Exercise Induced Pulmonary Hypertension

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Pulmonary Hypertension Clinical Topics Series
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Outline

- Historical perspective
- Current guidelines
- Defining the normal exercise response
- Proposal for new criteria
Historical Definitions

• The upper limit of normal resting PAP 20 mmHg
• Fishman thought that the mPAP would not exceed 25 mmHg in normal subjects
• Generally agreed that PH should be defined as:
  • mPAP >25 mmHg
  • mPAP >30 mmHg with exercise

Limitations with Definition

- Did not account for:
  - Level of exercise
  - Exercise method
  - Posture for Exercise
  - Age
• Inclusion:
  • Studies with original data of right heart catheterization and exercise
  • Studies in which subjects were asymptomatic without significant medical conditions

• Exclusions:
  • Studies referring to / interpreting previous examinations
  • Studies in which the original data was not clearly identified
  • Studies in which detailed description of methods or complete hemodynamic data was not included
  • Studies examining drug-induced changes
  • Studies at high altitude or hypoxic changes
Studies

Retrieved

16 studies
Included

• Exercise Type:
  • Cycle ergometry
  • Treadmill exercise
  • Leg or arm presses in supine or upright

• Populations:
  • Younger / Older
  • Untrained / Trained
  • Female / Male preponderance

• Data were stratified for:
  • Gender
  • Age
    • <30
    • 30-50
    • >50
  • USA / Europe
  • Body position
  • Exercise levels
    • Slight
    • Submaximal
    • Maximal

72 separate study populations

1187 Subjects
Normal Resting Hemodynamics

**TABLE 1** Haemodynamics at rest (supine)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tilde{P}_{pa}$ mmHg</td>
<td>14.0±3.3</td>
</tr>
<tr>
<td>Systolic $P_{pa}$ mmHg</td>
<td>20.8±4.4</td>
</tr>
<tr>
<td>Diastolic $P_{pa}$ mmHg</td>
<td>8.8±3.0</td>
</tr>
<tr>
<td>$P_{paw}$ mmHg</td>
<td>8.0±2.9</td>
</tr>
<tr>
<td>Heart rate min⁻¹</td>
<td>76±14</td>
</tr>
<tr>
<td>Cardiac output L.min⁻¹</td>
<td>7.3±2.3</td>
</tr>
<tr>
<td>Cardiac index L.min⁻¹.m⁻²</td>
<td>4.1±1.3</td>
</tr>
<tr>
<td>PVR dyn.s.cm⁻⁵</td>
<td>74±30</td>
</tr>
</tbody>
</table>

Data are presented as weighted mean±weighted s.d. $\tilde{P}_{pa}$: mean pulmonary arterial pressure; $P_{pa}$: pulmonary arterial pressure; $P_{paw}$: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance. n=882 healthy volunteers.

ULN Resting mPAP 20.6 mmHg supine, 19.8 mmHg upright

Kovacs, G, ERJ 2009; 34:888-894
Normal Exercise Hemodynamics

- ULN at slight exercise: 28.8 mmHg
- ULN at maximal exercise: 36.8 mmHg
- 21% of subjects < 50 yo, reached mPAP > 30 mmHg with maximal exercise!

### TABLE 2: Haemodynamics during upright exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Slight</th>
<th>Maximal</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\bar{P}_p$ mmHg</td>
<td>13.8±3.1</td>
<td>20.8±4.0</td>
<td>25.6±5.6</td>
</tr>
<tr>
<td>$P_{paw}$ mmHg</td>
<td>5.9±2.8</td>
<td>9.1±4.2</td>
<td>14.9±7.9</td>
</tr>
<tr>
<td>Heart rate min⁻¹</td>
<td>82±16</td>
<td>103±14</td>
<td>170±14</td>
</tr>
<tr>
<td>Cardiac output L·min⁻¹</td>
<td>7.4±2.2</td>
<td>14.9±3.9</td>
<td>20.0±3.8</td>
</tr>
</tbody>
</table>

Data are presented as weighted mean±weighted sd. $\bar{P}_p$: mean pulmonary arterial pressure; $P_{paw}$: pulmonary arterial wedge pressure. n=193 healthy volunteers.
Hemodynamics by Age

- With slight exercise:
  - ULN Age <50: 29 mmHg
  - ULN Age ≥50: 46.2 mmHg
- Insufficient data to compare higher levels of exercise for subjects >50

- PAWP
  - Rest: <50: 8.0±2.8 mmHg, ≥50 7.7±3.0 mmHg, p=0.61
  - Exercise: <50: 10.9±3.9 mmHg, ≥50 16.8±6.5 mmHg, p<0.001

Kovacs, G, ERJ 2009; 34:888-894
<table>
<thead>
<tr>
<th>Exercise</th>
<th>mPAP Supine ULN (mmHg)</th>
<th>mPAP Upright ULN (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slight (HR 100-110)</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Submaximal (HR 130-135)</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Maximal (HR 160)</td>
<td>37</td>
<td>35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>mPAP ULN with Slight Exercise (mmHg)</th>
<th>mPAP ULN with Submaximal Exercise (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>30-50</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>&gt;50</td>
<td>45</td>
<td>47</td>
</tr>
</tbody>
</table>
Diagnosis and Assessment of Pulmonary Arterial Hypertension

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and Warsaw, Poland

Recommendations. Based on this literature review, we recommend simplifying the definition of PH, as follows:

• The exercise and PVR criteria should be eliminated.
mPAP-CO relationship

\[ mPAP = \left[ (1 + \alpha \cdot LAP)^{\frac{1}{5}} + 5 \alpha \cdot R_0 \cdot Q \right]^{\frac{1}{5}} - \frac{1}{\alpha} \]

- mPAP = mean pulmonary artery pressure
- LAP = left atrial pressure
- \( R_0 \) = total pulmonary vascular resistance
- \( Q \) = CO
- \( \alpha \) = pulmonary vascular distensibility

Naeije, R, AJRCCM 2013;187(6)576-583
mPAP-CO relationship

\[
mPAP = \left( (1 + \alpha \text{LAP})^{\frac{5}{2}} + 5 \alpha R \downarrow \text{Q} \right)^{\frac{1}{5}} - \frac{1}{\alpha}
\]

Kovacs, G, ERJ 2009; 34:888-894
Naeije, R, AJRCCM 2013;187(6)576-583
Pulmonary vascular distensibility

- mPAP measured by RHC with increasing exercise in normal subjects
- Upper limit of the mPAP-CO slope is 3 mmHg*min/L
- Upper limit of normal mPAP at 10 L/min is 30 mmHg

Naeije, R, AJRCCM 2013;187(6)576-583

mPAP-CO modeled at progressively increased distensibility

$\alpha$ is usually < 2%/mmHg
mPAP-CO relationship

Lewis, GD, Circ 2013;128:1470-1479
Left Atrial Pressure

• Previously thought to remain constant

• Linear increasing in PAWP with CO with slopes close to 1 (i.e. 1 mmHg increase in LAP with 1 L/min CO)

• Mechanism:
  • LV diastolic compliance decreased with increasing diastolic volume, which reaches maximum at mild-moderate exercise
    • Due to intrinsic mechanical properties of LV, competition for space with RV, within nondistensible pericardium
• Retrospective study of patients being evaluated for dyspnea
• Supine lower limb cycle ergometer
• Staged workload until exhaustion / exercise limiting symptoms
Study Groups

- **Controls:**
  - Normal PFTs, echo, chest CT, VQ scan
  - No risk factors for PH
  - PAWP normal with exercise

- **PVD:**
  - Previous h/o PH, now normal with therapy
  - Development of PH in follow up
  - + VQ scan and pulmonary angiogram
  - Lung biopsy with PVOD

- **LHD:**
  - PAWP ≥ 20 mmHg

Herve, P, ERJ 2015;46:583-586
Results

[Flowchart image showing patient population for study inclusion.]

**FIGURE 1.** Flow chart of patient population for study inclusion. mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; TPR: total pulmonary resistance.
Results

- Exercise measures were more predictive than rest measures.
- Exercise TPR, mPAP were more predictive than PVR.
- TPR, mPAP were independent predictors of PVD / LHD.

Herve, P, ERJ 2015;46:583-586
Results

- Combining criteria of mPAP $\geq 30$ mmHg with TPR $\geq 3.0$ WU was sensitive and specific for disease
- Sensitivity: 0.93
- Specificity: 1.0
- At submaximal exercise, 63% of LHD / PVD met criteria

Herve, P, ERJ 2015;46:583-586
Subgroup Analysis

| TABLE 3 Diagnostic accuracy of the association of the two criteria: mPAP_{max} >30 mmHg and TPR_{max} >3 WU for entire study population and subgroups |
|---------------------------------|-----------------|-----------------|-------|-------|-------|
|                                | n               | Sensitivity (95% CI) | Specificity (95% CI) | NPV   | PPV   | Accuracy |
| **All**                        | 169             | 0.93 (0.86–0.96)    | 1.0 (0.95–1.0)       | 0.91  | 1     | 0.96     |
| **Sex**                        |                 |                  |                  |       |       |          |
| Male                           | 55              | 0.82 (0.68–0.96)   | 1.0 (0.88–1.0)      | 0.84  | 1     | 0.90     |
| Female                         | 114             | 0.93 (0.87–0.99)   | 1.0 (0.91–1.0)      | 0.89  | 1     | 0.96     |
| **Age**                        |                 |                  |                  |       |       |          |
| >50 years                      | 95              | 0.94 (0.89–0.99)   | 1.0 (0.87–1.0)      | 0.87  | 1     | 0.96     |
| ≤50 years                      | 74              | 0.81 (0.67–0.95)   | 1.0 (0.92–1.0)      | 0.87  | 1     | 0.92     |
| **Diagnosis**                  |                 |                  |                  |       |       |          |
| PVD                             | 49              | 0.94 (0.84–0.98)   | 1.0 (0.95–1.0)      | 0.92  | 1     | 0.95     |
| LHD                             | 52              | 0.92 (0.82–0.97)   | 1.0 (0.95–1.0)      | 0.94  | 1     | 0.97     |

*: the test was considered positive only if both criteria mPAP_{max} >30 mmHg and TPR_{max} >3 WU were satisfied. mPAP_{max}: mean pulmonary artery at maximal exercise; TPR_{max}: total pulmonary resistance at maximal exercise; NPV: negative predictive value; PPV: positive predictive value; PVD: pulmonary vascular disease; LHD: left heart disease.
Conclusions

TABLE 5 Proposed standardised protocol of exercise haemodynamic testing

1. Include patients with resting mPAP<25 mmHg
2. Brachial or jugular vein approach
3. Dynamic exercise in supine position on bicycle
4. Number of work step and work increment to reach the maximum within 10–15 min
5. Successive stages: baseline supine, legs on cycle pedal, unloaded pedalling (0 W) and at constant workload increments of 10–30 W depending on estimated exercise capacity (usually 1–3 work load steps)
6. Measurement of mPAP and PAWP averaged over the respiratory cycle and CO in triplicate using thermodilution or direct Fick method
7. Measure mPAP, PAWP and CO at steady state at each step: i.e. unchanged mPAP and heart rate; usually during the last 2 min of each exercise step
8. Interpretations
   If at submaximal workload, mPAP >30 mmHg with CO <10 L·min⁻¹; (TPR >3 WU) you can stop the test: exercise PH
   If not, continue the test until maximum tolerable workload:
   If TPRmax ≤3 WU with mPAP >30 mmHg: no exercise PH
   If TPRmax ≤3 WU with mPAP ≤30 mmHg: no exercise PH
   If TPRmax >3 WU with mPAP ≤30 mmHg: no exercise PH
   If TPRmax >3 WU with mPAP >30 mmHg: exercise PH

mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; TPRmax: total pulmonary resistance at maximal exercise; PH: pulmonary hypertension.

Herve, P, ERJ 2015;46:583-586
Questions?

Thoughts?