Πνευμονική υπέρταση στην καρδιακή ανεπάρκεια

Στέλλα Μπρίλη
Ιπποκράτειο ΓΝΑ
Α΄ Πανεπιστημιακή Καρδιολογική Κλινική
PH-LHD

• An abnormal increase of pressures in the pulmonary vascular bed, or PH, can be a relatively common consequence of several cardiac, pulmonary, and systemic disorders but also of the aging process.
PH-LHD

- Presence of PH-LHD is associated with a decrease in exercise tolerance, worsening of dyspnea, and reduced survival.
Current hemodynamic definition of PH-LHD

- \((mPAP) \geq 25 \text{ mm Hg} + (PAWP) \geq 15 \text{ mm Hg}\), + normal or reduced \((CO)\)
PH-LHD vs PAH

- older
- male
- with a history of systemic hypertension
- metabolic syndrome (or most of its features)
The true prevalence of PH-LHD in HF remains unknown

- scarce data (epidemiological studies in community-based HF populations or tertiary HF referral centers)
- the definition of PH was based on echocardiography, with a variety of cutoff values
- heterogeneous populations (symptoms, age, and level of EF)
- measurements of pulmonary arterial and left atrial filling pressures were not assessed by right (RHC) and/or left heart catheterization, with the exception of single-center reports

Wide ranged reported prevalence:

25%->100% prevalence of PH-LVD in the patients examined
Determinants of PH-LHD

- Passive ↑ in mPAP
- Added component
- Further ↑ in mPAP
- Significant PVD
- RV failure
- Death

<table>
<thead>
<tr>
<th>Loss of LA compliance</th>
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</thead>
<tbody>
<tr>
<td>Diastolic dysfunction</td>
</tr>
<tr>
<td>Pulsatile load by PAWP</td>
</tr>
<tr>
<td>Exercise-induced MR</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>↓ NO and ↑ ET-1 activity</td>
</tr>
<tr>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>↓ BNP induced vasodilation</td>
</tr>
<tr>
<td>Vascular remodelling</td>
</tr>
<tr>
<td>Decreased vascular compliance</td>
</tr>
<tr>
<td>Blunted response to vasodilators</td>
</tr>
</tbody>
</table>

Figure 1: Mechanism of Pulmonary Hypertension Due to Left Heart Disease

(J Am Coll Cardiol 2013;62:D100–8)
Current hemodynamic definition of PH-LHD

In function to the trans-pulmonary pressure gradient

• “passive” PH (TPG $\leq 12$ mm Hg)
• “reactive” PH (TPG $>12$ mm Hg)
• “out of proportion” PH (TPG $>12$ mm Hg)
• “mixed” PH (TPG $>12$ mm Hg)

$TPG = mPAP - PAWP$
Identification of different hemodynamic presentations

• elevated PAWP, but no significant change in the pulmonary circulation (i.e., absence of pulmonary vascular disease or vascular remodeling) (PVD)

• an elevated PAWP, with PVD

• a previously elevated but meanwhile normalized PAWP, with persistence of PVD (in patients who have undergone forced diuresis in the presence of HF-pEF, atrial fibrillation and corrected valve disease)
Areas of confusion between PH-LHD and PAH/pre-capillary PH

Lack of a clear definition of “out-of-proportion” PH causes confusion with PAH, it might encourage physicians to treat some patients suffering from PH-LHD with PAH-approved therapies, despite the lack of evidence

• complex surgery (transplantation, LV assist device, valve surgery) might be considered too high risk because of significant PH

• vasoreactivity testing in PH-LHD is often performed without clear guidelines about which vasodilator should be used to perform testing

-> risk for increased PCWP and pulmonary edema
How can we define a change in the pulmonary circulation that is not in relation with the increase in PAWP and that is measurable by RHC (1)

- **it should reflect changes of the pulmonary circulation and be a clear marker of PVD**
- **it must be less dependent on (or as independent as possible) of the change in PAWP**
How can we define a change in the pulmonary circulation that is not in relation with the increase in PAWP and that is measurable by RHC (2)

- **it should be minimally influenced by changes in blood flow and stroke volume (SV)**
- **it should reflect changes in compliance and take into account the distensibility of the pulmonary arteries.**
Which one?

Pulmonary vascular resistance? No.

PVR = mPAP - PCWP / CO X 80

*a composite variable, with an interdependent numerator and denominator (changes in flow influence pressure in the pulmonary circulation). Therefore, it is highly sensitive to changes in both flow and filling pressures but does not reflect changes in the pulmonary circulation at rest*
Which one?

Transpulmonary gradient? No

\[ TPG = mPAP - PAWP \]

- at a constant SV, an increase of PAWP has a more pronounced effect on systolic PAP and mPAP than diastolic PAP. This impact is even greater when SV increases. As a result, TPG is influenced by all determinants of mPAP, including flow, resistance, and left heart filling pressure.
Which one?

\[ DPG = dPAP - PAWP \]
Diastolic pressure difference
DPAP-meanPAWP

• In normal subjects, DPD lies in the 1-mm Hg to 3-mm Hg range, and in patients evaluated for cardiac disease (excluding shunts), the DPD remains 5 mm Hg in most cases.
How important is pulmonary hypertension due to left heart disease?

- The available data confirm that prognosis of HFpEF is comparable to or only faintly better than that of HFrEF.
- Moreover, in both conditions, the decrease in survival is similarly proportional to the elevation of pulmonary systolic pressure even if the majority of patients will present with only a mild to moderate degree of PH.
How important is pulmonary hypertension due to left heart disease?

• **Accuracy of risk estimation can be further increased on the basis of the PH subtype:** mixed PH (or combined pre and post-capillary PH, PVR of at least 3 Wood units) has a largely higher risk of death than passive PH (or isolated post-capillary PH, PVR of less than 3 Wood units –hazard ratio 1.55)
Independent and Additive Prognostic Value of Right Ventricular Systolic Function and Pulmonary Artery Pressure in Patients With Chronic Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Normal PAP/Preserved</th>
<th>Normal PAP/Low RVEF</th>
<th>High PAP/Preserved</th>
<th>High PAP/Low RVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Group 1, n = 73)</td>
<td>(Group 2, n = 68)</td>
<td>(Group 3, n = 21)</td>
<td>(Group 4, n = 215)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>62/11</td>
<td>53/15</td>
<td>20/1</td>
<td>186/29</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52 ± 10</td>
<td>51 ± 11</td>
<td>52 ± 10</td>
<td>51 ± 10</td>
</tr>
<tr>
<td>Etiology (DCM/IHD)</td>
<td>53/20</td>
<td>51/17</td>
<td>14/7</td>
<td>132/83</td>
</tr>
<tr>
<td>NYHA functional class III or IV (%)</td>
<td>40%</td>
<td>53%</td>
<td>48%</td>
<td>87%*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>75 ± 13</td>
<td>79 ± 14</td>
<td>75 ± 17</td>
<td>88 ± 18*</td>
</tr>
<tr>
<td>Rhythm (SR/AF)</td>
<td>69/4</td>
<td>49/19†</td>
<td>21/0</td>
<td>165/50†</td>
</tr>
<tr>
<td>LBBB/RBBB (%)</td>
<td>53/3</td>
<td>39/6</td>
<td>48/5</td>
<td>43/7</td>
</tr>
<tr>
<td>Bilirubin, direct (mg)</td>
<td>0.17 ± 0.11</td>
<td>0.20 ± 0.16</td>
<td>0.23 ± 0.18</td>
<td>0.77 ± 0.31*</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25.1 ± 5.8</td>
<td>22.9 ± 6.2</td>
<td>23.8 ± 6.2</td>
<td>20.6 ± 5.7†</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>39 ± 7</td>
<td>40 ± 5</td>
<td>39 ± 5</td>
<td>41 ± 6</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>33 ± 6</td>
<td>34 ± 5</td>
<td>33 ± 5</td>
<td>35 ± 6</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>13 ± 4</td>
<td>13.8 ± 3.8</td>
<td>29 ± 8.6§</td>
<td>37.4 ± 9.1§</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>8.2 ± 4.3</td>
<td>8.1 ± 3.6</td>
<td>20.3 ± 8.8§</td>
<td>26.6 ± 7.4§</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>1.2 ± 3.7</td>
<td>1.3 ± 2.3</td>
<td>4.5 ± 4.3§</td>
<td>7.9 ± 5.7*</td>
</tr>
<tr>
<td>CI (ml/min per m²)</td>
<td>2.7 ± 0.6</td>
<td>2.5 ± 0.6</td>
<td>2.6 ± 0.6</td>
<td>1.9 ± 0.6*</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>42 ± 5</td>
<td>27 ± 7†</td>
<td>41 ± 5</td>
<td>16 ± 8†</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates (%)</td>
<td>45</td>
<td></td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>Frusemide (mg)</td>
<td>45 ± 46</td>
<td>64 ± 60</td>
<td>67 ± 41</td>
<td>105 ± 122*</td>
</tr>
</tbody>
</table>

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Vol. 37, No. 1, 2001
Independent and Additive Prognostic Value of Right Ventricular Systolic Function and Pulmonary Artery Pressure in Patients With Chronic Heart Failure

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Gaps in evidence

• the respective value of the TPG and the DPD should be further explored, including their role in predicting outcome. Multicenter data collection and analysis of established databases might be helpful to address the issue in an acceptable timeframe.
Gaps in evidence

- the importance of fluid loading and exercise in uncovering PH due to LHD requires standardization and validation
Hemodynamic Thresholds for Pre-capillary Pulmonary Hypertension

CHEST 2016; 149(4):1061-1073
• The primary goal of therapy of PH-LHD must be to improve global management of the underlying condition before considering specific measures to treat PH
Treatment Insights

• the implantation of an LV assist device has been shown to lower pulmonary pressures through LV unloading without increasing the risk of post-implantation RV failure

• risk factors for cardiovascular diseases and features of the metabolic syndrome should be controlled

• concomitant disorders leading to PH should be identified and treated, including chronic obstructive pulmonary disease, sleep apnea syndrome, and pulmonary embolism

• there is no strong evidence-based recommendation for the treatment for HF-pEF
Recommendations

• Vasoreactivity testing in PH-LHD should not be performed with selective pulmonary vasodilators (e.g., IV prostacyclin) in patients with PCWP >15 mm Hg, due to the risk of increased PCWP and pulmonary edema. The role of vasoreactivity testing remains to be explored further.
TREATMENT

There is no new evidence supporting the use of PAH therapies in PH-LHD, due to the absence of studies specifically stratifying patients for PH and/or targeting this specific condition.
<table>
<thead>
<tr>
<th>Drug/Author Year</th>
<th>Study Acronym (Ref. #)</th>
<th>Patients</th>
<th>Design</th>
<th>Primary Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iloprost/nolilla 1996</td>
<td>FIRST (31)</td>
<td>n = 471 Severe HF</td>
<td>1:1 randomization event-driven mean dose 4 mg/kg/min</td>
<td>Survival</td>
<td>Early termination (treatment survival in treated)</td>
</tr>
<tr>
<td>Bosentan/Packer 2001</td>
<td>REACH1 (29)</td>
<td>n = 174 Severe HF</td>
<td>2:1 randomization 26-week duration 500 mg bid</td>
<td>Change in clinical state</td>
<td>Early termination (deterioration in the treated)</td>
</tr>
<tr>
<td>Sitara 2002</td>
<td>ENABLE (30)</td>
<td>n = 1,613 Severe HF</td>
<td>1:1 randomization 18-month duration 125 mg bid</td>
<td>Mortality + hospital stays</td>
<td>No effect</td>
</tr>
<tr>
<td>Bosentan/Buscher 2002</td>
<td>HEAT (33)</td>
<td>n = 179 NYHA III</td>
<td>3:1 randomization 3-week duration doses of 30, 100, 300 mg</td>
<td>Hemodynamic (changes in PAWP/CO)</td>
<td>Increased CO No change in PAWP</td>
</tr>
<tr>
<td>Sand 2004</td>
<td>EARTH (32)</td>
<td>n = 642 NYHA II-IV</td>
<td>5:1 randomization 6-month duration doses 10, 25, 50, 100, 300 mg</td>
<td>LV changes by MRI + clinical events</td>
<td>No effect</td>
</tr>
</tbody>
</table>

**Table 3** Completed RCTs Using Prostanoids and Endothelin Receptor Antagonists in HF

**JACC 2013**
Why?

- The population of HF is more heterogeneous than in PAH and more male, with older patients,
- Patients receive extensive background therapy resulting in complex polypharmacy,
- The target population has not been properly defined.
**Recommendations for RCTs**

**Population**

- patients with PH due to HF-pEF and PH due to HF with reduced EF should be studied separately.
- patients with uncorrected valvular heart diseases should be excluded.
- patients with corrected valvular heart diseases might be studied as well.
Recommendations for RCTs

Population

- **patients** should be on optimal regimens of HF therapy and fluid balance before randomization.

- **patients** with combined post-capillary and pre-capillary PH should represent the target population.

- recruitment should be based on RHC, although pre-screening by echocardiography might be considered.
Recommendations for RCTs
Endpoint

- a change in DPD
+/- peak VO\textsuperscript{2}
+/- ventilatory efficiency
+/- increase in 6-min walking distance
THANK YOU