**Objectives**

- The student will know the structure, function, distribution and control of pulmonary blood supply
  - Compare pulmonary and bronchial circulation
  - Compare and contrast pulmonary and systemic circulation
  - Describe and explain the effects of cardiac output and lung volume on pulmonary vascular resistance
  - Describe the effects of hypoxia on pulmonary vascular resistance
  - Describe the effects of gravity of pulmonary blood flow
  - Explain Starling’s equation
  - Describe the mechanisms of pulmonary edema

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**Two Circulations in the Lung**

- **Pulmonary Circulation.**
  - Arises from Right Ventricle.
  - Receives 100% of blood flow.

- **Bronchial Circulation.**
  - Arises from the aorta.
  - Part of systemic circulation.
  - Receives about 2% of left ventricular output.

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**The Bronchial Circulation**

- Circulation of oxygenated blood from the aorta returning to nourish following lung structures
  - Conducting airways to terminal bronchioles
  - Parenchyma supporting structures
    - Pleura
    - Interlobar septal tissues
    - Pulmonary arteries & veins
  - Bronchial blood flows at systemic pressures and is 1-2% of cardiac output
  - 50% of Bronchial blood circulation returns to right atrium via azygos vein
  - The rest of the bronchial blood exits lung by small anastomoses with pulmonary veins contributing to normal venous admixture (right-to-left shunt)

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**Pulmonary Circulation Volume**

- Total blood volume from main pulmonary artery to left atrium is 500 ml
- Lung is 40-50% blood by weight
- This volume fraction > than any other organ
- Equal distribution of blood between artery & vein
- Capacitance reservoir for the left atrium- pulmonary vasculature acts as a reservoir and can alter its volume from 50% to 200% of resting volume
- Prevents changes in blood return to right ventricle from affecting left ventricular diastolic filling pressures over 2-3 cardiac cycles
Pulmonary Circulation

- In series with the systemic circulation.
- Receives 100% of cardiac output (3.5L/min/m²).
- RBC travels through lung in 4-5 seconds.
- 280 billion capillaries, supplying 300 million alveoli.
  - Surface area for gas exchange = 60 – 100 m²

The Pulmonary Capillaries

- Extensive network within alveolar walls
- 70-80% of alveolar surface area covered by capillary bed
- Total capillary surface area almost equals alveolar surface area
- Functional capillary volume
  - Capillary volume increases by opening closed segments (recruitment)
  - 70 ml (1 ml/kg body weight) normal volume at rest
  - 200 ml at maximal anatomical volume

Alveolocapillary Network

- Continuous network over several alveoli
- Average distance RBC travels through network is 600 to 800 μm
- Capillary network blood volume equal to RV stroke volume
- RBC remain in network for one cardiac cycle (0.75 sec)
- RBC require less than 0.25 seconds for gas exchange equilibrium

Alveolar Architecture

- Gas exchange: across small pulmonary arteriolar vessels (anatomically not capillaries-functionally capillaries) & pulmonary capillaries
- There are about 280 billion pulmonary capillaries for about 300 million alveoli, resulting in a gas exchange surface of about 60-100 m²
Pressures of the Pulmonary System

- Blood flow varies throughout lung as result of low vascular pressures, gravity & distensible pulmonary vessels
- Right ventricle ejection fraction of blood is distributed into lungs & equals LV cardiac output
- Pulmonary blood pressure lower because the resistance to flow in pulmonary system is one tenth of systemic circulation
- Pulmonary artery is thin walled (1/3 thickness of aorta) and very compliant
- Consequences of this anatomy - the vessels are: Distensible and Compressible

Reasons Why Pressures Are Different in Pulmonary and Systemic Circulations?

- Gravity and Distance:
  - Distance above or below the heart adds to, or subtracts from, both arterial and venous pressure
  - Distance between Apex and Base
Regional Pulmonary Blood Flow Depends Upon Position Relative to the Heart

Main PA 15 mmHg
Apex 2 mmHg
Base 25 mmHg

Reasons Why Pressures Are Different in Pulmonary and Systemic Circulations?

- Control of regional perfusion in the systemic circulation:
  - Large pressure allows alterations in local vascular resistance to redirect blood flow to areas of increased demand (e.g., to muscles during exercise).
  - Pulmonary circulation is all performing the same job, no need to redirect flow (exception occurs during hypoxemia).

- Consequences of pressure differences:
  - Left ventricle work load is much greater than right ventricle
  - Differences in wall thickness indicates differences in work load

Gravity & Circulation

- Gravity effects on systemic blood pressure
  - Degree of pressure change from level of the heart
  - Pressure gradient of 0.74 mm Hg/cm
  - Postural dependent relationship with gravity
  - In supine person: arterial pressure higher in feet than head

- Effects of gravity on pulmonary circulation
  - Greater alterations in flow occur because pulmonary circulation pressures much lower
  - Distribution of blood flow in the lung affected by gravity
  - Changes in pulmonary arterial pressure affect distribution of blood flow over the height of the lung
Hydrostatic Pressure

The pressure effect gravity has on a column of fluid

- Hydrostatic pressure alters the potential energy of the fluid column
  - The right atrium level & middle of lung are considered zero reference points
  - Supine or prone position = hydrostatic pressures minimized
- Gravity affects the perfusion of blood in the different zones of the lung
  - Lung base receives greater portion of RV ejection fraction than apex of lung
  - Hydrostatic pressure causes distension & recruitment of pulmonary capillaries in base of lung.

The Pulmonary Circulatory System

Physiologic Anatomy

Pulmonary Vessels Divided Into Alveolar & Extra-alveolar

- Alveolar vessels are closely related to acini
  - Alveolo-capillary network involved in gas exchange
  - Alveolar vessels directly affected by alveolar pressure
  - High positive pressure during lung expansion collapses alveolar vessels
  - Alveolar capillaries can be compressed so that they contain no blood
- Extra-alveolar vessels are the arteries & veins which convey blood to-and-from the respiratory units
  - Larger vessels with thicker walls & substructure connective tissue
  - These vessels not directly affected by pressures in the lung
  - Compression during positive pressure does not occur
  - Surrounding lung tissue pushes these vessels open during lung volume increases

Pulmonary Blood Flow Regulation

Capillary Resistance

- Alveolar vessels provide longitudinal resistance to flow
  - Alveolar vessel network dimensions & distensibility resist pulmonary blood flow
  - Network dimensions are not regulated by autonomic or hormone control
  - Alveolar capillary walls contribute 40% of total resistance
  - Alveolar arterioles contribute 50% of resistance (in the body - arterioles are major resistance vessels = 75% total systemic circulation resistance)
- Resistance of Capillary vessels dependant on lung conditions
  - Reduced resistance at low lung volumes
  - Reduced resistance at high blood flow rates
  - Greater resistance at lower blood pressures or less vascular distending pressures
- Passive Regulation of blood flow through capillaries occurs in response to changes in cardiac output
  - Increases in blood flow accommodated by recruitment & distention
  - Prevent rise in pulmonary driving pressure with increase in blood flow

Pulmonary Vascular Resistance

Vascular Resistance = \( \frac{\text{input pressure} - \text{output pressure}}{\text{blood flow}} \)

\[ 
\text{PVR} = \frac{\text{mean PA pressure} - \text{left atrial pressure}}{\text{cardiac output (index)}}
\]

Therefore PVR is 1/10 of SVR
Influences on Pulmonary Vascular Resistance

Pulmonary vessels have:
- Little vascular smooth muscle.
- Low intravascular pressure.
- High distensibility and compressibility.

Vessel diameter influenced by extravascular forces:
- Gravity
- Body position
- Lung volume
- Alveolar pressures/intrapleural pressures
- Intravascular pressures

Effect of Transmural Pressure on Pulmonary Vessels During Inspiration

Resistance ∝ Length and Resistance ∝ 1/(Radius)^4

Lung Volumes & PVR

Changes in lung volumes during breathing affect PVR
- PVR minimal when lung volume close to FRC (functional residual capacity=residual volume + expiratory reserve vol)
- PVR increased with higher & lower lung volumes
- Extra-alveolar vessels dilate during inspiration
  - Radial traction exerted on these distributing arteries & veins increase diameter and reduce flow resistance
  - These vessels receive increased blood volume as higher alveolar pressure compresses alveolar vessels
- Alveolar vessels compress during inspiration
  - Capillary resistance increases during elevated alveolar pressures
  - Pulmonary capillaries are vessels of major vascular resistance

Lung Volume Affects Pulmonary Vascular Resistance

Total lung capacity = residual vol + expiratory reserve vol + tidal vol + inspiratory reserve vol. It is the max amount of air that is contained in lungs
Capillary Volume Changes

**Recruitment**
- Process of increasing capillary volume by opening closed vessels
- Increased CO raises pulmonary vascular pressures, BUT decreases pulmonary vascular resistance
- Occurs during periods of stress & increased tissue oxygen demand
- Chief mechanism for fall in PVR

**Distension**
- Internal vessel pressures raise & open capillary beds
- Elevated left atrial pressure distends capillary beds (mitral regurgitation, LV failure)
- Leads to lung congestion & ultimately heart failure
- Mechanism seen at high vascular pressures

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**Pulmonary Vascular Resistance During Exercise**
- During exercise cardiac output increases (e.g. 5-fold), but with little change in mean pulmonary artery pressure
  - How is this possible?
  - Vascular Resistance = \( \frac{\text{input pressure} - \text{output pressure}}{\text{blood flow}} \)
- \( \Delta \text{Pressure} = \text{Flow} \times \text{Resistance} \)
- If pressure does not change, then PVR must decrease with increased blood flow
  - Passive effect (seen in isolated lung prep)
    - Recruitment: Opening of previously collapsed capillaries
  - Distensibility: Increase in diameter of open capillaries.

---

**Passive Influences on PVR**
- Increase in perfusion pressure (pulmonary artery pressure) results in distension & recruitment → decreasing PVR.

**Control of Pulmonary Vascular Resistance (PVR)**
- Cardiac output
- How can vessels be open but have no flow?
  - Consider very low pressure systems, e.g. garden hose with multiple small holes. At low enough pressure, only a few holes trickle water. Sufficient difference in resistance that flow is diverted to the path with least resistance.

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**Capillary Volume During Exercise**
- Strenuous exercise increases cardiac output significantly
- Increased CO raises pulmonary arterial pressure
- More alveolar wall capillaries are recruited
- Capillary volume doubles to give time for adequate gas exchange during increased blood flow
Control of Pulmonary Vascular Resistance

- Passive Influences on PVR:

<table>
<thead>
<tr>
<th>Influence</th>
<th>Effect on PVR</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Lung Volume (above FRC)</td>
<td>Increase</td>
<td>Lengthening and Compression</td>
</tr>
<tr>
<td>↓ Lung Volume (below FRC)</td>
<td>Increase</td>
<td>Compression of Extraalveolar Vessels</td>
</tr>
<tr>
<td>↑ Flow, ↑Pressure</td>
<td>Decrease</td>
<td>Recruitment and Distension</td>
</tr>
<tr>
<td>Gravity</td>
<td>Decrease in Dependent Regions</td>
<td>Recruitment and Distension</td>
</tr>
<tr>
<td>↑ Interstitial Pressure</td>
<td>Increase</td>
<td>Compression</td>
</tr>
<tr>
<td>Positive Pressure Ventilation</td>
<td>Increase</td>
<td>Compression and Drecruitment</td>
</tr>
</tbody>
</table>

The part of respiratory passage whose air doesn't take part in pulmonary gas exchange is called physiological dead space. It is estimated by the body weight in pound expressed in ml, e.g., 150 lbs = anatomical dead space is 150 ml. 1 kg = 2.2 lbs.

Alveolar Ventilation

Alveolar ventilation is the portion of breathing that reaches the alveoli and participates in gas exchange.

Breathing Pattern | Tidal Volume (ml) | Breathing Frequency (breaths/min) | Minute Ventilation (ml/min) | Dead Space Ventilation (ml/min) | Alveolar Ventilation (ml/min)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>normal quiet breathing</td>
<td>500</td>
<td>12</td>
<td>6000</td>
<td>150 \times 12 = 1800</td>
<td>4200</td>
</tr>
<tr>
<td>shallow &amp; fast</td>
<td>150</td>
<td>40</td>
<td>6000</td>
<td>150 \times 40 = 6000</td>
<td>0</td>
</tr>
<tr>
<td>deep &amp; slow</td>
<td>1000</td>
<td>6</td>
<td>6000</td>
<td>150 \times 6 = 600</td>
<td>5100</td>
</tr>
</tbody>
</table>

Minute Ventilation

\[ V = V_t \times \text{breathing frequency} \]

- Total breath duration
- Tidal volume
- \( V_t \)
- Breathing frequency

Dead Space Ventilation \([V_{ds}]\)

The part of respiratory passage whose air doesn't take part in pulmonary gas exchange is called physiological dead space. It includes ventilation of both:

1. the anatomic dead space: the portion of the breath that enters and leaves the conducting zones of the airways (nose to terminal bronchioles)
2. the alveolar dead space: air that reaches the alveoli but does not participate in gas exchange.

It is estimated by the body weight in pound expressed in ml, e.g., 150 lbs = anatomical dead space is 150 ml. 1 kg = 2.2 lbs.

Alveolar DS = Anatomic DS = Physiologic DS

Ventilation: Minute, Alveolar & Dead Space

\[ V_t = 150 \text{ ml} \]
\[ V_a = 150 \text{ ml} \]
\[ FRC = 2400 \text{ ml} \]
Measurement of Dead Space (The Bohr Equation)

The Bohr equation is based on the principle that any gas coming out of the lungs is a mixture of gas in the dead space & gas in the alveoli.

\[
\frac{V_{DS}}{VT} = 1 - \frac{P_{ACO_2}}{P_{ACO_2}}
\]

or

\[
\frac{V_{DS}}{VT} = \frac{P_{ACO_2} - P_{ACO_2}}{P_{ACO_2}}
\]

\(A\): alveolar; \(P\): Partial pressure;
\(VT\): Total Volume; \(E\): expired air

A couple of important points:

1. In the normal lung anatomy, dead space = physiologic dead space, there is little alveolar dead space.

2. Alveolar dead space is not necessarily an anatomically identifiable alveolus either any alveolus with relatively low perfusion than normal.

Examples:
- Pulmonary embolus: pulmonary vasculature occluded by blood clot
- Herniation: low venous return RV output less milibar perfusion
- PEEP: pulmonary capillary squeezed by adjacent high alveolar pressure

Using the Bohr Equation in Disease States

Consider alveoli that are ventilated but not perfused:

\[
\frac{V_{DS}}{VT} = 1 - \frac{P_{ACO_2}}{P_{ACO_2}}
\]

\(P_{ACO_2}\) will be less than in health

\(V_{DS}\) will be \(\%\) less than in health

The Bohr equation measures the physiologic DS [sum of Alveolar DS & Anatomic DS]

Summary & Query

- Summarize how dead space is measured by the Bohr versus the Fowler technique.
- Specify what characteristic of the measured gas makes it a suitable candidate for determining the type of dead space. Explain why.

Ref: CO2 participates in gas exchange and its end expired value will be affected by gas exchange which in turn depends on perfusion.

Fowler: \(N_2\) does not participate in gas exchange, merely diluted by the anatomic dead space.
Perfusion of the lung (Q)
- The amount of blood passing through the pulmonary capillaries per min which is available for the gas exchange.
- Same with cardiac output passes through pul capillaries, 5L/min.
- Pulmonary circulation pressure is low.
- Coz of the effect of gravity, blood flow in base is higher than apex.
- If pulmonary pressure further falls, apex blood flow may collapsed.
- If blood flow increases due to distensibility mechanism, previously collapsed capillaries will be opened and even stretching/distension of the operating capillaries will happen—key factor during exercise.

Ventilation/perfusion ratio (V/Q)
- It is the ratio of alveolar ventilation to the perfusion in the lungs.
- It should be normal otherwise the gas exchange will not be normal.
**Distribution of Ventilation**

- Normal lung is not uniformly ventilated in standing lung
  - Tidal volume is unevenly distributed throughout lung
  - Most of volume changes occur at more compliant base of lung
  - Linear reduction in regional tidal volumes from base to apex

- Variation in airway resistance, compliance & hydrostatic effects cause nonuniform regional & local (acini) ventilation

- Regional nonuniform ventilation
  - Gravity causes hydrostatic interpleural pressure gradient
  - Regional lung volume changes vary because transpulmonary pressures are influenced by interpleural pressure gradient
  - Differences in transpulmonary pressure affect lung compliance

- Local nonuniform ventilation is caused by variable airway resistance & localized differences in compliance of lung
  - Healthy lungs have essentially equal time constants in all acini
  - Acini ventilation not as effected by hydrostatic pressure changes

**Regional Ventilation Distribution**

- Nonuniform ventilation caused by effects gravity on the parenchyma of lung
  - Gravity pulls down on lung
  - Alveoli are more expanded at top than at base of lung
  - Alveolar volume parallels lung compliance curve

- Lower portion of lung tends to be ventilated more than the apex of lung
  - End expiratory volume (FRC) is less at base
  - Compliance of base of lung is greater than the top of lung
  - More movement of air into & out of alveoli at base of lung

**Gravity, Alveolar Pressure and Blood Flow**

- Pressure in the pulmonary arterioles depends on both mean pulmonary artery pressure and the vertical position of the vessel in the chest, relative to the heart.

- Driving pressure (gradient) for perfusion is different in the 3 lung zones:
  - Flow in zone 1 may be absent because there is inadequate pressure to overcome alveolar pressures
  - Flow in zone 3 is continuous and driven by the pressure in the pulmonary arteriole – pulmonary venous pressure
  - Flow in zone 2 may be pulsatile and driven by the pressure in the pulmonary arteriole – alveolar pressure (collapsing the capillaries)
Zones of West

Typically no zone 1 in normal healthy person

Large zone 1 in positive pressure ventilation + PEEP

Gravity, Alveolar Pressure, and Blood Flow

Regional Distribution of Blood Flow
Matching Ventilation to Perfusion

- V/Q distribution regulated to maintain systemic arterial partial pressure range between 85 to 100 mmHg
- Healthy lung (A-a) PO2 gradient is 10 to 15 mmHg
- Larger (A-a) PO2 gradients indicate intrinsic pulmonary disease
- Hypoxemia with normal (A-a) PO2 gradient indicates hypoventilation
- Mismatched V/Q ratio most common cause of inefficient O2 & CO2 exchange
- Wasted ventilation & venous admixture are both causes of abnormal (A-a) PO2 differences
Control of Pulmonary Vascular Resistance

Active Regulation of Blood Flow

- Active regulation occurs by altering vascular smooth muscle tone in pulmonary vessels (arterioles)
- The pulmonary capillary smooth muscle alters PVR
- Vasomotor tone of pulmonary vessels is affected by many factors

Passive Influences on PVR:

- ↑ Lung Volume (above FRC)
- ↓ Lung Volume (below FRC)
- ↑ Flow, ↓ Pressure
- ↑ Interstitial Pressure
- Gravity
- Positive Pressure Ventilation
- Influence: Lengthening and Compression
- Influence: Compression of Extraalveolar Vessels
- Influence: Recruitment and Derecruitment
- Influence: Compression and Distension

Active Influences on PVR:

- Sympathetic Innervation
- α-Adrenergic Agonists
- Thromboxane/PGE2
- Endothelin
- Angiotensin
- Histamine
- Alveolar Hypoxemia
- Parasympathetic Innervation
- Acetylcholine
- β-Adrenergic Agents
- Prostaglandin 1
- Prostacyclin
- Nitric Oxide
- Bradykinin
Pulmonary Blood Flow

Effect of Alveolar Oxygen Tension

• Partial pressure of Oxygen (PAO2) in alveoli - critical factor governing pulmonary circulation
• PO2 in alveoli more important than oxygen tension in mixed venous blood
• Oxygen diffusing into pulmonary arteriole walls causes smooth muscle dilation
  – As alveolar oxygen tension decreases – surrounding arterioles constrict
  – Low alveolar PO2 causes increase in local vascular resistance
  – Blood flow shifted to areas of lung with higher PO2
  – These small changes in local resistance do not effect overall PVR (provided < 20% of lung volume involved)
• Global reduction in alveolar oxygen tension increases total PVR by constriction of arterioles & small arteries

Alveolar Hypoxia & Vasoconstriction

• Alveolar hypoxia produces hypoxic pulmonary vasoconstriction (HPV)
  – Localized response of pulmonary arterioles
  – Caused by hypoxia and enhanced by hypercapnia & acidosis
  – Contraction of smooth muscle in small arterioles in hypoxic region
• Opposite reaction than systemic circulation to hypoxia
• HPV is an important mechanism of balancing V/Q ratio
  – Shift of flow to better ventilated pulmonary regions
  – Results from decreased formation & release of Nitric Oxide by pulmonary endothelium in hypoxic region

Control of Pulmonary Vascular Resistance (PVR)

Hypoxia

Opposite to systemic circulation where hypoxia ⇒ vasodilation
Mechanisms: hypoxia inhibits Kv Channels, depolarizes, opens Ca++ Channels, muscle contracts
B2 agonists dilate

Pulmonary Hypertension

• Increased resistance to blood flow in the lung
• High pulmonary vascular resistance (PVR) elevated pulmonary artery pressures
  – Generalized alveolar hypoxia increases total pulmonary resistance
  – Hyperventilation
  – Low inspired PCO2
  – Increased PO2
  – Pain
  – Hypoxemia resister
  – High altitudes
• Pulmonary Hypertension causes increased work for the right ventricle
  – Right ventricular hypertrophy
  – Transsp lid separation
  – Right heart failure (cor pulmonale)

Pulmonary Hypertension

Serious pulmonary vascular condition

• Small muscular pulmonary arteries narrow
• Pulmonary arterial pressure increases
• Right ventricle pressures rise to compensate until occurrence of RV failure
• Lung Transplant is only effective treatment
Barrier Function of Alveolar Wall

- Capillary endothelial cells:
  - permeable to water, small molecules, ions.
  - barrier to proteins.

- Alveolar epithelial cells:
  - more effective barrier than the endothelial cells.
  - recently found to pump both salt and water from the alveolar space.

Osmotic Gradient Counteracts Hydrostatic Gradient

- Hydrostatic pressure in the pulmonary capillary bed > hydrostatic pressure in the interstitium
  - hydrostatic pressure drives fluid from the capillaries into the pulmonary interstitium

- Osmotic pressure in the plasma > osmotic pressure in the interstitium
  - osmotic pressure normally would draw fluid from the interstitial space into the capillaries

Starling’s Equation

$$Q = K \left( \frac{P_c - P_i}{\sigma \left( \pi_c - \pi_i \right)} \right)$$

- $Q$ = flux out of the capillary
- $K$ = filtration coefficient
- $P_c$ and $P_i$ = capillary and interstitial hydrostatic pressures
- $\pi_c$ and $\pi_i$ = capillary and interstitial osmotic pressures
- $\sigma$ = reflection (sieving) coefficient

Normally Starling’s Forces Provide Efficient Protection

- Normal fluid flux from the pulmonary capillary bed is approximately 20 ml/hr.
  - recall that cardiac output through the pulmonary capillaries at rest is ~5 l/min.
  - < 0.0066% leak.

- Abnormal increase in fluid flux can result from:
  - Increased hydrostatic pressure gradient (cardiogenic pulmonary edema).
  - Decreased osmotic pressure gradient (cirrhosis, nephrotic syndrome).
  - Increased protein permeability of the capillary wall (ARDS).