Pulmonary Hypertension: Pathophysiology and Classification

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Pulmonary hypertension is a disease of the pulmonary circulation with many facettes.

- Normal
- Chronic hypoxia
- Thrombo-embolic disease
- Pulmonary arterial hypertension
- Chronic LV failure
- Pulmonary venoocclusive disease

Fishman AP. in: Pulmonary diseases and disorders, 1988, 2: 999-1048
Patients may present in the ICU at any stage of the disease.
Epidemiology of Pulmonary Hypertension in Swiss ICUs

1519 ICU Patients

- Known PH: 1036
- New diagnosis PH (PAC): 286
- CTEPH: 28
- Other: 12
- PAH: 6

Ethiology in 120 Patients

- PAH: 8%
- L-Heart Dis.: 60%
- Lung Dis.: 17%
- CTEPH: 3%
- Other: 12%

Wenger U. for the Swiss Society for Pulmonary Hypertension
WHO-Classification of Pulmonary Hypertension (Dana Point 2008)

1. Pulmonary arterial hypertension
2. Pulmonary hypertension due to left heart disease
3. Pulmonary hypertension due to lung disease and/or hypoxemia
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear or multifactorial mechanisms

Simonneau et al. JACC 2009, 54:S43
**Definition of Pulmonary Hypertension**

As assessed by right heart catheter

| Definition                  | Characteristics                                | Clinical group(s)
b | Pulmonary arterial hypertension | 1. Pulmonary arterial hypertension | 2. PH due to left heart disease |
<table>
<thead>
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<tbody>
<tr>
<td>Pulmonary hypertension (PH)</td>
<td>Mean PAP ≥ 25 mmHg</td>
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<td></td>
<td>Passive TPG ≤ 12 mmHg</td>
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<td></td>
<td>Reactive (out of proportion) TPG &gt; 12 mmHg</td>
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ESC Guidelines 2009
EHJ 2009 30:2493
Assessment of Pulmonary Hypertension by ECHO

ESC Guidelines 2009, EHJ 2009 30:2493

<table>
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<tr>
<th>Echocardiographic diagnosis: PH unlikely</th>
<th>Class(^a)</th>
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<td>Tricuspid regurgitation velocity ≤ 2.8 m/s, PA systolic pressure ≤ 36 mmHg, and no additional echocardiographic variables suggestive of PH</td>
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<td>C</td>
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<tr>
<td>Tricuspid regurgitation velocity 2.9–3.4 m/s, PA systolic pressure 37–50 mmHg with/without additional echocardiographic variables suggestive of PH</td>
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<td>Tricuspid regurgitation velocity &gt; 3.4 m/s, PA systolic pressure &gt; 50 mmHg, with/without additional echocardiographic variables suggestive of PH</td>
<td>I</td>
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</tr>
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Table 9: Arbitrary criteria for estimating the presence of PH based on tricuspid regurgitation peak velocity and Doppler-calculated PA systolic pressure at rest (assuming a normal right atrial pressure of 5 mmHg) and on additional echocardiographic variables suggestive of PH

Exercise Doppler echocardiography is not recommended for screening of PH
Pulmonary Arterial Hypertension (Class 1 WHO-Classification)

Pulmonary arterial hypertension (PAH) is a clinical condition characterized by the presence of pre-capillary pulmonary hypertension (PH) in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH or other rare diseases. PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation.
WHO- Classification of Pulmonary Arterial Hypertension (Class 1)

1. Pulmonary arterial hypertension
   1.1 Idiopathic
   1.2 Hereditable (BMPR II, ALK 1, Endoglin, unknown)
   1.4 Drugs and Toxines
   1.3 Related to associated conditions
      1.3.1 Connective tissue disease
      1.3.2 Cardiac abnormalities (Shunts)
      1.3.3 HIV
      1.3.4 Porto pulmonary
      1.3.5 Schistosomiasis
      1.3.6 Chronic haemolytic anaemia
   1.5 Persistent PAH of the newborn

1’. Pulmonary veno-occlusive disease and/or Pulmonary capillary hemangiomathosis

Simonneau et al. JACC 2009, 54:S43
Endothelial dysfunction in PH: Imbalance between vasoconstrictors and vasodilators

Humbert et al. NEJM 2004; 351: 1425
Structural changes in pulmonary arterial hypertension

- Media hypertrophy
- Arterial occlusion
- Plexiform lesion
- Endothelial proliferation
- Venous occlusion
- Septal capillary proliferation

Images showing various histological changes with labels and measurements of 50µm.
Venoocclusive pulmonary hypertension and vasodilators therapy

**Right heart catheter**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tr>
<td>Ppa (s/m/d)</td>
<td>77/54/33 mmHg</td>
</tr>
<tr>
<td>Pra</td>
<td>2 mmHg</td>
</tr>
<tr>
<td>Paop</td>
<td>? 18, 8, 4 mmHg</td>
</tr>
<tr>
<td>CI</td>
<td>3.6 l/min/m²</td>
</tr>
</tbody>
</table>

BAL
PAH-Pathophysiology

↑ Contraction

↑ Proliferation

↓ Apoptosis

Morrell JACC 2009 54:20
Genetic basis of pulmonary artery hypertension

Control of cell proliferation, recognition, differentiation, apoptosis and determination of developmental fate in tissues

Heterozygous mutation of the bone morphogenetic protein (BMP) receptor II gene coding for a type II receptor member of the TGF-β family

Mutations of the BMPR-2 are identified in ~70% of inherited familial pulmonary artery hypertension and 10-20% of idiopathic pulmonary hypertension.
BMPR-2 mutation status and pulmonary arterial hypertension after fenfluramine intake

Duration of fenfluramine exposure according to BMPR-2 mutation status

- positive
- negative

Presence of BMPR-2 mutation

Cumulative survival in patients with and without fenfluramine associated PH

- Idiopathic/familial
- fenfluramine


p = 0.3 (long rank test)

p = 0.007
Pathophysiologic mechanisms of pulmonary arterial hypertension

- **RISK FACTORS**
  - autoimmunity, toxins, HIV ...

- **GENETIC PREDISPOSITION**
  - BMPR2, ALK-1 ...

**Inflammation**
- (IL-1, IL-6, chemokines RANTES, fractalkine)

**ENDOTHELIAL CELL DYSFUNCTION**
- NO, PGI1, ET-1 ...

**SMOOTH MUSCLE CELL DYSFUNCTION**
- KV1.5, 5-HTT, ...

**vascular injury and dysfunction**

**Disease progression**
WHO-Classification of Pulmonary Hypertension (Dana Point 2008)

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Simonneau et al. JACC 2009, 54:S43
Pulmonary Hypertension of Left Heart Disease
(Class 2 of WHO-Classification)

Following left ventricular systolic and/or diastolic dysfunction or valvular disease lead to a remodeling of pulmonary veins, capillaries and arteries.

\[ \text{mPpa} \approx 45 \text{ mmHg} \]
\[ \text{Ppao} \approx 32 \text{ mmHg} \]

\[ \text{TPG : mPpa} - \text{Ppao} > 12 \text{ mmHg} \implies \text{reactive PH} \]

Simonneau et al. JACC 2009, 54:S43
Pathophysiology of Pulmonary Hypertension of Left Heart Disease

Mean PA (mmHg)

PAOP (mmHg)

Passive PH: TPG (mPpa – Ppao) ≤ 12 mmHg

Reactive PH: TPG (mPpa – Ppao) > 12 mmHg
Vascular Pathology of Pulmonary Hypertension of Left Heart Disease

Pulmonary lesions in congestive vasculopathy

Pulmonary arteries
- Prominent medial hypertrophy and arteriolar muscularization
- Intimal fibrosis, generally eccentric and not obstructive

Pulmonary veins
- Prominent medial hypertrophy and arterialization
- Moderate fibrosis of the intima

Lymphatic
- Dilation

Pulmonary tissue
- Interstitial edema, interstitial fibrosis, and hemosiderosis

Delgado et al. Eur J Heart Failure 2005 7:1011
Delgado Rev Esp Cardiol 2010 63:334
Pulmonary Hypertension due to left heart disease

Valvular heart disease
- Mitral stenosis
- Aortic stenosis
- Mitral regurgitation

Diastolic dysfunction
WHO-Classification of Pulmonary Hypertension (CLASS 3 – 5)

3. Pulmonary hypertension due to lung disease and/or hypoxemia
   3.1 COPD and other lung disease with mixed restrictive and obstructive pattern Interstitial lung diseases
   3.2 Chronic exposure to high altitude
   3.3 Sleep-desordered breathing, Alveolar hypoventilation

4. Chronic thromboembolic pulmonary hypertension

5. Miscellaneous
   5.1 Haematological disorders
   5.2 Systemic disorders: Sarcoidosis, Langerhans Hystocitosis
   5.2 Metabolic disorders: Gaucher’s disease, Thyroidosis, glycogen storage disease
   5.4 Others: Tumor obstruction, Chronic dialysis, ...
WHO-Classification of Pulmonary Hypertension (CLASS 3 – 5)

3. Pulmonary hypertension due to lung disease and/or hypoxemia
   3.1 COPD and other lung disease with mixed restrictive and obstructive pattern Interstitial lung diseases
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   5.4 Others: Tumor obstruction, Chronic dialysis, ...
Pulmonary hypertension in COPD

1264 COPD patients with CRF

998 COPD patients had a RHC including 899 males

971 patients with a Ppa < 40 mm Hg including 875 males

27 patients with a Ppa ≥ 40 mm Hg (0.03%)

16 patients with at least one associated disease

11 patients with a unique diagnosis of COPD (0.01%)

30 patients randomly drawn from the 875 males COPD patients with a Ppa < 40 mm Hg

14 patients with a Ppa 20 < mm Hg

16 patients with a Ppa 20 ≥ mm Hg and < 40 mm Hg

Comparison of these 4 groups of patients
Pulmonary Hypertension in COPD

- Cumulative survival (%)
  - Ppa < 20 mm Hg
  - Ppa ≥ 20 mm Hg and < 40 mm Hg
  - Ppa ≥ 40 mm Hg

- Time (months)

- Subjects at risk
  - n
    - 41
    - 32
    - 25
    - 18
    - 14
    - 11
    - 8
    - 4
    - 3
    - 2
    - 1

- P < 0.01
- NS
Thromboembolic pulmonary hypertension

Poststenotic vasodilation

Abrupt cutoffs

Intravascular bands
Mechanisms of small vessel disease in CTEPH

Sub-segmental arteries

Small muscular arteries distal of non-obst, a.

Small muscular arteries distal of obst. a.
## Classification of CTEPH

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Central organized clot (main/lobar pulmonary arteries)</td>
</tr>
<tr>
<td>II</td>
<td>Intimal thickening and fibrosis proximal to the segmental arteries</td>
</tr>
<tr>
<td>III</td>
<td>Disease within distal segmental and sub-segmental arteries only</td>
</tr>
<tr>
<td>IV</td>
<td>PAH with hypertensive distal vasculopathy without visible thromboembolic disease</td>
</tr>
</tbody>
</table>
Evaluation of Pulmonary Hypertension in the ICU setting

Adapted from ESC/ERS Guidelines 2009

**Symptoms evaluation**
- Exercional dyspnea
- Fatigue or weakness
- Angina
- Syncopy
- Peripheral edema
- Abdominal distention

**Screening**
- Clinical examination
- Chest-X-ray
- ECG
- Echocardiography

**Incidental discovery**
- Scleroderma, Lupus E.
- Sleep-апnea/hypopnea
- COPD
- Liver cirrhosis
- Others ......

**Suspect pulmonary hypertension**

**Characterization**
- Additional testing: CT-scan, CTD screening, HIV, liver func., antiphospholipids, thyroid func., measure BNP, right ventricular function (ECHO)

**Make the diagnosis and assess severity using right heart catheter**
- Perform vasoreactivity testing
## Table 15 Parameters with established importance for assessing disease severity, stability and prognosis in PAH (adapted from McLaughlin and McGoon<sup>94</sup>)

<table>
<thead>
<tr>
<th>Better prognosis</th>
<th>Determinants of prognosis</th>
<th>Worse prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Slow</td>
<td>Rate of progression of symptoms</td>
<td>Rapid</td>
</tr>
<tr>
<td>No</td>
<td>Syncope</td>
<td>Yes</td>
</tr>
<tr>
<td>I, II</td>
<td>WHO-FC</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;500 m)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6MWT</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Peak O&lt;sub&gt;2&lt;/sub&gt; consumption &gt;15 mL/min/kg</td>
<td>Cardio-pulmonary exercise testing</td>
<td>Peak O&lt;sub&gt;2&lt;/sub&gt; consumption &lt;12 mL/min/kg</td>
</tr>
<tr>
<td>Normal or near-normal</td>
<td>BNP/NT-proBNP plasma levels</td>
<td>Very elevated and rising</td>
</tr>
<tr>
<td>No pericardial effusion</td>
<td>Echocardiographic findings&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>TAPSE&lt;sup&gt;b&lt;/sup&gt; &gt;2.0 cm</td>
<td>Haemodynamics</td>
<td>TAPSE&lt;sup&gt;b&lt;/sup&gt; &lt;1.5 cm</td>
</tr>
<tr>
<td>RAP &lt;8 mmHg and CI ≥2.5 L/min/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>RAP &gt;15 mmHg or CI ≤2.0 L/min/m&lt;sup&gt;2&lt;/sup&gt;</td>
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<sup>a</sup>Depending on age.

<sup>b</sup>TAPSE and pericardial effusion have been selected because they can be measured in the majority of the patients.

BNP = brain natriuretic peptide; CI = cardiac index; 6MWT = 6-minute walking test; RAP = right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; WHO-FC = WHO functional class.
Pulmonary Hypertension in the ICU: Conclusive Remarks

**Epidemiology, Definition, Classification, Pathophysiology and diagnostics**

- Overall incidence of pulmonary hypertension in the ICU setting is probably close to 10%
- Major cause is passive or reactive following left heart disease
- Think about it, identify risk factor using patient medical history and labor diagnostics
- Screen your patients using ECHO
- Make the diagnosis using PAC
- Assess right ventricular function