Pulmonary Vascular Changes in Heart Disease

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

Normal Circulatory Dynamics After Postnatal Adaptation (I)

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

- **Systemic Circulation**
  - Pressure = Pressure drop across systemic circulation (mmHg) = Systemic Arterial Pressure (SAPm) - Systemic Venous Pressure (RAPm)
  - Flow = Systemic Blood Flow\(^1\) = Cardiac Index (CI; l/min/M\(^2\))
  - Resistance = Systemic Vascular Resistance (SVR; units • M\(^2\))

- **Pulmonary Circulation**
  - Pressure = Pressure drop across pulmonary circulation (mmHg) = Pulmonary Artery Pressure (PAPm) - Pulmonary Venous Pressure (PCWPm)
  - Flow = Pulmonary Blood Flow\(^1\) = Cardiac Index (CI; l/min/M\(^2\))
  - Resistance = Pulmonary Vascular Resistance (PVR; units • M\(^2\))

\(^*\)pressure drop across vascular bed
\(^1\)without congenital systemic to pulmonary shunts

- **Pressure** = Flow x Resistance

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**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>

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**Normal Circulatory Dynamics (II)**

- **SVC**
- **Pulmonary Veins**
- **IVC**
- **Pulmonary Artery**
- **Pulmonaryartery**
- **RV**
- **LV**
- **Aorta**
- **Pressures in mmHg**
  - O\(_2\) % saturation

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**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
- Postcapillary Pulmonary Hypertension

Localizing the Problem

- Post-capillary

Pulmonary Hypertension: Classification

- PAH pre-capillary
- LH disease post-capillary
- PH
- Lung disease Hypoxemia
- Misc
- CTEPH

Pre-capillary PH: 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\(^2\)
  - Normal LVEF
  - No left-sided valvular disease

Localizing the Problem

- Pre-capillary
Pulmonary Hypertension - Pre-Capillary (II) (Pulmonary Arterial Hypertension)

- RA
- LA
- RV
- LV
- IVC
- SVC
- Pulmonary Artery
- Pulmonary Veins

Pressures in mmHg
O₂ % saturation
75%
8%
8%
75%
95%
100/60
83
100/25
50/20
35
50/3
95%
95%

Pressure = Flow x Resistance

Pre-capillary PH:
Classification

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

High PA pressure and normal “downstream” pressures

Post-capillary PH:
Definition

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

AND

- PCWP or LVEDP >15mmHg

Post-capillary PH:
Classification

Left-sided atrial or ventricular heart disease

Left-sided valvular heart disease

LH disease
• 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

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

Pulmonary Venous Hypertension

<table>
<thead>
<tr>
<th>Pulmonary arterial</th>
<th>Lung</th>
<th>Pulmonary venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 mmHg</td>
<td>No obstruction</td>
<td>25 mmHg</td>
</tr>
<tr>
<td>45-100 mmHg</td>
<td>Pulmonary arteriolar obstruction</td>
<td>25 mmHg</td>
</tr>
</tbody>
</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
**Pathophysiology: Rest and Exercise**

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**Pulmonary Hemodynamics**

\[ \Delta P = R \]

<table>
<thead>
<tr>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>( \frac{15 \text{mmHg}}{5 \text{L/min/M}^2} \times \frac{10 \text{mmHg}}{5 \text{L/min/M}^2} = 30 \text{units} )</td>
</tr>
<tr>
<td>PAH (Pre-Cap)</td>
<td>( \frac{50 \text{mmHg}}{5 \text{L/min/M}^2} \times \frac{10 \text{mmHg}}{8 \text{L/min/M}^2} = 8 \text{units} )</td>
</tr>
<tr>
<td>Pulm Venous PH (post-cap)</td>
<td>( \frac{35 \text{mmHg}}{5 \text{L/min/M}^2} \times \frac{25 \text{mmHg}}{2 \text{L/min/M}^2} = 2 \text{units} )</td>
</tr>
<tr>
<td>Mixed PH (Pre-cap &amp; Post-cap)</td>
<td>( \frac{50 \text{mmHg}}{5 \text{L/min/M}^2} \times \frac{25 \text{mmHg}}{8 \text{L/min/M}^2} = 5 \text{units} )</td>
</tr>
</tbody>
</table>

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**Pathology: Pulmonary Vascular Disease**

**Heath Edwards Classification**

- Grade 1 - Medial hypertrophy in the small pulmonary arteries.
- Grade 2 - Concentric or eccentric cellular intimal proliferation and thickening within the smaller pulmonary arteries and arterioles.
- Grade 3 - Relatively acellular intimal fibrosis with accumulation of concentric or eccentric masses of fibrous tissue leading to wide spread occlusion of the smaller pulmonary arteries and arterioles.
- Grade 4 - Progressive, generalized dilatation of the muscular arteries and the appearance of plexiform lesions, complex vascular structures composed of a network or plexus of proliferating endothelial tissue, frequently accompanied by thrombus, within a dilated thin-walled sac.
- Grade 5 - Thinning and fibrosis of the media superimposed upon the formation of numerous complex dilatation lesions.
- Grade 6 - Necrotizing arteritis within the media with surrounding areas of inflammatory reaction and granulation tissue.

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**PH: Intimal Fibrosis**

**PAH: Plexiform Lesions**

**PH: Medial Hypertrophy**

**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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Normal Aortic Pressure and LV Coronary Flow

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Pathophysiology: Hemodynamic Progression of PAH

**Pre-symptomatic/Compensated**

**Symptomatic/ Decompensating**

**Declining/ Decompensated**

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Coronary Driving Pressure Gradient and the Effect of Pulmonary Hypertension

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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

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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.
**Fluorodeoxyglucose PET images of a patient with mild (A, mean pulmonary artery pressure, 33 mm Hg) and severe pulmonary hypertension (B, mean pulmonary artery pressure, 81 mm Hg)**

**Pulmonary Arterial Hypertension: Clinical Manifestations - Symptoms**
- Dyspnea on Exertion/Rest
- Fatigue
- Chest Discomfort/Pain
- Cough
- Syncope/Presyncope
- Cerebral Vascular Accidents
- Seizures
- Hemoptysis
- Poor Appetite
- Nausea/Vomiting
- Edema
- Hoarseness
- Gout
- Heart Failure

**PH: Progressive Right Heart Failure**
- Hypotension
- RVEDP
- Reduced RV Coronary Blood Flow
- RV Ischemia
- Cardiac Output

**PAH: Clinical Manifestations**
- Dyspnea
  - Reduced O2 diffusion
  - Ventilation-perfusion mismatching
  - R-L shunting
  - 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
  - Tricuspid regurgitation

**FDG PET images of a patient with pulmonary arterial hypertension before and after therapy**

**PAH: Findings on Physical Examination**
- Tachypnea, cough, wheezing
- 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
- Initial respiratory alkalosis, then combined acidosis (lactic acidosis)
- Central and peripheral cyanosis
- Specific signs Re: Left Heart or Venous Etiology
- Signs of PAH

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

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
PAH: Echocardiogram

Echocardiogram

• $4V^2 = \text{Pressure Gradient (}\Delta P\text{)}$
  (Modified Bernoulli Equation)

• $\text{RVSP} - \text{RAP} = \Delta P$

• $\text{RVSP} = \text{RAP} + \Delta P$

PAH: RV, RA Enlargement on Echocardiogram

Echocardiogram

Doppler Estimation of RV Systolic Pressure

$2.5 V = 25 \text{ mmHg}$

$2.5 V = 34 \text{ mmHg}$

$4.5 V = 74 \text{ mmHg}$

$5.5 V = 121 \text{ mmHg}$
PH: Congestive Heart Failure - CXR
hilar fullness and haziness

Diagnosis of Pulmonary Hypertension

• High index of suspicion
• Thorough and complete evaluation

Diagnosis of PH: ECHO May Suggest an Underlying Etiology

• LV diastolic dysfunction
• MS or MR
• LV systolic dysfunction
• Congenital systemic to pulmonary shunt lesion (ASD, VSD, PDA, etc)

Pulmonary Hypertension Workup

Suspect Pulmonary Hypertension

TEE  
?  
CXR, ECG, TT Echo

PFTs, CPET, CVD w/u, Hematologic w/u, HIV, V/Q scan

Sleep Study
HRCT

?CT Angiogram
Pulm Angiogram

Right Heart Cath
Acute VD Study

?  
Lung Biopsy

Transplantation Evaluation

Cardiac Catheterization

• To exclude congenital heart disease
• To measure wedge pressure or LVEDP
• To establish severity and prognosis
• Acute vasodilator drug testing

Cardiac catheterization should be performed in patients with suspected pulmonary hypertension

Pre-capillary PH: Classification

PAH

Idiopathic or Familial PAH Associated with (APAH)

• Connective tissue disease
• Congenital syst-pulm shunts
• Portal hypertension
• HIV infection
• Drugs and toxins
• Other

• High PA pressure and normal "downstream" pressures

• thyroid disorders
• glycogen storage disease
• Gaucher disease
• hereditary hemorrhagic telangiectasia
• hemoglobinopathies
• myeloproliferative disorders
• splenectomy
Treatment: Pre-capillary PH - Pulmonary Arterial Hypertension

- Early surgery to repair congenital systemic to pulmonary shunts, e.g. VSD, PDA

However, if no longer “operable” due to progressive pulmonary vascular obstructive disease
- Anticoagulation
- Vasodilator/Antiproliferative Therapy
- Lung or Heart-Lung Transplantation

Post-capillary PH: Localizing the Problem

- Venous Etiologies
  - Pulmonary Veins
  - stenosis
  - mediastinal fibrosis
  - neoplasm
  - pulmonary veno-occlusive disease

Post-capillary PH: Classification

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

Post-capillary PH: Localizing the Problem

- Left Heart Etiologies
  - Aorta - cocrt, 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

Treatment: Post-capillary PH - Pulmonary Venous Hypertension

- Surgery to eliminate obstruction
- Heart transplantation for left ventricular failure
- Treatment - Medical and/or Interventional
  - Specific Re: Left Heart or Venous Etiology
  - PAH treatment

Why Diagnose Pulmonary Arterial Hypertension?

Why Treat Pulmonary Arterial Hypertension?
**Why Treat Pulmonary Arterial Hypertension?**

Idiopathic PAH: PPH NIH Registry Data

- Median survival 2.8 years

NIH = National Institutes of Health


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**Pathobiology of Pulmonary Arterial Hypertension**

- Genetic Predisposition
- Vascular Injury
- Endothelial Proliferation and Dysfunction
- Vasoconstrictor Imbalance
  - Deficient prostacyclin
  - Excess thromboxane
  - Excess endothelin
  - Deficient nitric oxide

Plexogenic and Thrombotic
Pulmonary Arteriopathy

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**In IPAH, Prostacyclin Synthase Expression in the Lung is Decreased**

Tuder et al. AJRCCM 1999

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**Expression of Endothelin in the Lungs of Patients with IPAH**

Plexiform Lesions in IPAH

Guil A et al. NEJM 1993

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**Pathobiology of Pulmonary Arterial Hypertension**

- Genetic Predisposition
- Vascular Injury
- Endothelial Proliferation and Dysfunction
- Coagulation Abnormalities
  - Thrombosis in situ
- Vascular Smooth Muscle Hypertrophy
- Pulmonary Vasoconstriction
  - Plexogenic and Thrombotic
Pulmonary Arteriopathy

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**Vasodilator/Vasoconstrictor Imbalance**

- Appetite suppressants
- Other exogenous toxins
- Hepatic toxins
- HIV
- Autoimmune Dysfunction
- Shear Stress
Nitric Oxide: Impact on Vascular Tone

- NO → Soluble guanylate cyclase
- Cyclic nucleotide phosphodiesterases
- GTP → cGMP → Inactive
- Vascular smooth muscle relaxation
- Decreased [Ca^{2+}]_i

GTP = guanosine triphosphate; GMP = guanosine monophosphate; cGMP = cyclic GMP

Endothelin System in Vascular Tissue

- ET-1 = endothelin 1
- Big-ET-1 = proendothelin 1
- ECE = endothelin-converting enzyme
- NO = nitric oxide
- PG12 = prostacyclin

Dupuis. Lancet 2001

In IPAH, Nitric Oxide Synthase Expression in the Lung is Decreased

Griep et al. NEJM 1999

Humbert M, Sitbon O, Simonneau G: NEJM 2004;351:1425
Mechanisms Behind Current 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</td>
<td>▶ Enhance NO pathway</td>
</tr>
<tr>
<td>endothelial cells</td>
<td></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