Pulmonary Vascular Changes in Heart Disease

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

Normal Circulatory Dynamics in Late-Gestation Fetus

<table>
<thead>
<tr>
<th>Structure</th>
<th>Pressure</th>
<th>O₂ % Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>70/45/55</td>
<td>55%</td>
</tr>
<tr>
<td>LA</td>
<td>70/3</td>
<td>65%</td>
</tr>
<tr>
<td>RV</td>
<td>70/4</td>
<td>65%</td>
</tr>
<tr>
<td>LV</td>
<td>70/3</td>
<td>65%</td>
</tr>
<tr>
<td>Pulmonary Artery</td>
<td>70/45/55</td>
<td>55%</td>
</tr>
<tr>
<td>IVC</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>SVC</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Veins</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Aorta</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Patent Ductus Arteriosus</td>
<td></td>
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</tbody>
</table>

Pressures in mmHg
O₂ % saturation
Normal Post-Natal Changes in the Pulmonary Circulation

- Medial muscle % vessel diameter
- Pulmonary vascular resistance – units * m²
- Pulmonary flow l / min / m²
- Pulmonary arterial mean pressure - mmHg

Normal Circulatory Dynamics After Postnatal Adaptation (I)

- SVC
- IVC
- RA
- LA
- RV
- LV
- Pulmonary Artery
- Aorta
- Pressures in mmHg

O₂ % saturation

RA 75%
LA 95%
RV 30/3
LV 100/8
Pulmonary Artery 30/10 20/75%
Aorta 100/60 83/95%
SVC 75%
IVC 8 95%
Pulmonary Veins 8
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/M²)
  - 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 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>

Fig. 1. Characteristic intracardiac pressure wave forms during passage through the heart.
Normal Circulatory Dynamics (II)

Pressure = Flow \times Resistance

Systemic Circulation
\[ \text{SAPm} - \text{RAPm} = \text{CI} \times \text{SVR} \]
\[ 83\text{mmHg} - 3\text{mmHg} = 5 \text{ l/min/M}^2 \times 16 \text{ U/M}^2 \]

Pulmonary Circulation
\[ \text{PAPm} - \text{PCWPm} = \text{CI} \times \text{PVR} \]
\[ 20\text{mmHg} - 8\text{mmHg} = 5 \text{ l/min/M}^2 \times 2 \text{ U/M}^2 \]

Pulmonary Hypertension: Definition

\[ \text{PAP mean} \geq 25 \text{ mm Hg at rest} \]
\[ \text{or} \geq 30 \text{ mmHg with exercise} \]
Pulmonary Hypertension: The Clinical Context

- Precapillary Pulmonary Hypertension
- Postcapillary Pulmonary Hypertension

Pulmonary Hypertension: Classification

- PAH pre-capillary
- LH disease post-capillary
- Lung disease Hypoxemia
- CTEPH
- Misc
Localizing the Problem

Pre-capillary

Localizing the Problem

Post-capillary
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 $\cdot \text{m}^2$
  - Normal LVEF
  - No left-sided valvular disease
Pulmonary Hypertension - Pre-Capillary (II)
(Pulmonary Arterial Hypertension)

Pressures in mmHg
O₂ % saturation

Pressure = Flow x Resistance

Systemic Circulation
83mmHg-3mmHg=5 l/min/M²x16 U•M²

Pulmonary Circulation
68mmHg-8mmHg=5 l/min/M²x12 U•M²

Pre-capillary PH: 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 syst-pulm shunts
- Portal hypertension
- HIV infection
- Drugs and toxins
- Other

High PA pressure and normal “downstream” pressures
Post-capillary PH: Definition

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

AND

- PCWP or LVEDP $>15$mmHg
Pulmonary Hypertension - Post-Capillary (II)  
(Pulmonary Venous Pulmonary Hypertension)

**Systemic Circulation**
83 mmHg - 3 mmHg = \( \frac{5 \text{l/min}}{\text{M}^2} \times 12 \text{U} \cdot \text{M}^2 \)

**Pulmonary Circulation**
35 mmHg - 25 mmHg = \( \frac{5 \text{l/min}}{\text{M}^2} \times 2 \text{U} \cdot \text{M}^2 \)

Pressure = Flow x Resistance

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**Post-capillary PH: Classification**

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

**Pressures**
- RA: 75%
- LA: 95%
- RV: 75%
- LV: 95%
- Pulmonary Veins: 25
- SVC: 95%
- IVC: 75%
- Pulmonary Artery: 50/3
- Pulmonary Veins: 35
- Aorta: 95%

**Saturation**
- O2 % saturation: 75%
- O2 % saturation: 95%

**Blood Pressure**
- 100/25
- 50/25
- 100/60
### Post-capillary PH: 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

#### Venous Etiologies
- **Pulmonary Veins**
  - stenosis
  - mediastinal fibrosis
  - neoplasm
  - pulmonary veno-occlusive disease
**Pulmonary Venous Hypertension Physiology**

Pulmonary arterial → Lung → Pulmonary venous

<table>
<thead>
<tr>
<th>35 mmHg</th>
<th>No obstruction</th>
<th>25 mmHg</th>
</tr>
</thead>
<tbody>
<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
Pulmonary Hypertension - Mixed (Pulmonary Venous and Pulmonary Arteriolar Hypertension) (I)

Pressures in mmHg
O₂ % saturation

Pulmonary Hypertension - Mixed (Pulmonary Venous and Pulmonary Arteriolar Hypertension) (II)

Pressure = Flow x Resistance

Systemic Circulation
83mmHg-3mmHg=5 l/min/M²x16 U•M²

Pulmonary Circulation
60mmHg-25mmHg=5 l/min/M²x7 U•M²

Pressures in mmHg
O₂ % saturation
Pathophysiology: Rest and Exercise Pulmonary Hemodynamics

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

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

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 widespread 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.
PH: Medial Hypertrophy

PH: 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 PAH

Time

CO
PAP
PVR

Pre-symptomatic/Compensated
Symptomatic/Decompensating
Declining/Decompensated

Symptom Threshold

Right Heart Dysfunction
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
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
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)

PH: Progressive Right Heart Failure

- Hypotension
- RVEDP
- Reduced RV Coronary Blood Flow
- RV Ischemia
- Cardiac Output
FDG PET images of a patient with pulmonary arterial hypertension before and after therapy


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
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

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

- Prominent Hilar Pulmonary Arteries
- Peripheral “Pruning”
- RV Enlargement

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: RV, RA Enlargement on Echocardiogram

PAH: Echocardiogram

Enlarged RV

Small D-shaped LV

Flattened Septum
Echocardiogram

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

Echocardiogram

Doppler Estimation of RV Systolic Pressure

- $2.5^2 \times 4 = 25 \text{ mmHg}$
- $2.9^2 \times 4 = 34 \text{ mmHg}$
- $4.3^2 \times 4 = 74 \text{ mmHg}$
- $5.5^2 \times 4 = 121 \text{ mmHg}$

Tricuspid Regurgitation Doppler Signal

$RVSP = TR \text{ gradient} + RAP$
Diagram of 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 systemic to pulmonary shunt lesion (ASD, VSD, PDA, etc)

Post-capillary pulmonary venous hypertension
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

Diagnosis of Pulmonary Hypertension
- High index of suspicion
- Thorough and complete evaluation
**Pulmonary Hypertension Workup**

Suspect Pulmonary Hypertension

- CXR, ECG, TT Echo
- TEE
- Sleep Study
- HRCT
- ?CT Angiogram
- Pulm Angiogram

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

- Right Heart Cath
- Acute VD Study
- ? Lung Biopsy
- Transplantation Evaluation

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**Pre-capillary PH: 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 syst-pulm shunts
- Portal hypertension
- HIV infection
- Drugs and toxins
- Other

High PA pressure and normal “downstream” pressures
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: 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 - 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
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?


- Median survival 2.8 years
- NIH = National Institutes of Health

Pathobiology of Pulmonary Arterial Hypertension

- ~15% prevalence of positive family history
  - Autosomal dominant
- Co-ancestry in sporadic cases
- PPH1 locus on chromosome 2q31-q32
- BMPR2 mutations

- Appetite suppressants
- Other exogenous toxins
- Hepatic toxins
- HIV
- Autoimmune Dysfunction
- Shear Stress
Plexogenic and Thrombotic Pulmonary Arteriopathy

Vascular Smooth Muscle Hypertrophy

Thrombosis in situ

Endothelial Proliferation and Dysfunction

Vasodilator/Vasoconstrictor Imbalance

Deficient prostacyclin
Excess thromboxane
Excess endothelin
Deficient nitric oxide

Pulmonary Vasoconstriction

Genetic Predisposition + Vascular Injury

Coagulation Abnormalities

Pathobiology of Pulmonary Arterial Hypertension
In IPAH, Prostacyclin Synthase Expression in the Lung is Decreased

Tuder et al. AJRCCM 1999

Expression of Endotheulin in the Lungs of Patients with IPAH

Giaid A et al. NEJM 1993

Plexiform Lesions in IPAH
Endothelin System in Vascular Tissue

ET-1 = endothelin-1; Big-ET-1 = proendothelin-1; ECE = endothelin-converting enzyme; NO = nitric oxide; PGI2 = prostacyclin

Dupuis. Lancet 2001
In IPAH, Nitric Oxide Synthase Expression in the Lung is Decreased

Giaid et al. NEJM 1995

Decreased [Ca^{2+}]_{ii}

GTP

NONO Soluble guanylate cyclase

Vascular smooth muscle relaxation

Inactive GMP

Cyclic nucleotide Phosphodiesterases

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

Nitric Oxide: Impact on Vascular Tone

GTP → Soluble guanylate cyclase → cGMP → Inactive GMP → Decreased [Ca^{2+}]_{i}

Vascular smooth muscle relaxation
Sildenafil
- if vasodilation in corpus cavernosum - erection
- then vasodilation in PAs
  - ?treatment for PAH

Cyclic nucleotide Phosphodiesterases
- PDE1
- PDE2
- PDE3
- PDE4
- PDE5
- PDE6 - 11

Humbert M, Sitbon O, Simonneau G: NEJM 204;351:1425
Mechanisms Behind Current Therapeutic Options

Abnormality in PAH

↓ Prostacyclin synthase in endothelial cells

↓ Nitric oxide synthase expression in endothelial cells

↑ Lung and circulating endothelin-1 levels

Therapeutic Implication

• Administer prostacyclin

• Enhance NO pathway

• Use endothelin receptor antagonist

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