm Hg</td>
<td>Epidemiological</td>
<td>91%</td>
<td>79%</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>Damy (51)*</td>
<td>1,380</td>
<td>Echocardiography</td>
<td>TTG ≥35 mm Hg</td>
<td>Hull HF clinic</td>
<td>26%</td>
<td>26%</td>
<td>25%</td>
<td>7%</td>
</tr>
<tr>
<td>Lam (7)†</td>
<td>244</td>
<td>Echocardiography</td>
<td>TTG+RAP ≥35 mm Hg</td>
<td>Olmsted County</td>
<td>Only EF ≥50%</td>
<td>83%</td>
<td>83%</td>
<td>69%</td>
</tr>
<tr>
<td>Leung (52)†</td>
<td>455</td>
<td>Invasive</td>
<td>mPAP ≥25 LVEF 15%</td>
<td>Cath lab</td>
<td>NA</td>
<td>52%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robbins (5)†</td>
<td>122</td>
<td>Invasive</td>
<td>mPAP ≥25 PAWP &gt;15</td>
<td>PH reference</td>
<td>Mixed</td>
<td>NA</td>
<td>23%</td>
<td>20%</td>
</tr>
</tbody>
</table>

See text for references. *All-comer patients with heart failure (HF); †patients from HF/pulmonary hypertension (PH) specialized centers. Cath lab = catheterization laboratory; EF = ejection fraction; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; RAP = right atrial pressure (estimated from the inferior vena cava); TRV = tricuspid regurgitant jet velocity; TTG = transtricuspid gradient.

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Vachiéry JL et al, *J Am Coll Cardiol* 2013
What is the impact of pulmonary hypertension on survival?

- Community based study with incident and prevalent patients (n=1049)
- 60% had LVEF > 45%

Bursi F et al. J Am Coll Cardiol 2012
What is the impact of pulmonary hypertension on outcome in HFpEF?

Lam C et al, J Am Coll Cardiol 2009

Figure 4: Kaplan-Meier Survival Curves in HFpEF Patients With PASP Above and Below the Median

HFpEF patients with PASP above the median value of 48 mm Hg (in red) had reduced survival compared with patients with PASP <48 mm Hg (in black) over 3 years (log-rank p = 0.002). Abbreviations as in Figure 1.
Pathophysiology of pulmonary hypertension in left heart disease

Isolated post capillary pulmonary hypertension
(Ipc-PH - DPG <7mmHg or PVR <3WU)
Pathophysiology of pulmonary hypertension in left heart disease

Combined pre and post capillary pulmonary hypertension (Cpc-PH - DPG ≥ 7mmHg or PVR ≥ 3WU)
Impact of right ventricular function on survival in HFpEF

Melenovsky V et al, Eur Heart J 2014

2437 patients having CMR and suspected severe PH, 116 with HFpEF

Johns CS et al (unpublished work)
Remember there are multiple influences on pulmonary artery pressure

Optimising heart failure treatment can significantly improve pulmonary haemodynamics and improve outcome

Overview

• Overview of the pulmonary hypertension (PH) landscape?
• How common is PH in left heart disease and what is its impact?
• How do I investigate a patient with suspected PH and what are the diagnostic challenges?
Making a diagnosis

- Symptoms non-specific and signs often subtle
- Diagnosis confirmed at cardiac catheterisation
  - mPAP ≥ 25mmHg
- 2 complementary approaches
  - Systematic evaluation of the breathless patient
  - Consider diagnosis in high risk groups

“The ringing in your ears - I think I can help.”
Steps to making a diagnosis of pulmonary hypertension

Be aware of varied clinical presentation
Breathlessness, fatigue, chest tightness, syncope, haemoptysis, ankle oedema (late sign)

Be aware of populations with a high prevalence of PAH and CTEPH
Connective tissue disease (10% of SSc patients)
Portal hypertension (2-6%)
HIV infection (0.5%), PAH family history
Pulmonary thromboembolism (2-4%)
Congenital heart disease (approx 5 %)

Be aware of respiratory/cardiac diseases complicated by PH
COPD, ILD, alveolar hypoventilation
Valvular heart disease, systolic and diastolic dysfunction
Diagnostic approach to suspected pulmonary hypertension in the breathless patient

CXR and ECG may suggest pulmonary hypertension in a breathless patient

Abnormal CXR or ECG seen in up to 90% of patients with IPAH

Abnormalities of lung function are common PH-LHD seen at a PH referral centre

<table>
<thead>
<tr>
<th></th>
<th>IPAH</th>
<th>LV systolic dysfunction</th>
<th>LV diastolic dysfunction</th>
<th>Valvular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>175</td>
<td>17</td>
<td>98</td>
<td>42</td>
</tr>
<tr>
<td>Age yrs</td>
<td>55±16#^,%,,,*</td>
<td>69±8,^</td>
<td>69±11,^</td>
<td>67±10,^</td>
</tr>
<tr>
<td>Female</td>
<td>67#</td>
<td>41,%,,,*</td>
<td>69#</td>
<td>79#</td>
</tr>
<tr>
<td>WHO III/IV</td>
<td>67/20,^</td>
<td>59/12</td>
<td>67/3,^</td>
<td>67/10</td>
</tr>
<tr>
<td>ISWD m</td>
<td>183±173</td>
<td>151±106</td>
<td>164±155</td>
<td>131±130</td>
</tr>
<tr>
<td>$\tilde{P}_{ra}$ mmHg</td>
<td>11±6,%,,,*</td>
<td>17±7,^</td>
<td>15±6,^</td>
<td>14±6,^</td>
</tr>
<tr>
<td>$\tilde{P}_{pa}$ mmHg</td>
<td>53±13,%,,,*</td>
<td>43±9,^</td>
<td>37±9,^</td>
<td>48±12,^</td>
</tr>
<tr>
<td>CI L·min⁻¹·m⁻²</td>
<td>2.3±0.8,%,,,*</td>
<td>2.7±0.8</td>
<td>3.0±0.8,^</td>
<td>2.8±0.4,^</td>
</tr>
<tr>
<td>$P_{pcw}$ mmHg</td>
<td>10±3,%,,,*</td>
<td>24±6,^</td>
<td>22±4,^</td>
<td>26±7,^</td>
</tr>
<tr>
<td>PVR dyn·s·cm⁻⁵</td>
<td>960±465,%,,,*</td>
<td>283±155,^</td>
<td>244±181,^</td>
<td>406±301,^</td>
</tr>
<tr>
<td>SvO₂ %</td>
<td>61±9,^</td>
<td>62±10</td>
<td>65±7,^</td>
<td>62±11</td>
</tr>
<tr>
<td>FEV₁ % pred</td>
<td>86±15,%,,,*</td>
<td>60±19,^</td>
<td>68±20,^</td>
<td>67±22,^</td>
</tr>
<tr>
<td>FVC % pred</td>
<td>97±18,%,,,*</td>
<td>67±23,^</td>
<td>77±21,^</td>
<td>77±23,^</td>
</tr>
<tr>
<td>TL CO % pred</td>
<td>52±21,^</td>
<td>60±14</td>
<td>66±17,^</td>
<td>55±17,^</td>
</tr>
</tbody>
</table>

Data are presented as mean±sd or %, unless otherwise stated. Idiopathic pulmonary arterial hypertension (IPAH) data are shown for comparison. LV: left ventricular; WHO: World Health Organization functional class; ISWD: incremental shuttle walking distance; $\tilde{P}_{ra}$: mean right atrial pressure; $\tilde{P}_{pa}$: mean pulmonary artery pressure; CI: cardiac index; $P_{pcw}$: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; SvO₂: mixed venous oxygen saturation; FEV₁: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; TL CO: transfer factor of the lung for carbon monoxide. \#: p<0.05 in comparison to LV systolic dysfunction; \,*: p<0.05 in comparison to LV diastolic dysfunction; ^: p<0.05 in comparison to valvular disease; \,\,*: p<0.05 in comparison to IPAH.
Lung function its not rocket science!

Reduced lung volumes

Increased Tlco 135%
Echocardiography is the most useful non-invasive tool in the initial assessment of suspected PH

RV and RA dilatation
RV function TAPSE
Paradoxical septal motion
Valvular assess + LA size

sPAP = 4V² + RA

Detecting wave reflections with Doppler flow envelopes


Normal

Late systolic notching

Mid systolic notching

B.

C.

Systematic assessment of CT: vessels, cardiac, lungs may suggest pulmonary hypertension

Perfusion lung scanning

Recommended to exclude CTEPH, Galie N et al, *Eur Heart J* 2009
MRI has diagnostic and prognostic value in pulmonary hypertension

JACC Cardiovasc imaging 2015, JMRI 2015
The challenges of navigating the Pulmonary Hypertension maze

• Does the patient have pulmonary hypertension?
• Is it PH-LHD or could it be another form of PH?
• Common dilemmas:
  – IPAH vs HFpEF
  – IPAH vs other forms of PAH
  – IPAH vs CTEPH
  – IPAH vs severe PH respiratory disease
• Older patients have more comorbidities

HFpEF, heart failure with preserved ejection fraction; PHOOP, out-of-proportion pulmonary hypertension.
“sPAP 80 mmHg in a 75 yr old lady with good LV systolic function - please consider for targeted therapy”

- Essential hypertension for 20 years
- NIDDM
- Long history of tiredness and unrefreshing sleep
- Increasing SOB

- BMI 32, SaO₂ 93%
- Loud P2, PSM, JVP 5 cm
- Ankle oedema
- Echo sPAP 80mmHg, Large LA, mild RV impairment
- ECG: SR, LAD
Cardiac catheter confirms left heart disease

- RA 17 mmHg
- mPAP 49 mmHg
- PAWP 28 mmHg
- CI 2.9 L/min/m²
- PVR 287 dyn·s·cm⁻⁵
- MvO₂ 65%

Learning point: patients with PH should undergo systematic investigation. Multiple problems may exist. Targeted therapy should not be commenced without comprehensive assessment.
Distinguishing between HFpEF and PAH

Thenappan T et al, Circ Heart Fail 2011
# IPAH vs HFPeF

<table>
<thead>
<tr>
<th></th>
<th>IPAH Group 1</th>
<th>PH due to LH disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>–</td>
<td>BP, DM, AF</td>
</tr>
<tr>
<td>ECG</td>
<td>RVH, RAD</td>
<td>LAD, LVH</td>
</tr>
<tr>
<td>Left atrial size</td>
<td>Normal</td>
<td>Enlarged</td>
</tr>
<tr>
<td>RV morphology</td>
<td>Hypertrophy, dilated</td>
<td>Dilated when severe TR</td>
</tr>
<tr>
<td>RV function</td>
<td>Impaired</td>
<td>Well preserved</td>
</tr>
<tr>
<td>Septal displacement</td>
<td>Paradoxical motion</td>
<td>Paradoxical motion rare</td>
</tr>
<tr>
<td>Mitral flow and tissue Doppler</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>RHC</td>
<td>PAWP normal CI low PVR high RA high RA high if severe</td>
<td>PAWP elevated CI normal PVR mildly elevated RA high</td>
</tr>
</tbody>
</table>

Good exercise capacity in a 22-year-old woman with sPAP 120 mmHg mild exercise limitation
Breathlessness in a 50-year-old woman with Raynaud’s and TLco 40%
Understanding the importance of accurate phenotyping in PAH

\[ p < 0.005 \text{ IPAH vs. other groups} \]

<table>
<thead>
<tr>
<th>Years from diagnosis</th>
<th>108</th>
<th>98</th>
<th>85</th>
<th>67</th>
<th>46</th>
<th>32</th>
<th>PAH–Eisenmenger’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH–SSc</td>
<td>175</td>
<td>143</td>
<td>102</td>
<td>67</td>
<td>44</td>
<td>30</td>
<td>IPAH</td>
</tr>
<tr>
<td>PAH–SSc</td>
<td>156</td>
<td>123</td>
<td>83</td>
<td>51</td>
<td>31</td>
<td>14</td>
<td>PAH–SSc</td>
</tr>
<tr>
<td>Total</td>
<td>439</td>
<td>364</td>
<td>270</td>
<td>185</td>
<td>121</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>
“sPAP 70 mmHg in a 78 yr old man with previous PE and ‘normal CT’
...but careful assessment confirms operable CTEPH

Learning point: Q scanning excellent screening test for CTEPH, diagnosis may be missed on CT by non-specialists
How common is CTEPH post PE and who gets it?

- Risk factors for CTEPH
  - Previous PE (OR 19.0)
  - Younger age (OR 1.79/10 years)
  - Larger perfusion defect (OR 2.22/decile decrement in perfusion)
  - Idiopathic PE (OR 5.70)

- At time of acute PE presentation significant number of patients have CTEPH features
  - Elevated sPAP on echo
  - CT imaging

Prospective long-term study of 223 patients with acute PE

Cumulative incidence of symptomatic CTEPH (%)

<table>
<thead>
<tr>
<th>Time</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>1.0%</td>
</tr>
<tr>
<td>1 year</td>
<td>3.1%</td>
</tr>
<tr>
<td>2 years</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

2. Ribeiro et al, Circulation 1999
Increasing breathlessness in a 78 year old male smoker sPAP 100 mmHg

- 3-year history of SOB, rapid deterioration over 6 months
- SaO₂ 81%, loud P2, no RV heave
- PFT’s
  - FEV₁ 2.55 (99%)
  - FVC 3.45 (105%)
  - TLco 1.2 (16%)
Severe PH in association with respiratory disease

PAP 103/36 mmHg; mPAP 59 mmHg; RA 17 mmHg; CO 3.7 L/min; CI 1.9 L/min/m²; PAWP 11 mmHg; PVR 1029 dyn·s·cm⁻⁵

Severe IPAH
What is the spectrum of PH in COPD and what is the prevalence of severe PH?

- 998 patients underwent right heart catheterisation
- Current or ex-smokers
- \( \text{FEV}_1/\text{FVC} \ < 60\% \)
- 60\% of patients with severe PH >40 mmHg had other causes
- 1\% of patients had severe PH-COPD

....but survival of severe PH-COPD (30 \% mortality at one year) much worse than IPAH *

Chaouat A et al, *Am J Respir Crit Care Med* 2005
Sheffield approach to identifying pre-capillary PAH in a heart failure clinic

**Risk factors for HF-pEF**
- Clinical
  - Hypertension
  - Age >65 years
  - Obesity
  - CAD
  - DM
  - AF
- ECHO
  - LA dilatation
  - LVH

**ECHO**
- HF-rEF
- LVEF ≥50% sPAP >36mmHg
- Valve Disease
- Risk factors for PAH/CTEPH
  - ≥2 Risk factors for HFpEF
    - *Echo features of PAH/CTEPH or RAD on ECG*
  - Yes
    - HFpEF unclear
      - *Ix for other causes of PH*
  - No
    - HFpEF

**Risk factors for PAH/CTEPH**
- Incidence
  - Systemic sclerosis: 10%
  - Mixed connective tissue: 5%
  - Previous PE/DVT: 3.8%
  - Liver cirrhosis: 2%
  - SLE: <1%
  - HIV: 0.5%
  - Family history of PAH
  - Recreational drug use

**ECHO Features of PAH/CTEPH**
- Mod-severe RV impairment
- Paradoxical septal motion
- sPAP > 70 mmHg

Conclusion

- PH is common in LHD and associated with a worse outcome
- PH is diagnosed by systematic assessment of the breathlessness patient and screening high risk groups
- Navigating the PH “maze” requires careful history and examination and basic investigations such as Echo, lung function, Q scan and CT will suggest the diagnosis in the majority of cases
- If you suspect PAH or CTEPH do not delay referral to complete investigations
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