Pathophysiology II

Pulmonary Vascular Changes in Heart Disease

- Normal Circulatory Dynamics
  - Physiology
- Pulmonary Hypertension
  - Definition
  - Classification
  - Pathology
  - Pathophysiology
  - Clinical Manifestations
  - Diagnosis
  - Treatment

Pulmonary Circulation

- Low resistance, high compliance vascular bed
- Only organ to receive entire cardiac output (CO)
- Changes in CO as well as pleural/alveolar pressure affect pulmonary blood flow
- Different reactions compared to the systemic circulation
- Normally in a state of mild vasodilation
Exercise

- Pulmonary blood flow increases up to 4-5x BL
- Increased flow accommodated by both recruitment and vasodilation
- Net effect is a decrease in pulmonary vascular resistance (PVR)
- No further decrease in PVR once all vessels fully recruited and dilated

Normal Hemodynamic Measurements During Right Heart Catheterization

Normal Pulmonary Hemodynamics at Sea Level (Rest and Mild Exercise) and at Elevated Altitude (Rest)

<table>
<thead>
<tr>
<th></th>
<th>Sea level Rest</th>
<th>Sea level Mild Exercise</th>
<th>Altitude (~15,000 ft) Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arterial pressure, (mean), mmHg</td>
<td>20/10(15)</td>
<td>30/13(20)</td>
<td>38/14(26)</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>6.0</td>
<td>12.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Left atrial pressure (mean), mmHg</td>
<td>5.0</td>
<td>9.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, units</td>
<td>1.7</td>
<td>0.9</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Pulmonary Hypertension: Definition

PAP mean ≥ 25 mm Hg at rest or ≥ 30 mmHg with exercise

Pulmonary Hypertension: The Clinical Context

- Precapillary Pulmonary Hypertension
- Pulmonary Hypertension

- Postcapillary Pulmonary Hypertension
Localizing the Problem

Pre-capillary

Post-capillary

Pulmonary Hypertension: Classification

PAH pre-capillary

Pulmonary Venous Hypertension post-capillary

Lung disease Hypoxemia

Misc, e.g. sarcoidosis, schistosomiasis

CTEPH
Pre-capillary PH: Pulmonary Arterial Hypertension
Definition

- PAP mean ≥ 25 mmHg at rest or ≥ 30 mmHg with exercise
  AND
- PCWP or LVEDP ≤ 15 mmHg
- PVRI ≥ 3 units \( \cdot \) m²
- No left-sided heart disease

Pre-capillary PH: Pulmonary Arterial Hypertension
Classification

<table>
<thead>
<tr>
<th>Idiopathic or Familial PAH</th>
<th>Associated with (APAH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue disease</td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>HIV infection</td>
</tr>
<tr>
<td>Drugs and toxins</td>
<td>Other</td>
</tr>
</tbody>
</table>

High PA pressure and normal “downstream” pressures

Post-capillary PH: Pulmonary Venous Hypertension
Definition

- PAP mean ≥ 25 mmHg at rest or ≥ 30 mmHg with exercise
  AND
- PCWP or LVEDP >15 mmHg
Post-capillary PH: Pulmonary Venous Hypertension
Classification

LH disease

Left-sided atrial or ventricular heart disease

Left-sided valvular heart disease

Post-capillary PH: Pulmonary Venous Hypertension
Localizing the Problem

• Left Heart Etiologies
  – Aorta - coarct, stenosis
  – LV - AS, AR, CM, constriction, myocardial disease, MS, MR, ischemic heart disease, congestive heart failure, diastolic dysfunction
  – LA - Ball-valve thrombus, myxoma, cor triatriatum

Post-capillary PH: Pulmonary Venous Hypertension
Localizing the Problem

• Venous Etiologies
  – Pulmonary Veins
    – stenosis
    – mediastinal fibrosis
    – neoplasm
    – pulmonary veno-occlusive disease
Pulmonary Venous Hypertension Physiology

<table>
<thead>
<tr>
<th>Pulmonary arterial → Lung → Pulmonary venous</th>
<th>Normal</th>
<th>PAP mean 15 mmHg → No obstruction → PCWP mean 5 mmHg</th>
<th>PVPH</th>
<th>PAP mean 35 mmHg → No obstruction → PCWP mean 25 mmHg</th>
<th>Mixed PH</th>
<th>PAP mean 45-100 mmHg → Pulmonary arteriolar obstruction → PCWP mean 25 mmHg</th>
</tr>
</thead>
</table>

Mixed (Pulmonary Venous and Pulmonary Arterial Hypertension): Definition

- PAP mean ≥25 mmHg at rest or ≥30 mmHg with exercise
- PCWP or LVEDP >15 mmHg
- PVRI ≥3 units • M²
- Increased Transpulmonary Gradient Across Pulmonary Vascular Bed

PH: Medial Hypertrophy

Medial Hypertrophy
Internal & External Elastic Lamina
Adventitial Fibrosis
PH: Intimal Fibrosis

PAH: Plexiform Lesions

Pulmonary Venous Hypertension
Microscopic Features

Thickened Pulmonary Vein (VVG Stain)
**Pulmonary Venous Hypertension**

**Microscopic Features**

Thickened Muscular Pulm Art (VVG Stain)

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**Pathophysiology:**

**Hemodynamic Progression of PH**

<table>
<thead>
<tr>
<th>CO</th>
<th>PAP</th>
<th>PVR</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-symptomatic/Compensated</td>
<td>Symptomatic/Decompensating</td>
<td>Declining/Decompensated</td>
<td></td>
</tr>
</tbody>
</table>

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**Right Ventricular Dysfunction in Pulmonary Hypertension**

Right ventricular failure is a consequence of chronic ischemia on a hypertrophied pressure overloaded ventricle
Coronary Driving Pressure Gradient and the Effect of Pulmonary Hypertension

Myocardial perfusion goes from being both systolic and diastolic to mostly diastolic

The RV hypertrophies, but coronary blood supply remains unchanged

RV work is dramatically increased without a compensatory increase in coronary blood flow

Tachycardia makes everything worse

Effects of pulmonary hypertension on RV myocardial perfusion

PH: Progressive Right Heart Failure
### Pulmonary Arterial Hypertension: Clinical Manifestations - Symptoms

- Dyspnea on Exertion/Rest
- Fatigue
- Chest Discomfort/Pain
- Cough
- Syncope/Presyncope
- Hemoptysis
- Edema
- Hoarseness

### PAH: Clinical Manifestations

- **Dyspnea**
  - Reduced O2 diffusion
  - Ventilation-perfusion mismatching
  - Low O2 transport
- **Angina**
  - RV ischemia
  - Left main coronary compression
- **Syncope**
  - Hypotension due to systemic vasodilation and fixed pulmonary resistance
  - Arrhythmia
- **Edema, hepatic congestion, ascites**
- **RV failure**

### Pulmonary Venous PH: Symptoms

- **Angina**
- **Syncpe**
- **Congestive heart failure**
- **Dyspnea**
- **Hemoptysis**
- **Hoarseness**
- **Edema**
- **Ascites**
- **Paroxysmal nocturnal dyspnea**
- **Orthopnea**
- **Central and peripheral cyanosis**
Diagnosis of PH: Procedures
- Electrocardiogram
- Chest radiography
- Echocardiogram
- Ventilation perfusion scan (V/Q scan)
- Serologic studies, HIV
- Pulmonary function tests (PFT)
- Sleep study (if indicated)
- Right-heart catheterization (with acute vasodilator testing if PAH)

PAH: Screening - ECG

PAH: Screening - CXR
Pulmonary Hypertension: Echocardiogram

Echocardiogram Estimate of RVSP

- $4V^2 = $ Pressure Gradient ($\Delta P$) (Modified Bernoulli Equation)
- RVSP - RAP mean = $\Delta P$
- RVSP = RAP mean + $\Delta P$
Echocardiogram

Diagnosis of PH: ECHO May Suggest an Underlying Etiology
- LV diastolic dysfunction
- MS or MR
- LV systolic dysfunction
- Congenital heart disease, e.g. ASD, VSD, PDA

PH: Congestive Heart Failure - CXR
hilar fullness and haziness
Cardiac Catheterization

- To exclude congenital heart disease
- To measure PCWP or LVEDP
- To establish severity and prognosis
- Acute vasodilator drug testing

Cardiac catheterization should be performed in patients with suspected pulmonary hypertension

Diagnosis of Pulmonary Hypertension

- High index of suspicion
- Thorough and complete evaluation

Pre-capillary PH: Pulmonary Arterial Hypertension Classification

- PAH
  - thyroid disorders
  - glycogen storage disease
  - Gaucher disease
  - hereditary hemorrhagic telangiectasia
  - hemoglobinopathies
  - myeloproliferative disorders
  - splenectomy

- Idiopathic or Familial PAH
- Associated with (APAH)
  - Connective tissue disease
  - Congenital heart disease
  - Portal hypertension
  - HIV infection
  - Drugs and toxins
  - Other

  High PA pressure and normal “downstream” pulmonary venous pressures

Pathophysiology II 1-2-08
Treatment: Pre-capillary PH - Pulmonary Arterial Hypertension

- Treat associated conditions, e.g. thyroid disease
- Early surgery to repair congenital heart disease, e.g. VSD, PDA
  - However, if no longer “operable” due to progressive pulmonary vascular obstructive disease, “corrective” surgery is contra-indicated
  - Medical PAH Therapy
  - Lung or Heart-Lung Transplantation

Post-capillary PH: Pulmonary Venous Hypertension

Classification

- LH disease
- Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease

Acute Pulmonary Edema

- Cardiogenic Pulmonary Edema
- Noncardiogenic Pulmonary Edema
Physiology of Microvascular Fluid Exchange in the Lung

Representative Chest Radiograph from Patient with Cardiogenic Pulmonary Edema
Physiology of Microvascular Fluid Exchange in the Lung

Representative Chest Radiograph from Patient with Noncardiogenic Pulmonary Edema

Treatment: Post-capillary PH - Pulmonary Venous Hypertension

- Surgery to eliminate left-sided cardiac obstruction
- Heart transplantation for left ventricular failure
- Additional medical and/or surgical treatment as needed
  - Specific re: left heart or pulmonary venous hypertension etiology
  - PAH treatment
Chronic Heart Failure Treatment

- Sodium restriction
- Afterload reduction, e.g. ACE inhibitors
- Inotropic support, e.g. digitalis
- Diuretics
- Beta-blockers
- Identification and treatment of underlying cause(s)

Pulmonary Venous Hypertension

Targeted Pulmonary Arterial Hypertension Medical Treatment
PAH: Decreased Expression of Prostacyclin Synthase in the Lung

Tuder et al. AJRCCM 1999

PAH: Increased Thromboxane A2 Production

Genetic Predisposition △ Vascular Injury

Endothelial Proliferation and Dysfunction

Vasodilator/Vasoconstrictor Imbalance

Pulmonary Vasoconstriction

*p<0.05

Christman et al. NEJM 1992

PAH: Increased Expression of Endothelin in the Lung

Giaid A et al. NEJM 1993
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### Mechanisms Behind Current Targeted PAH Medical Therapeutic Options

<table>
<thead>
<tr>
<th>Abnormality in PAH</th>
<th>Therapeutic Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Prostacyclin synthase in endothelial cells</td>
<td>• Administer prostacyclin</td>
</tr>
<tr>
<td>↓ Nitric oxide synthase expression in endothelial cells</td>
<td>• Enhance NO pathway</td>
</tr>
<tr>
<td>↑ Lung and circulating endothelin-1 levels</td>
<td>• Use endothelin receptor antagonist</td>
</tr>
</tbody>
</table>

### Experience and Reason

“In Medicine one must pay attention not to plausible theorizing but to experience and reason together . . . I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes its deductions from what is observed . . . But conclusions drawn from unaided reason can hardly be serviceable; only those drawn from observed fact.”

Hippocrates (460-377 BC): *Precepts*