Acute Vasodilator Testing in Pulmonary Hypertension: 
What, When, and How?

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Disclosures:
• Grants/Research: United Therapeutics, Lung Biotechnology, Pfizer, Reata
• Consultant/Honoraria: Actelion, Gilead, Bayer, Cardiokinetics, Bellepharon
• I will discuss off-label use of drugs

Objectives

Review:
• Definition and classification of pulmonary hypertension (PH)
• The role of right heart catheterization and acute vasodilator testing in:
  – Pulmonary arterial hypertension (WHO Group 1)
  – PH due to left heart disease (WHO Group 2)
• How to perform and interpret results of the testing
Pulmonary Hypertension (PH)

- Sustained elevation of mean pulmonary artery pressure*: 

\[ \geq 25 \text{ mmHg} \] (Normal: 8 - 20 mmHg)

* MPAP = 1/3(PAs - PAd) + Pad

ePASP echo Doppler \( \geq 40 \text{ mmHg} \)


5th WSPH Updated Classification of Pulmonary Hypertension, Nice 2013

GROUP 1 – Pulmonary Arterial Hypertension (PAH)
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and Toxin-induced
  - 1.3.1 Connective Tissue Disease
  - 1.3.2 Human Immunodeficiency Virus (HIV) Infection
- 1.4 Associated with
  - 1.4.3 Portal Hypertension
- 1.4.4 Congenital Heart Disease
- 1.4.5 Schistosomiasis
- 1.5 Persistent Pulmonary Hypertension of the Newborn (PPHN)

GROUP 2 – PH Due to Left Heart Disease
- 2.1 LV Systolic Dysfunction
- 2.2 LV Diastolic Dysfunction
- 2.3 Valvular Disease
- 2.4 Congenital-Acquired Left Heart Inflow/Outflow Tract Obstruction and Congenital Cardiomyopathies

GROUP 3 – PH Due to Lung Disease and/or Hypoxia
- 3.1 Chronic Obstructive Pulmonary Disease
- 3.2 Interstitial Lung Disease
- 3.3 Other Pulmonary Diseases With Mixed Restrictive and Obstructive Pattern
- 3.4 Sleep-disordered Breathing
- 3.5 Alveolar Hypoventilation Disorders
- 3.6 Chronic Exposure to High Altitude
- 3.7 Developmental Lung Diseases

GROUP 4 – Chronic Thromboembolic PH (CTEPH)

GROUP 5 – PH With Unclear Multifactorial Mechanisms
- 5.1 Hematologic Disorders: Chronic Hemolytic Anemia, Myeloproliferative Disorders, Splenectomy
- 5.2 Systemic Disorders: Sarcoidosis, Pulmonary Histiocytosis, Lymphangioleiomyomatosis
- 5.3 Metabolic Disorders: Glycogen Storage Disease, Gaucher Disease, Thyroid Disorders
- 5.4 Others: Tumoral Obstruction, Fibrosing Mediastinitis, Chronic Renal Failure, Segmental PH

Etiology of PH on Echocardiogram

- Single center study from Australia
- 6,994 screened → 936 pts (9.1%) with PH on ECHO (defined as ePASP >40 mmHg)

PH Diagnostic Guidelines

Echocardiography Indicates PH

Right Heart Catheterization
- Establish diagnosis based on hemodynamics
- Ascertain etiology
- Establish severity & prognosis
- Evaluate vasoreactivity
- Guide treatment

**PH Hemodynamic Profiles:**

*Where is the lesion?*
(mean PAP ≥ 25 mmHg)

- **Isolated post-capillary PH** (Passive PH)
- **Combined post- & pre-capillary PH** (Mixed PH)
- **High flow PH**
  - Increased PVR
  - (CHD, AV fistula, thyrotoxicosis, chronic anemia)
  - High flow PH
  - PVR > 3 Wu

**Pre-capillary PH**

- PAWP < 15 mmHg
- TPG > 12; DPG > 7 mmHg
- PVR > 3 Wu

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**Group 1 – PAH**

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**PAWP:** Normal 4-12 mmHg
**TPG:** mPAP - PAWP
  - Normal < 10 mmHg
**DPG:** dPAP - PAWP
  - Normal < 5 mmHg
**PVR:** mPAP - PAWP/CO
  - Normal ≤ 1 Wu

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Vachiery JL et al, *J Am Coll Cardiol* 2013;62: D100-8
Fang J et al, *J Heart Lung Transplant* 2012;31:913–33

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Fang J et al. *J Heart Lung Transplant* 2012;31:913–33
Vachiery JL et al, *J Am Coll Cardiol* 2013;62: D100-8
Algorithm for Assessment of Vasoreactivity in Patients with PAH (I/H/D)

**Right Heart Catheterization With Acute Vasoreactivity Testing**

(iNO, epoprostenol, adenosine)

**Responder (<15%)**

- [Better prognosis]

Consider:

- Hemodynamically-monitored trial of
  - *Calcium Channel Blocker* ([<10% respond long-term])

**Non-responder**

Consider:

- Oral ERAs/PDE5-I/sGC stim.
- IV Epoprostenol
- Inhaled Iloprost
- SQ/IV/inhaled/po Treprostinil

**Therapeutic Targets for PAH**

- *Endothelin pathway*
  - Pre-proendothelin → Proendothelin
  - Endothelin receptor A
  - Endothelin receptor B
  - Endothelin 1
  - Vasoconstriction and proliferation
  - Smooth muscle cells

- *Nitric oxide pathway*
  - L-arginine → L-citrulline
  - Nitric oxide
  - cGMP
  - Phosphodiesterase type 5
  - Exogenous nitric oxide sGC stim.
  - Vasodilation and antiproliferation

- *Prostacyclin pathway*
  - Arachidonic acid → Prostaglandin I₂
  - Prostacyclin (prostaglandin I₃)
  - cAMP
  - Prostacyclin derivatives
  - Vasodilation and antiproliferation

FDA-Approved Specific Therapies for PAH

**Endothelin Receptor Antagonists (oral)**
- Bosentan
- Ambrisentan
- Macitentan

**Phosphodiesterase Type-5 Inhibitors (oral)**
- Sildenafil
- Tadalafil

**Prostacyclin Derivatives**
- Epoprostenol: IV
- Iloprost: inhalational
- Treprostinil: inhalational, oral, SQ or IV

**Soluble Guanylate Cyclase Stimulators (oral)**
- Riociguat (also approved for CTEPH)

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**FDA-Approved for PH in LHD (Group 2)**
**PH Classification**

**Group 2:**
PH due to left heart disease

- LV Systolic dysfunction
- LV Diastolic dysfunction
- Valvular disease
- LH obstruction & Congenital CMP

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**PH: Where is the lesion?**
(mean PAP ≥ 25 mmHg)

**Isolated Post-Capillary PH**

- PAWP > 15 mmHg
- TPG ≤ 12; DPG < 7 mmHg
- PVR nl range

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**PH: Where is the lesion?**

**Isolated Post-Capillary PH**

- PAWP > 15 mmHg
- TPG ≤ 12; DPG < 7 mmHg
- PVR nl range

**Systemic HTN**

**AoV Disease**

- **Myocardial Disease**
  - Dilated CMP-ischemic/non-isc.
  - Obesity-related CMP
  - Hypertrophic CMP
  - Restrictive/infiltrative CMP
  - **Pericardial disease**

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**MV Disease**

**Cor Triatriatum**

- Atrial Myxoma

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**PV compression**

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**MV Disease**

**Cor Triatriatum**

- Atrial Myxoma
**PH: Where is the lesion?**

- **Left sided filling pressure**
- **Neurohormones, cytokines, other mediators**

**Combined post- & pre-capillary (Cpc) PH**

- Mixed hemodynamic profile
  - PAWP > 15 mmHg
  - TPG > 12 - 15; DPG > 7
  - PVR > 3 Wu

- “Responsive” vs. “Not-responsive”
- “Reversible” vs. “Irreversible”

(Diuretics, NTP, Inodilators, Sildenafil, Other agents)

**PH due to Left HF: Prevalence & Prognosis**

- **Prevalence:**
  - ≈ 25% to 80% in HF population (definition of PH is highly variable; referral bias; HFrEF vs HFP EF; acute vs chronic HF; mild vs severe HF)
  - Cpc or Mixed PH: 47% in ADHF (ESCAPE); ≈ 35% in other series

- **PH complicating left HF:**
  - Worse prognosis due to RV failure
  - Increases morbidity and mortality (2X PVR > 3 Wu)
  - Associated with ↓exercise capacity
    - Inverse relationship: peak VO₂ and resting mean PAP or PVR
    - Positive correlation: resting RV ejection fraction and peak VO₂ in heart transplant candidates

*Pre-heart transplant, acutely irreversible, mixed PH is associated with high post-transplant mortality (up to 40%)*

Butler et al, J Am Coll Cardiol; 1999;34:1802
Cappola et al, Circ 2002;105:1663
Erickson et al, J Heart Transpl 1990;9:526
DiSalvo et al, J Am Coll Cardiol; 1995;25:1143
Kirklin et al, J Heart Lung Transpl 1988; 7:331
Khush et al, Am Heart J; 2009;157:1026
Abramson et al, Ann Int Med; 1992;116:888
Ghio et al, J Am Coll Cardiol; 2001;37:183
Moraes et al, Circ 2000; 1718
Severity of Cpc* or Mixed PH in Left HD

<table>
<thead>
<tr>
<th></th>
<th>Mean PAP (mmHg)</th>
<th>TPG (mmHg)</th>
<th>PVR (Wood units)</th>
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</thead>
<tbody>
<tr>
<td>Mild</td>
<td>25-34</td>
<td>10-12</td>
<td>2.5-3.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>35-44</td>
<td>13-15</td>
<td>3.5-4.9</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;45</td>
<td>&gt;15</td>
<td>&gt;5</td>
</tr>
</tbody>
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In OHT: Morbidity & mortality risk is a continuous risk that increases with progressive elevation in MPAP, TPG, PVR
* Combined post- & pre- capillary PH

Murali S. Advances in PH 2006; 5:30 Kirklin et al. J Heart Lung Transpl 1988: 7:331

Proposed Algorithm For Management of Mixed PH in Left HF

Cpc-PH or Mixed PH due to Left HF
On standard, guidelines directed therapy

Transplant eligible

Not transplant eligible

Acute/Subacute Vasoreactivity Testing (NTP, Milrinone)

Vasoreactive/Reversible
PAP < 50 mmHg
TPG ≤ 15 mmHg
PVR ≤ 2.5-3 Wood units
SAP > 85 mmHg

Not vasoreactive “Irreversible”

PH resolves or becomes vasoreactive

Persistent PH < 1%

• Continue HF rx
• Invest. trials
• DT VAD (RV)

Consider heart-lung transplantation

Heart transplant

* Investigational/Off-label

Adapted from Murali S, Adv in PH 2006:5:33
Mehra et al. J Heart Lung Transplant 2006; 25:1024
Summary

- PH is characterized by different hemodynamic profiles depending on the underlying pathophysiology
- Right heart catheterization is an important modality in the evaluation of PH
- Goals of vasodilator testing in PH:
  - Assess prognosis & severity of disease
  - Guide therapy
- Therapeutic modalities are variable depending on etiology of PH