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
**Physiology: Circulatory Hemodynamics**

**Pressure* = Flow x Resistance**

- **Systemic Circulation**
  - Pressure = Pressure drop across systemic circulation (mmHg) = Systemic Arterial Pressure (SAPm) - Systemic Venous Pressure (RAPm)
  - Flow = Systemic Blood Flow† = Cardiac Index (CI; l/m/M)
  - Resistance = Systemic Vascular Resistance (SVR; units • M²)

- **Pulmonary Circulation**
  - Pressure = Pressure drop across pulmonary circulation (mmHg) = Pulmonary Artery Pressure (PAPm) - Pulmonary Venous Pressure (PCWPm)
  - Flow = Pulmonary Blood Flow† = Cardiac Index (CI; l/m/M²)
  - Resistance = Pulmonary Vascular Resistance (PVR; units • M²)

*pressure drop across vascular bed
† without congenital systemic to pulmonary shunts
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 $\geq 25$ mm Hg at rest or $\geq 30$ mmHg with exercise

Pulmonary Hypertension: The Clinical Context

Precapillary Pulmonary Hypertension  \rightarrow  Pulmonary Hypertension  \rightarrow  Postcapillary Pulmonary Hypertension
Localizing the Problem

Pre-capillary

Localizing the Problem

Post-capillary
Pulmonary Hypertension: Classification

PAH pre-capillary

Pulmonary Arterial Hypertension

Definition

- PAP mean $\geq 25$ mmHg at rest or $\geq 30$ mmHg with exercise

AND

- PCWP or LVEDP $\leq 15$ mmHg
- PVRI $\geq 3$ units $\cdot m^2$
- No left-sided heart disease
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” pressures

Post-capillary PH: Pulmonary Venous Hypertension
Definition

- PAP mean ≥ 25 mmHg at rest or ≥ 30 mmHg with exercise

AND

- PCWP or LVEDP >15mmHg
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</th>
<th>Lung</th>
<th>Pulmonary venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAP mean 35 mmHg</td>
<td>No obstruction</td>
<td>PCWP mean 25 mmHg</td>
</tr>
<tr>
<td>PAP mean 45-100 mmHg</td>
<td>Pulmonary arteriolar obstruction</td>
<td>PCWP mean 25 mmHg</td>
</tr>
</tbody>
</table>
Mixed (Pulmonary Venous and Pulmonary Arterial Hypertension): Definition

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

Pathophysiology: Rest and Exercise Pulmonary Hemodynamics

\[ P = F \times R \quad \frac{\Delta P}{F} = R \]

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>15mmHg-10mmHg = 1 unit-M² 5 L/min/M²</td>
<td>30mmHg-12mmHg = &lt;1 unit-M² 20 L/min/M²</td>
</tr>
<tr>
<td>PAH (Pre-Cap)</td>
<td>50mmHg-10mmHg = 8 units-M² 5 L/min/M²</td>
<td>90mmHg-10mmHg = 10 units-M² 8 L/min/M²</td>
</tr>
<tr>
<td>Pulm Venous PH (post-cap)</td>
<td>35mmHg-25mmHg = 2 units-M² 5 L/min/M²</td>
<td>55mmHg-35mmHg = 2 units-M² 10 L/min/M²</td>
</tr>
<tr>
<td>Mixed PH (Pre-cap &amp; Post-cap)</td>
<td>50mmHg-25mmHg = 5 units-M² 5 L/min/M²</td>
<td>75mmHg-35mmHg = 5 units-M² 8 L/min/M²</td>
</tr>
</tbody>
</table>
PH: Medial Hypertrophy

- Medial Hypertrophy
- Internal & External Elastic Lamina
- Adventitial Fibrosis

PH: Intimal Fibrosis

- Media
- Layered Intimal Fibrosis
PAH: Plexiform Lesions

Thickened Pulmonary Vein (VVG Stain)

Thin-walled Distal Segment

Plexiform Lesion

Pulmonary Venous Hypertension

Microscopic Features

Thickened Pulmonary Vein (VVG Stain)
Pulmonary Venous Hypertension
Microscopic Features

- Thickened Muscular Pulm Art (VVG Stain)

Pathophysiology:
Hemodynamic Progression of PH

- Time
  - Pre-symptomatic/Compensated
  - Symptomatic/Decompensating
  - Declining/Decompensated

- Right Heart Dysfunction

- CO, PAP, PVR
- Symptom Threshold
Right Ventricular Dysfunction in Pulmonary Hypertension

Right ventricular failure is a consequence of chronic ischemia on a hypertrophied pressure overloaded ventricle.

Normal Aortic Pressure and LV Coronary Flow

![Diagram showing normal aortic pressure and LV coronary flow over time.](chart)

- **Aortic Pressure**: mmHg
- **Coronary Flow**: ml/min/100g

- **Diastole**
- **Systole**
- **Time (sec)**
Coronary Driving Pressure Gradient and the Effect of Pulmonary Hypertension

Effects of pulmonary hypertension on RV myocardial perfusion

- 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
PH: Progressive Right Heart Failure

- Systemic Hypotension
- Reduced RV Coronary Blood Flow
- RV Ischemia
- Cardiac Output
- \( \uparrow \) RV EDDP

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**

PAH: Findings on Physical Examination

- **Tachypnea**
- **Jugular venous distention**
- **Right ventricular heave**
- **Right-sided fourth heart sound**
- **Loud pulmonic valve closure (P2)**
- **Tricuspid regurgitation murmur**
- **Pulmonary insufficiency murmur**
- **Hepatomegaly (pulsatile)**
- **Peripheral edema, ascites, pleural effusions**
- **Decreased peripheral perfusion**
- **Cyanosis**
Pulmonary Venous PH: Symptoms

- Angina
- Syncope
- Congestive heart failure
- Dyspnea
- Hemoptysis
- Hoarseness
- Edema
- Ascites
- Paroxysmal nocturnal dyspnea
- Orthopnea
- Central and peripheral cyanosis

Pulmonary Venous PH: Findings on Physical Examination

- Tachypnea, cough, wheezing
- Basilar crackles
- Central and peripheral cyanosis
- Specific signs Re: Left Heart or Pulmonary Venous Hypertension
  - Etiology
- Signs of PH
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)
- Arterial blood gases (ABG) (if indicated)
- Right-heart catheterization (with acute vasodilator testing if PAH)

PAH: Screening - ECG
Prominent Hilar Pulmonary Arteries

Peripheral “Pruning”

RV Enlargement

PAH: Screening - CXR

PAH: Findings on the Echocardiogram

- TR (tricuspid regurgitation)
- RVE (right ventricular enlargement)
- RAE (right atrial enlargement)
- RVH (right ventricular hypertrophy)
- Flattening of IVS (interventricular septum)
- Dilated IVC/Hepatic veins
Pulmonary Hypertension: Echocardiogram

- Enlarged RV
- Small D-shaped LV
- Flattened Septum
• $4V^2 = \text{Pressure Gradient (}\Delta P\text{)}$
  (Modified Bernoulli Equation)

- $\text{RVSP} - \text{RAP mean} = \Delta P$
- $\text{RVSP} = \text{RAP mean} + \Delta P$

Echocardiogram
Estimate of RVSP
PH: Congestive Heart Failure - CXR
hilar fullness and haziness

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

Post-capillary pulmonary venous hypertension
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

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

Treatment
- Upright posture
- Increase FiO2
- Intravenous diuretic, e.g. furosemide
- Vasodilator therapy, e.g. nitroprusside
- Intubation and mechanical ventilation
- Hemodynamic monitoring
- Narcotics, e.g. morphine
- Inotropic support, e.g. dopamine
Acute Pulmonary Edema

- Cardiogenic Pulmonary Edema
- Noncardiogenic Pulmonary Edema

Physiology of Microvascular Fluid Exchange in the Lung

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
Radiographic Features That May Help to Differentiate Cardiogenic from Noncardiogenic Pulmonary Edema

<table>
<thead>
<tr>
<th>Radiographic Feature</th>
<th>Cardiogenic Edema</th>
<th>Noncardiogenic Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart size</td>
<td>Normal or greater than normal</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Vascular distribution</td>
<td>Balanced or inverted</td>
<td>Normal or balanced</td>
</tr>
<tr>
<td>Distribution of edema</td>
<td>Even or central</td>
<td>Patchy or peripheral</td>
</tr>
<tr>
<td>Pleural effusions</td>
<td>Present</td>
<td>Not usually present</td>
</tr>
<tr>
<td>Peribronchial cuffing</td>
<td>Present</td>
<td>Not usually present</td>
</tr>
<tr>
<td>Septal lines, i.e. Kerley’s B lines</td>
<td>Present</td>
<td>Not usually present</td>
</tr>
<tr>
<td>Air bronchograms</td>
<td>Not usually present</td>
<td>Usually present</td>
</tr>
</tbody>
</table>

Adapted from: Ware L and Matthay M. N Engl J Med 2005;353:2788-2796

Algorithm for the Clinical Differentiation between Cardiogenic and Noncardiogenic Pulmonary Edema

Noncardiogenic Pulmonary Edema Likely

- Pulmonary or nonpulmonary infection or history of aspiration
- Hyperdynamic state
  - white-cell count, pancreatitis or peritonitis
  - Brain natriuretic peptide level <100 pg/ml
- Normal cardiac silhouette
- Peripheral infiltrates
- Absence of Kerley’s B lines

Patient with Acute Pulmonary Edema

- History, Physical Examination, and Routine Laboratory Examination
  - And
  - Chest Radiograph
    - Diagnosis uncertain?
      - Echocardiogram
        - Diagnosis uncertain?
          - PCWP ≤18 mmHg
            - Right Heart Catheterization
              - PCWP >18 mmHg

Cardiogenic Pulmonary Edema Likely

- History of myocardial infarction or congestive heart failure
- Low output state, third heart sound, peripheral edema
- Elevated cardiac enzymes
- Brain natriuretic peptide level >500 pg/ml

- Enlarged cardiac silhouette
- Central infiltrates
- Presence of Kerley’s B lines

- Normal or small LV size
- Normal LV function

- Elevated LV size
- Decreased LV function

- Right Heart Catheterization
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

Pulmonary Venous Hypertension

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)
Targeted Pulmonary Arterial Hypertension Medical Treatment

Pathobiology of Pulmonary Arterial Hypertension

- Genetic Predisposition
- Vascular Injury
- Endothelial Proliferation and Dysfunction
- Coagulation Abnormalities
- Thrombosis in situ
- Vascular Smooth Muscle Hypertrophy
- Vasodilator/Vasoconstrictor Imbalance
- Pulmonary Vasoconstriction
- Plexogenic and Thrombotic Pulmonary Arteriopathy
Pathobiology of Pulmonary Arterial Hypertension

Genetic Predisposition + Vascular Injury

Endothelial Proliferation and Dysfunction

Vasodilator-antiproliferative/vasoconstrictor-proliferative Imbalance

- Deficient prostacyclin
- Excess thromboxane
- Excess endothelin
- Deficient nitric oxide

Vasodilator/Vasoconstrictor Imbalance

Pulmonary Vasoconstriction

Plexogenic and Thrombotic Pulmonary Arteriopathy

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

PAH: Increased Thromboxane A₂ Production

Units

PGF₁α: x100 pg/mg
TXB₂: x1000 pg/mg
TXB₂/PGF₁α

Normal (n=23)
PAH (n=20)

*p<0.05

Christman et al. NEJM 1992

PAH: Increased Expression of Endothelin in the Lung

Giaid A et al. NEJM 1993
PAH: Decreased Nitric Oxide Synthase Expression in the Lung

Giaid et al. NEJM 1995

Humbert M, Sitbon O, Simonneau G: NEJM 204;351:1425
## 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*