For the body to survive, there must be a constant supply of O₂ and a constant disposal of CO₂.

**Respiratory System - Overview:**

1. Provides surface area for gas exchange (between air / blood)
2. Moves air in / from gas exchange surface
3. Protects system (debris / pathogens / dessication)
4. Produces sound (vocalization)
5. Protects system (debris / pathogens / dessication)
6. Assists in the detection of odorants

**Upper Respiratory System**

- External nares
- Nasal cavity
- Uvula
- Pharynx
  - Nasopharynx
  - Oropharynx
  - Laryngopharynx

**Lower Respiratory System**

- Trachea
- Bronchial tree
- Alveoli

**Functional Anatomy:**

- Conduction of air
- Gas exchange
- Provides open area
- Oral air / food
- Voice production

**Epiglottis**

- Filters / warms / humidifies incoming air

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*Marieb & Hoehn (Human Anatomy and Physiology, 8th ed.)*

*Martini et. al. (Fundamentals of Anatomy and Physiology, 7th ed.)*
Functional Anatomy:

Naming of pathways:
- > 1 mm diameter = bronchus
- < 1 mm diameter = bronchiole
- < 0.5 mm diameter = terminal bronchiole

Green = Conducting zone
Purple = Respiratory zone

Respiratory System

Functional Anatomy:

Respiratory Mucosa / Submucosa:

Near trachea
Near alveoli

Epithelium:
Pseudostratified columnar → Simple cuboidal
Cilia: No cilia
Lamina Propria (areolar tissue layer):
↓ smooth muscle → ↑ smooth muscle
Mucous glands: No mucous glands
Cartilage:
Rings → Plates / none

Mucosa
Mucous membrane (epithelium / areolar tissue)

Mucus Escalator

Functional Anatomy:

How are inhaled debris / pathogens cleared from respiratory tract?

Nasal Cavity:
Particles > 10 µm
Conducting Zone:
Particles 5 – 10 µm
Respiratory Zone:
Particles 1 – 5 µm

Macrophages
Respiratory System

Functional Anatomy:

Respiratory System

Esophagus
- Tough, flexible tube (~1" diameter)
- 15 – 20 tracheal cartilages
- Protect airway

Pseudostratified ciliated columnar epithelium
- Goblet cells: Unicellular mucous secreting glands

Trachea
- Allow for food passage

Right primary bronchus
- Wider, shorter & steeper (↑ blockage hazard)

Extrapulmonary bronchi
- 1º

Intrapulmonary bronchi
- 2º →

Bronchus
- (≤ 1 mm diameter)

Bronchiole
- (< 1 mm diameter)

Sympathetic stimulation (NE; β2 receptors)
- Leads to bronchodilation

Synthetic drugs (e.g., albuterol)
- Triggers response

Parasympathetic stimulation (ACh, muscarinic receptors)
- Leads to bronchoconstriction

Allergic attack → Histamine → Bronchoconstriction

Mucus glands rare – Why?

Alveoli
- (300 million / lung)
Respiratory System

Functional Anatomy:

Type I Pneumocytes:
- Simple squamous; forms wall of alveoli
- Alveolar pores (1 – 6 / alveoli)

Type II Pneumocytes:
- Cuboidal / round; secretes surfactant
- Reduces surface tension (prevents alveoli collapse)

Alveolar macrophages:
- Clear debris on alveolar surface

Pneumonia:
- Thickening of respiratory membrane

Gas exchange occurs readily in the alveoli of the lung via simple diffusion across the respiratory membrane

Respiratory Membrane:
1) Type I pneumocytes
2) Endothelial cells of capillaries
3) Fused basement membranes

Respiratory Physiology:

Respiration includes:
1) Pulmonary ventilation (pumping air in / out of lungs)
2) External respiration (gas exchange @ blood-gas barrier)
3) Transport of respiratory gases (blood)
4) Internal respiration (gas exchange @ tissues)
Pressure relationships in the thoracic cavity:

1) **Intrapulmonary Pressure** (within the alveoli):
   - Static conditions: $P_{pul} = 0$ mm Hg
   - Exhalation (expiration): $P_{pul}$ slightly negative

2) **Intrapleural Pressure** (within pleural cavity):
   - Always relatively negative (~ -4 mm Hg)
   - Prevents lungs from collapsing

Intrapulmonary pressure ($P_{pul} = 0$ mm Hg)

**Why is the intrapleural pressure negative?**

**Answer:** Interaction of opposing forces

Forces acting to collapse lung:
1) Elasticity of lungs
2) Alveolar surface tension

Forces resisting lung collapse:
1) Elasticity of chest wall

Surface tension of serous fluids keep lungs "stuck" to chest wall

Costanzo (Physiology, 4th ed.) – Figure 5.9

Pneumothorax: ("sucking chest wound")
Puncture of chest wall; results in inability to generate negative pressure and expand the lungs

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Marieb & Hoehn (Human Anatomy and Physiology, 8th ed.) – Figure 22.12

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Pulmonary ventilation is a mechanical process that depends on thoracic cavity volume changes.

Boyle's Law:
\[ P_1V_1 = P_2V_2 \]

- \( P \) = pressure of gas (mm Hg)
- \( V \) = volume of gas (mm\(^3\))
- \( P_1 \) = initial pressure; \( V_1 \) = initial volume
- \( P_2 \) = resulting pressure; \( V_2 \) = resulting volume

Example:
\[ 4 \text{ mm Hg (2 mm}^3\text{)} = P_2 (4 \text{ mm}^3) \]

\[ P_2 = 2 \text{ mm Hg} \]

Respiratory System

Pulmonary Ventilation:

Inspiration:
- Muscular expansion of thoracic cavity
  - Contraction of diaphragm
    - Lengthens thorax (pushes liver down)
  - Contraction of external intercostal muscles
    - Widens thorax

Results in:
- Reduced intrapleural pressure (\( P_{ip} \))
- Reduced intrapulmonary pressure (\( P_{pul} \))

Results in decreased pressure in thoracic cavity and air enters.
Pulmonary Ventilation:

Pulmonary ventilation is a mechanical process that depends on thoracic cavity volume changes.

Expiration:
- Retraction of thoracic cavity

A) Passive Expiration
- Diaphragm / external intercostals relax
- Elastic rebound (lungs rebound)

- Diaphragm results in increased pressure in thoracic cavity; air exits

B) Active ("Forced") Expiration
- Abdominal muscles contract
- Internal intercostals contract

Eupnea:
- Quiet breathing (active inspiration; passive expiration)

Hyperpnea:
- Forced breathing (active inspiration; active expiration)

Airflow is directly proportional to pressure difference between outside air and alveoli and inversely proportional to resistance of the airway.

\[ Q = \frac{\Delta P}{R} \]

\( Q \) = Airflow (L/min)
\( P \) = Pressure gradient (mm Hg)
\( R \) = Airway resistance (mm Hg/L/sec)

Airway resistance determined by Poiseuille’s Law:

\[ R = \frac{8\eta L}{\pi r^4} \]

- \( R \) = Resistance
- \( \eta \) = Viscosity of inspired air
- \( L \) = Length of airway
- \( r \) = Radius of airway

Why don’t the smallest airways provide the highest resistance?

Reminder:
- Parasympathetic system produces bronchial constriction (\( \downarrow \) diameter = \( \uparrow \) resistance)
- Sympathetic system produces bronchial dilation (\( \uparrow \) diameter = \( \downarrow \) resistance)
Pulmonary Ventilation:

Several physical factors exist influence pulmonary ventilation

B) Surface tension in alveoli

Surface tension generated as neighboring liquid molecules on the surface of alveoli are drawn together by attractive forces

Law of Laplace:

\[ P = \frac{2T}{r} \]

Problem?

Respiratory Distress Syndrome (e.g., pre-mature babies)

Dipalmitoyl phosphatidylcholine (DPPC)

Surfactant

Costanzo (Physiology, 4th ed.) – Figure 5.12

C) Lung compliance

Measure of change in lung volume that occurs with a given transpulmonary pressure

\[ C_L = \frac{dV_L}{d(P_{pul} - P_{pl})} \]

\[ C_L = \text{Lung compliance (cm}^3\text{/mm Hg)} \]

\[ V_L = \text{Lung volume (cm}^3\) \]

\[ P_{pul} = \text{Intrapulmonary pressure (mm Hg)} \]

\[ P_{pl} = \text{Intrapleural pressure (mm Hg)} \]

The higher the lung compliance, the easier it is to expand the lungs at a given pressure

Determined by:

1) Elasticity of lung
2) Surface tension

- Emphysema: Increased lung compliance due to loss of elastic fibers
- Fibrosis: Decreased lung compliance due to scar tissue build-up

D) Respiratory Volumes / Capacities:

Total Volume:

Amount of air moved in / out of lung during single respiratory cycle

Respiratory Volumes / Capacities:

Increases with:

- Body size
- Gender
- Conditioning

Vital capacity (~ 4600 ml)

Decreases with:

- Age

Total lung capacity (~ 6000 ml)

Functional residual capacity (~ 2400 ml)

Inspiratory capacity (~ 3000 ml)

- Inspiratory reserve volume (~ 1200 ml)
- Total volume (~ 3100 ml)
- Residual volume (~ 1200 ml)
- Inspiratory reserve volume (~ 2100 ml)
- Functional residual capacity (~ 2400 ml)
**Pathophysiology:**

**Forced vital capacity (FVC)** is the total volume of air that can be forcibly expired after maximal inspiration; this is a useful measure of lung disease.

**Cardiovascular System – Vessels**

- Normal FEV<sub>1</sub> = 0.8
- Obstructive disease (reduced): FEV<sub>1</sub> < 0.8
- Restriction disease (reduced): FEV<sub>1</sub> > 0.8

**Respiratory System**

- **Pulmonary Ventilation:** Not all inhaled air participates in gas exchange; this volume is referred to as dead space.
- **Anatomic Dead Space:** Volume of air found in the conducting airways, including the nose → bronchioles.
- **Physiologic Dead Space:** Anatomic dead space plus any ventilated alveoli that might not participate in gas exchange.

- **Anatomic Dead Space:**
  
  \[ V_{AD} = f_{(breaths / minute)} \times V_{T} \]  
  
  \[ f = 12 \text{ breaths / minute} \]  
  
  \[ V_{T} = 500 \text{ mL} \]  
  
  \[ V_{AD} = 6000 \text{ mL / minute} \]  
  
  \[ = 6.0 \text{ liters / minute} \]  

- **Alveolar Ventilation:**
  
  \[ V_{A} = f_{(breaths / minute)} \times (V_{T} - V_{D}) \]  
  
  \[ f = 12 \text{ breaths / minute} \]  
  
  \[ V_{T} = 500 \text{ mL} \]  
  
  \[ V_{D} = 150 \text{ mL} \]  
  
  \[ V_{A} = 4200 \text{ mL / minute} \]  
  
  \[ = 4.2 \text{ liters / minute} \]
Respiratory Physiology:

1) Pulmonary ventilation (pumping air in / out of lungs)
2) External respiration (gas exchange @ blood-gas barrier)
3) Transport of respiratory gases (blood)
4) Internal respiration (gas exchange @ tissues)

Respiratory System

Pulmonary Ventilation:

Gas exchange in the respiratory system refers to diffusion of O₂ and CO₂ in the lung and in the peripheral tissues

Basic Properties of Gases:

A) Dalton's Law of Partial Pressures:

The total pressure of a gas is equal to the sum of the pressure of its constituents

For dry gases:

\[ P_X = P_B \times F \]

- \( P_X \) = Partial pressure of gas (mm Hg)
- \( P_B \) = Barometric pressure (mm Hg)
- \( F \) = Fractional concentration of gas

\[ P_{O_2} = 760 \times 0.21 \]

\[ P_{O_2} = 160 \text{ mm Hg} \]

Respiratory System

Gas Exchange:

Gas exchange in the respiratory system refers to diffusion of O₂ and CO₂ in the lung and in the peripheral tissues

Basic Properties of Gases:

A) Dalton's Law of Partial Pressures:

The total pressure of a gas is equal to the sum of the pressure of its constituents

For humidified gases:

\[ P_X = (P_B - P_{H_2}O) \times F \]

- \( P_X \) = Partial pressure of gas (mm Hg)
- \( P_B \) = Barometric pressure (mm Hg)
- \( P_{H_2}O \) = Water vapor pressure at 37°C (47 mm Hg)
- \( F \) = Fractional concentration of gas

\[ P_{O_2} = (760 - 47) \times 0.21 \]

\[ P_{O_2} = 150 \text{ mm Hg} \]
Gas exchange in the respiratory system refers to diffusion of $O_2$ and $CO_2$ in the lung and in the peripheral tissues.

Basic Properties of Gases:

**B) Henry's Law:**

Gases in a mixture dissolve in a liquid in proportion to their partial pressures.

\[ C_X = P_X \times \text{Solubility} \]

Where:
- $C_X$ = Concentration of dissolved gas (mL X/100 mL blood)
- $P_X$ = Partial pressure of gas (mm Hg)
- Solubility = Solubility of gas in blood (mL X/100 mL mm Hg)

**Example:**

\[ [O_2] = P_{O_2} \times \text{Solubility} \]

\[ [O_2] = 150 \times 0.003 \]

\[ [O_2] = 0.45 \text{ mL/100 mL blood} \]

**CO_2 >> O_2 >> N_2**

---

**C) Fick's Law:**

The transfer of a gas across a cell membrane depends on the driving force, gas solubility, and the surface area available for transport.

\[ V_X = \frac{DA \Delta P}{\Delta X} \]

Where:
- $V_X$ = Volume of gas transferred per unit time
- $D$ = Diffusion coefficient of the gas (includes solubility)
- $A$ = Surface area
- $\Delta P$ = Partial pressure difference of the gas
- $\Delta X$ = Thickness of the membrane

The driving force for diffusion of a gas is the partial pressure difference of the gas, not the concentration difference.

---

Gas exchange in the respiratory system refers to diffusion of $O_2$ and $CO_2$ in the lung and in the peripheral tissues.

Unlike alveolar air, where there is only one form of gas, blood is able to carry gases in addition forms.

**Bound gas**
- Gases bind directly to plasma proteins or to hemoglobin

**Dissolved gas**
- The higher the solubility of a gas, the higher the concentration of the gas in solution

**Chemically modified gas**
- Gases react with blood components to form new products

**Total gas concentration = Dissolved gas + Bound gas + Chemically modified gas**
Respiratory System

Gas Exchange:

Gas transport in the lungs:

P_{X} = P_{B} \times F

Lung air modified by gas exchange:
1) O_2 into blood; CO_2 out of blood
2) Mixture of fresh and residual air

Composition reflects metabolic activity of body

Due to rapid diffusion of gases, equilibrium reached

Diffusion-limited: The total amount of gas transported across the alveolar/capillary barrier is limited by the diffusional process.

Example: Carbon monoxide

Partial pressure gradient maintained across length of capillary (gas does not equilibrate)

1 gas transport = 1 diffusion rate

Perfusion-limited: The total amount of gas transported across the alveolar/capillary barrier is limited by blood flow.

Example: Nitrous oxide

Partial pressure gradient not maintained across length of capillary (gas equilibrates)

1 gas transport = 1 blood flow
Gas Exchange:

Under normal conditions, O₂ transport into pulmonary capillaries is a perfusion-limited process.

*Marieb & Hoehn (Human Anatomy and Physiology, 8th ed.)* – Figure 22.18

Rest

Exercise

“wiggle room”

P₀₂ does not equilibrate until hemoglobin saturated

Remember:

P₀₂ only measures free O₂ concentration

Respiratory System

Pathophysiology:

In certain pathologic conditions, O₂ transport becomes diffusion limited.

*Costanzo (Physiology, 4th ed.)* – Figure 5.19

Outcome:

Decreased P₀₂ in systemic arterial blood, especially during physical activity

\[ V_X = \frac{D_A \Delta P}{\Delta X} \]

A man climbs to the top of a tall mountain where the barometric pressure is measured at 50 mm Hg.

What are the implications to oxygen transport into pulmonary capillaries for A) PaO₂, B) rate, and C) exercise?

Driving force:

50 – 25 = 25 mm Hg

\[ V_X = \frac{D_A \Delta P}{\Delta X} \]
Respiratory Physiology:

Respiration includes:
1) Pulmonary ventilation (pumping air in / out of lungs)
2) External respiration (gas exchange @ blood-gas barrier)
3) Transport of respiratory gases (blood)
4) Internal respiration (gas exchange @ tissues)

Oxygen Transport in Blood:

O₂ is carried in two forms in blood: dissolved and bound to hemoglobin

A) Dissolved O₂:

Accounts for 2% of total O₂ content of blood

Henry’s Law:

\[ C_X = P_X \times \text{Solubility} \]

- \( C_X \): Concentration of dissolved gas (mL X / 100 mL blood)
- \( P_X \): Partial pressure of gas (mm Hg)
- Solubility = Solubility of gas in blood (mL X / 100 mL blood / mm Hg)

\[ [O_2] = P_{O_2} \times \text{Solubility} \]
\[ [O_2] = 100 \times 0.003 \]
\[ [O_2] = 0.30 \text{ mL / 100 mL blood} \]

Recall:

The concentration of dissolved O₂ is proportional to the partial pressure of O₂.

Grossly insufficient to meet the demands of the tissues

At rest, tissues require 250 mL O₂ / min

\[ \text{O₂ delivery} = \text{CO} \times \text{dissolved O₂} \]
\[ \text{O₂ delivery} = 5.0 \text{ L / min} \times 0.3 \text{ mL O₂ / 100 mL} \]
\[ \text{O₂ delivery} = 15 \text{ mL O₂ / min} \]

B) O₂ bound to hemoglobin:

Accounts for remaining 98% of total O₂ content of blood

Globular protein: 2 α & 2 β subunits each containing a heme moiety
- 4 O₂ / hemoglobin

Oxyhemoglobin = O₂ bound to hemoglobin

Deoxyhemoglobin = No O₂ present

Methemoglobin = Iron in ferric (Fe³⁺) state
- Does not bind O₂

Shouldn’t O₂ oxidize iron (ferrous state – Fe²⁺) bound to nitrogen?

No – nitrogen bonds prevent this…

But – if it does happen:

Methemoglobin reductase – reduces Fe³⁺ to Fe²⁺
Oxygen Transport in Blood:

O$_2$ is carried in two forms in blood: dissolved and bound to hemoglobin

B) O$_2$ bound to hemoglobin:

Hemoglobin structure demonstrates a developmental shift

**Amount of O$_2$ bound to hemoglobin determined by the hemoglobin concentration and by the O$_2$-binding capacity of that hemoglobin**

Under normal conditions:

- 1.0 g of hemoglobin can bind 1.34 mL O$_2$
- [hemoglobin A] = 15 g / 100 mL

**PUTTING IT ALL TOGETHER:**

**O$_2$ Content:**

The actual amount of O$_2$ per unit volume of blood

O$_2$ content = (O$_2$-binding capacity x % saturation) + dissolved O$_2$

**O$_2$ Delivery to Tissues:**

The actual amount of O$_2$ delivered to the tissues

O$_2$ delivery = Cardiac output x O$_2$ content of blood

**Reminder:**

Each hemoglobin is the capacity to bind 4 O$_2$ molecules

**O$_2$-hemoglobin Dissociation Curve:**

Describe relationship between percent saturation of Hb and partial pressure of oxygen

THE PERCENT SATURATION OF HEME SITES DOES NOT INCREASE LINEARLY AS P$_{O_2}$ INCREASES

**Subunit Cooperativity:**

Oxygenation of first heme group facilitates oxygenation of other heme groups

---

Costanzo (Physiology, 4th ed.) – Figure 5.20
Oxygen Transport in Blood:

O₂ is carried in two forms in blood: dissolved and bound to hemoglobin

B) O₂ bound to hemoglobin:

Under normal, resting conditions, arterial blood hemoglobin is 98% saturated and only ~ 25% of O₂ is unloaded at tissues

Points to Ponder:

1) Hemoglobin is almost completely saturated at a PₐO₂ of 70 mm Hg

ADAPTIVE SIGNIFICANCE?

2) The unloading of O₂ occurs on the steep portion of the dissociation curve

ADAPTIVE SIGNIFICANCE?

Costanzo (Physiology, 4th ed.) – Figure 5.22

Right shift = Decreased Hb affinity for O₂

- Facilitates unloading of O₂

A) ↑ PₐCO₂
B) ↓ pH
C) ↑ temperature
D) ↑ 2,3-DPG

Influence Hb saturation by modifying hemoglobin's three-dimensional structure

Costanzo (Physiology, 4th ed.) – Figure 5.23

Left shift = Increased Hb affinity for O₂

- Hinders unloading of O₂

A) ↓ PₐCO₂
B) ↑ pH
C) ↓ temperature
D) ↓ 2,3-DPG

Increased affinity of hemoglobin F (fetal) due to ↓ 2,3-DPG binding

Costanzo (Physiology, 4th ed.) – Figure 5.23
Carbon monoxide poisoning is catastrophic for O$_2$ delivery to tissues.

1) CO decreases O$_2$ bound to Hb
   - CO binds to Hb with an affinity that is 250x greater than that of O$_2$ (forms carboxyhemoglobin)
   - "cherry red"

2) CO causes left shift of dissociation curve
   - Hemoglobin not bound to CO has an increased affinity for O$_2$

Carbon Dioxide Transport in Blood:
CO$_2$ is carried in three forms in blood: dissolved, bound to hemoglobin, and as bicarbonate (HCO$_3^-$)

A) Dissolved CO$_2$:
   - Accounts for 5% of total CO$_2$ content of blood
   - Henry’s Law:
     \[ C_X = P_X \times \text{Solubility} \]
     \[ C_X = \text{Concentration of dissolved gas (mL X / 100 mL blood)} \]
     \[ P_X = \text{Partial pressure of gas (mm Hg)} \]
     \[ \text{Solubility} = \text{Solubility of gas in blood (mL X / 100 mL / mm Hg)} \]

   \[ [\text{CO}_2] = P_{\text{CO}_2} \times \text{Solubility} \]
   \[ [\text{CO}_2] = 40 \times 0.07 \text{ (Arterial blood)} \]
   \[ [\text{CO}_2] = 2.80 \text{ mL / 100 mL blood} \]

B) CO$_2$ bound to hemoglobin:
   - Accounts for 3% of total CO$_2$ content of blood
   - Commentary:
     - CO$_2$ binds to the terminal amino groups on globins
     - Carbaminohemoglobin = CO$_2$ bound to hemoglobin
     - When less O$_2$ is bound to Hb, the affinity of Hb for CO$_2$ increases
       (the Haldane effect)

In TURN

Reminder:
The binding of CO$_2$ to hemoglobin causes a conformational change reducing the affinity of Hb for O$_2$ (right shift)
Respiratory System

Carbon Dioxide Transport in Blood:

- CO₂ is carried in three forms in blood: dissolved, bound to hemoglobin, and as bicarbonate (HCO₃⁻).

C) CO₂ converted to HCO₃⁻:

Accounts for remaining 92% of total CO₂ content of blood

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- \\
\]

1) Carbon dioxide (CO₂) combines with water (H₂O) to form carbonic acid (H₂CO₃)
   - Reaction catalyzed by carbonic anhydrase (CA)
2) H₂CO₃ dissociates into hydrogen ion (H⁺) and bicarbonate ion (HCO₃⁻)
   - HCO₃⁻ released into plasma
   - H⁺ buffered in RBC by deoxyhemoglobin

Chloride shift:
- To maintain charge balance in RBCs, a Cl⁻ is exchanged with a HCO₃⁻ as the HCO₃⁻ leaves the cell
- Band three protein functions as passive transporter

Gas Transport - Review:

Tissue – Blood Interface:

- Randall et al. (Ecker et al. Animal Physiology, 5th ed.) – Figure 13.10
Respiratory System
Gas Transport:
Lung – Blood Interface:
Carbonic anhydrase also embedded in respiratory membrane

Note:

Respiratory System
Ventilation / Perfusion Relationships:
Pulmonary blood flow is regulated primarily by altering the resistance of the arterioles

Mechanisms of Regulation:

A) Partial pressure of alveolar \( O_2 \)

Hypoxic vasoconstriction

Mechanism of Action:
- If \( P_{A\ O_2} \) falls below 70 mm Hg, voltage-gated \( Ca^{2+} \) gates open in vascular smooth muscle, leading to contraction

Can act locally (blocked alveolus) or globally (high altitude)

B) Vasoactive Chemicals

Thromboxane A2
- Source: Endothelium
- Action: Vasoconstriction

Prostacyclin
- Source: Endothelium
- Action: Vasodilator

Respiratory System
Ventilation / Perfusion Relationships:
The distribution of pulmonary blood flow with the lung is uneven due to the effects of gravity

Zone 1: Apex of lung
- \( P_{A\ O_2} > P_{arterial} > P_{venous} \)
- Pulmonary capillaries compressed by surrounding alveoli
- Low blood flow

Zone 2: Middle of lung
- \( P_{A\ O_2} > P_{arterial} > P_{venous} \)
- Minimal compression; blood flow driven by partial vs. \( P_{alveoli} \) difference
- Medium blood flow

Zone 3: Base of lung
- \( P_{A\ O_2} > P_{arterial} > P_{venous} \)
- The greatest number of capillaries open; high arterial and venous pressures
- High blood flow
Control of Breathing:

Breathing is regulated so the lungs can maintain the PaO₂ and PaCO₂ within a normal range.

Modulatory Respiratory Centers:

1) Ventral Respiratory Group
   - Inspiratory center
   - ‘Pacesetter’ (12 – 15 breaths / min)

2) Dorsal Respiratory Group
   - Expiratory center
   - Active during forced exhalation

Pontine Respiratory Centers:

1) Apneustic Center
   - Triggers prolonged inspiratory gasps

2) Pneumotaxic Center
   - Turns off inspiration
   - Limits size of tidal volume

Most important factors regulating ventilation are chemical.

Peripheral chemoreceptors
- Carotid body (IX)
- Aortic arch (X)

Central chemoreceptors
- (CSF)

Chemical Factors:

- Increased P_{CO₂} in arterial blood
- Decreased P_{CO₂} in arterial blood

A) P_{CO₂}
   - Most potent respiratory stimulant (maintained at 3 mm Hg)
   - Mediated via central / peripheral chemoreceptors

Ultimately leads to change in pH of cerebral spinal fluid.

Costanzo (Physiology, 4th ed.) - Figure 5.32

Marieb & Hoehn (Human Anatomy and Physiology, 8th ed.) - Figures 22.23, 22.24
Control of Breathing:

Chemical Factors:

A) $P_{CO_2}$
   - Most potent respiratory stimulant (maintained at ~3 mm Hg)
   - Mediated via central/peripheral chemoreceptors

B) $P_{O_2}$
   - Minor respiratory stimulant ($O_2 + CO_2$ in respiratory gases)
   - Mediated via peripheral chemoreceptors
   - Stimulated by $P_{O_2} < 60$ mm Hg in arterial blood

C) Arterial pH
   - Independent of changes in arterial $P_{CO_2}$
   - Compensatory mechanism for metabolic acidosis
   - Mediated by peripheral chemoreceptors (carotid body)

Issue for individuals with COPD:
Continual high levels of $P_{CO_2}$ in system results in $P_{O_2}$ taking over regulation

If respiratory distress occurs:
Mediated by peripheral chemoreceptors (carotid body only)

Control of Breathing:

Depth and rate of breathing can be modified in response to changing demands on the body.

Addition factors contribute to ventilation regulation:

- **Hering-Breuer Reflex:**
  - When lung alveoli stretched, inspiratory center inhibited

- **Joint/muscle stretch receptors:**
  - Function in anticipatory response to exercise

- **Apnea (cessation of breathing):**
  - Epiglottis closes; thoracic cavity shrinks

- **Spasms (e.g., sarin gas):**
  - Laryngeal spasm, air forcefully released (~100 mph)

Nasal cavity = Sneeze
Lower conduction system = Cough
Apnea (cessation of breathing)
Epiglottis closes; thoracic cavity shrinks
Epiglottis opens; air forcefully released (~100 mph)
Control of Breathing:

Depth and rate of breathing can be modified in response to changing demands on the body.

Addition factors contribute to ventilation regulation:
- **Hyperventilation**: Increase breathing rate / depth
- **Hypoventilation**: Decrease breathing rate / depth

Rate / depth of respiration exceeds demands for O₂ delivery / CO₂ removal.

**Hyperventilation**:
- Pain / emotional stimuli acting through hypothalamus
- Pain / emotional stimuli acting through hypothalamus

**Hypoventilation**:
- Central chemoreceptors (CSF)
- Lung stretch receptors
- Vagus (X) nerve
- Joint / muscle stretch receptors
- Irritant receptors

Higher control centers:
- Voluntary control over breathing

Pain / emotional stimuli acting through hypothalamus

**Hypoventilation**:
- Decrease breathing rate / depth

Hyperventilation:
- Increase breathing rate / depth

Rate / depth of respiration exceeds demands for O₂ delivery / CO₂ removal.

Increase in lung cancer rates correlated with rise in smoking among adult man and woman.

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<thead>
<tr>
<th>Year</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>Rare</td>
</tr>
<tr>
<td>1956</td>
<td>29,000 deaths</td>
</tr>
<tr>
<td>1978</td>
<td>105,000 deaths</td>
</tr>
<tr>
<td>2004</td>
<td>160,440 deaths</td>
</tr>
</tbody>
</table>

Formaldehyde, benzene, vinyl chloride, arsenic, ammonia, hydrogen cyanide contribute to secondhand smoke. 

Increase in lung cancer rates correlated with rise in smoking among adult man and woman.