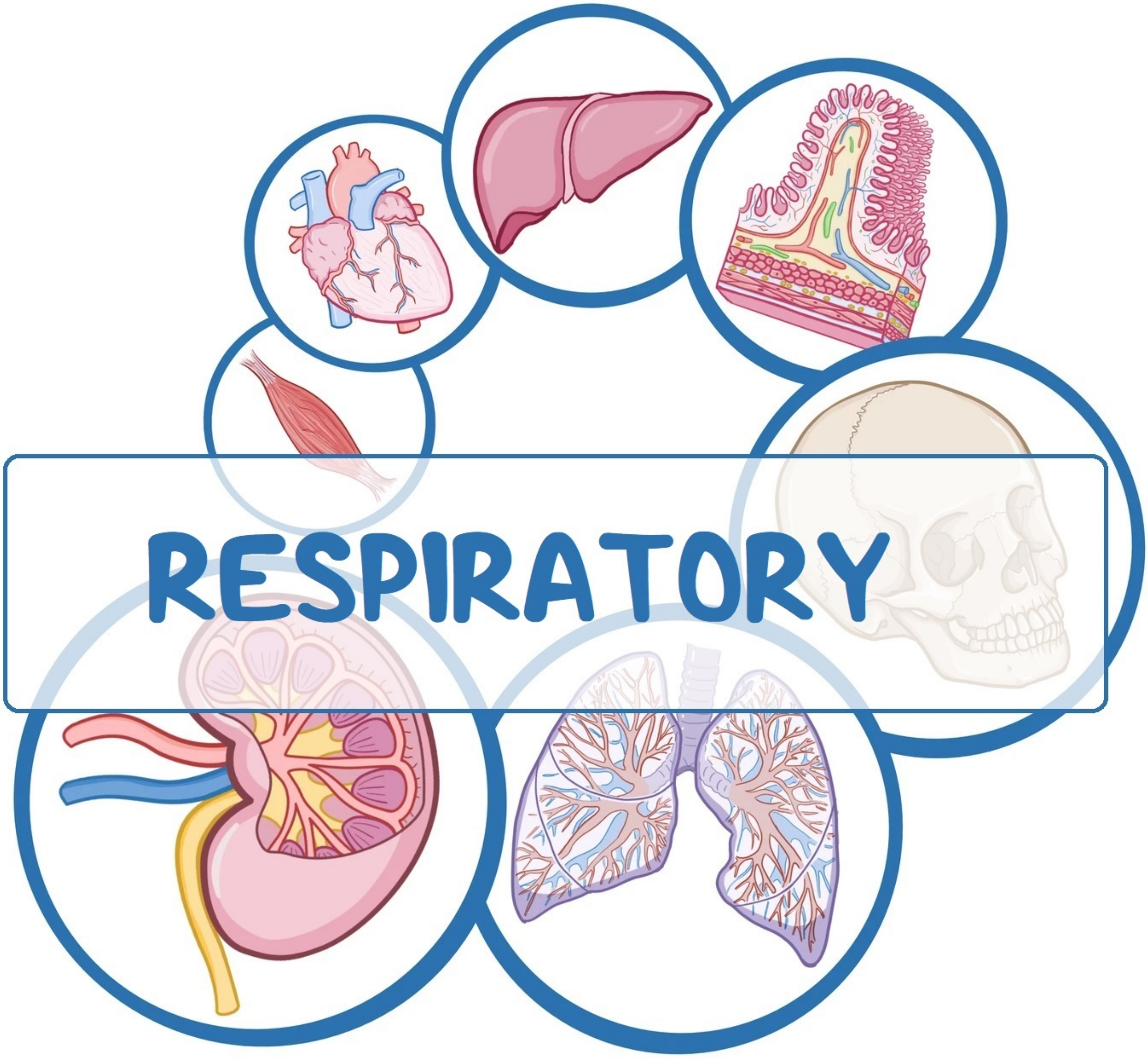
PHYSIOLOGY



RESPIRATORY

HIGH-YIELD NOTES

AfraTafreeh.com

Table of Contents

Anatomy % Physiology 1

Breathing Mechanics 7
Lung Volumes & Capacities 7
Anatomic & Physiologic Dead Space 8
Ventilation 9
Alveolar Gas Equation 10
Comliance of Lungs & Chest Wall 10
Combined Pressure-Volum Curves for the Lung & Chest wall 11
Alveolar Surface Tension & Surfactant 11
Airflow, Presure & Resistance 12
Breathing Cycle 13

Breathing Regulation 14
Breathing Control 14
Pulmonary Chemoreceptors & Mechanoreceptors 15

Gas Exchange 15
Ideal (General) Gas Law 16
Boyle's Law 17
Dalton's Law 17
Henry's Law 18
Fick's Laws of Diffusion 18
Graham's Law 19
Gas Exchange in The Lungs 20
Diffusion-limited & Perfusion Limited Gas Exchange 22

Gas Transport 24
Oxygen Binding capacity & Oxygen Content 24
Oxygen-Hemoglobin Dissociation Curve 25
Erythropoietin (EPO) 28
Carbon Dioxide Transport in Blood 28
Regulation of Pulmonary Blood Flow 29
Zones of Pulmonary Blood Flow 31
Pulmonary Shunts 32
Ventillation perfusion ratios & V Q Mismatch 34
Hypoxemia & Hypoxia 35

Normal Variations 38
Pulmonary Changes During Excercise 38
Pulmonary Chanes at High Altitude & Altitude Sickness 40

NOTES
ANATOMY & PHYSIOLOGY

RESPIRATORY SYSTEM

osms.it/respiratory-anatomy-physiology

RESPIRATORY SYSTEM

- Upper respiratory tract
  - Nose, pharynx, associated structures
- Lower respiratory tract
  - Larynx, trachea, bronchi, lungs

Respiratory system function

- Gas exchange between blood, atmosphere
- Protection against harmful particles, substances
- pH homeostasis
- Vocalization

Conducting vs. respiratory zone

- Conducting zone
  - Does not participate in gas exchange
  - Nose to terminal bronchioles
  - *Function*: inspire, warm, humidify, filter air before gas exchange
  - Smooth muscle layer contains autonomic nervous system (sympathetic, parasympathetic nerves)
  - Smooth muscle along trachea, first few bronchial branches have beta-2-adrenergic receptors
  - Sympathetic nerves stimulate beta-2-adrenergic receptors → ↑ airway diameter
  - Parasympathetic nerves stimulate muscarinic receptors → ↓ airway diameter
- Respiratory zone
  - Participates in gas exchange
  - Lined with alveoli
  - Terminal bronchioles–alveoli

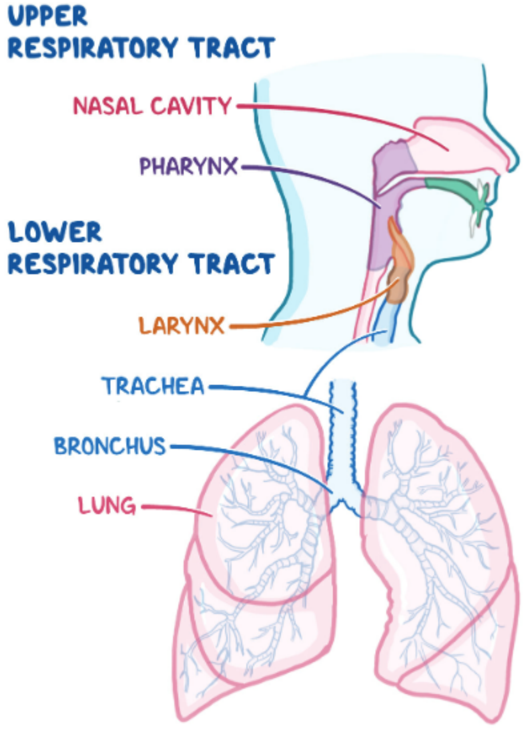


Figure 67.1 Respiratory system overview, categorized into upper, lower respiratory tracts.

RESPIRATORY SYSTEM ANATOMY

Nose

- *Function*: humidifies, warms, filters inspired air; voice resonance chamber; houses olfactory receptors
- Nasal vibrissae (hairs) coated with mucus → traps large particles (e.g. dust, pollen)

Nasal cavity

- Nasal cavity division
  - *Midline nasal septum*: composed of septal cartilage, anteriorly
  - *Vomer bone*: posteriorly
- Four paranasal sinuses (air-filled spaces inside bones) connected to nasal cavity
  - Ethmoid, frontal, sphenoid, maxillary sinuses
  - *Function*: warms, moistens inspired air; amplifies voice; lightens skull
- Roof formed by ethmoid, sphenoid bones
- Floor formed by palate
- Two mucous membrane types
  - *Olfactory mucosa*: olfactory epithelium containing smell receptors
  - *Respiratory mucosa*: pseudostratified ciliated columnar epithelium containing goblet cells; secretes mucus containing lysozyme, defensins
- Nasal conchae
  - Three mucosa-covered projections (superior, middle, inferior nasal conchae) of nasal cavity's lateral wall
  - *Meatus*: groove inferior to each conchae (superior, middle, inferior meatus)
  - *Function*: ↑ turbulence inside cavity to filter, humidify inspired air; reabsorb heat, moisture during nasal expiration

Palate

- Separates nasal cavity from oral cavity
  - *Hard palate*: anterior portion supported by palatine bones
  - *Soft palate*: posterior portion not supported by bones
  - Soft palate, uvula move together; forms valve that closes nasopharynx when swallowing (prevents food from entering nasopharynx)

Pharynx

- AKA throat
- Passageway connecting nasal cavity, larynx, oral cavity, esophagus
- *Nasopharynx*: region connecting nasal cavity to pharynx
  - Posterior to nasal cavity, inferior to sphenoid bone, superior to soft palate
  - Air-only passageway
  - Pharyngeal tonsils (adenoids); located on posterior wall; traps, kills pathogens
  - Pseudostratified ciliated epithelium (part of mucociliary escalator)
- *Oropharynx*: region connecting pharynx to oral cavity
  - Posterior to oral cavity, continuous with isthmus of fauces
  - Soft palate superior, epiglottis inferior
  - Food, air passageway
  - Pseudostratified columnar epithelium of nasopharynx → stratified squamous epithelium
  - Palatine tonsils located on lateral walls
  - Lingual tonsils cover posterior tongue
- *Laryngopharynx*: part of pharynx continuous with larynx (voice box)
  - Food, air passageway
  - Stratified squamous epithelium
  - Epiglottis anterior, esophagus posterior

Larynx

- Cartilage, connective tissue framework
  - Connects pharynx to trachea; houses vocal cords, epiglottis (cartilage flap atop larynx that seals airway off when swallowing—prevents food entering larynx)
- Location
  - Third to sixth cervical vertebra
  - *Superior*: hyoid bone
  - *Inferior*: trachea
- Function
  - Routes food, air into appropriate passageway; voice production
- Histology
  - *Superior portion*: contacts food; stratified squamous epithelium
  - *Inferior portion*: below vocal folds; pseudostratified ciliated columnar epithelium (part of mucociliary escalator)

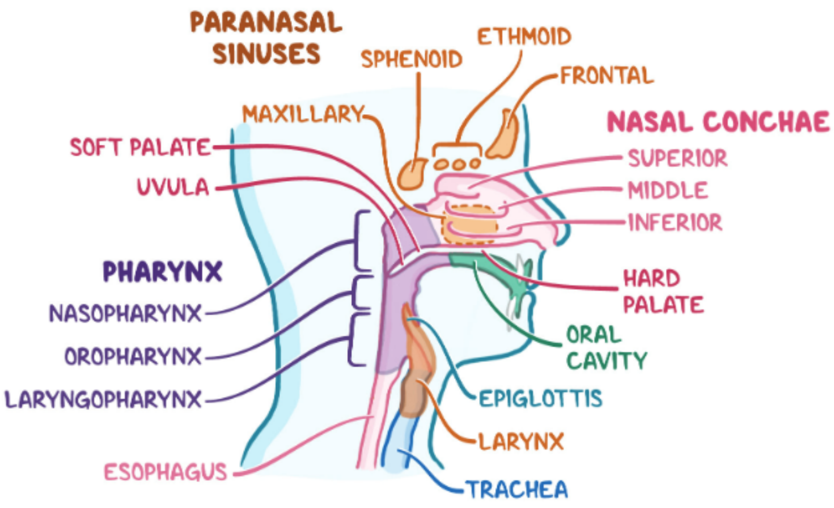


Figure 67.2 Anatomy of upper respiratory tract, surrounding structures.

- Contains nine cartilages
  - *Thyroid cartilage*: large shield-shaped midline cartilage, produces laryngeal prominence ("Adam's apple")
  - *Cricoid* cartilage: ring-shaped cartilage inferior to thyroid cartilage, superior to trachea
  - *Arytenoid, cuneiform, corniculate cartilages*: form posterior, lateral larynx walls (arytenoid cartilages anchor vocal cords)
  - *Epiglottis*: spoon-shaped cartilage is pulled superiorly to cover laryngeal inlet during swallowing (prevents food from passing through larynx)
- Vocal folds/ligaments
  - Attach arytenoid cartilages to thyroid cartilage
  - *True vocal cords*: sound production (function); composed of elastic fibers; core of mucosal folds; appears white (avascularity)
  - *False vocal cords*: superior to true vocal cords; does not participate in sound production; close glottis during swallowing (function)

Trachea

- AKA windpipe
- Mainstem bronchi, airways
- Trachea
  - Tube smooth muscle, connective tissue, C-shaped cartilage (provides support, maintains open passage for air)
  - Connected by trachealis muscle
  - Runs from larynx, divides into two main bronchi inferiorly at carina
- Layers (superficial to deep)
  - *Mucosa*: pseudostratified epithelium with goblet cells; mucociliary escalator
  - *Submucosa*: connective tissue layer (supported by 16–20 C-shaped cartilage rings)
  - *Adventitia*: connective tissue layer encasing cartilage rings

Right & left mainstem bronchus

- Right mainstem bronchus
  - Wider, more vertical
  - Something accidentally inhaled → goes into right lung (more likely)
- Inside lungs
  - Main bronchus subdivides into lobar bronchi → segmental bronchi → terminal bronchioles
- Trachea, first three bronchial generations
  - Wide, supported by cartilage rings
- Large airways lined by ciliated columnar cells, goblet cells (secrete mucus)
  - *Mucociliary escalator*: mucus traps particles → ciliated columnar cells beat rhythmically → moves mucus, trapped particles towards pharynx → spit out/ swallowed

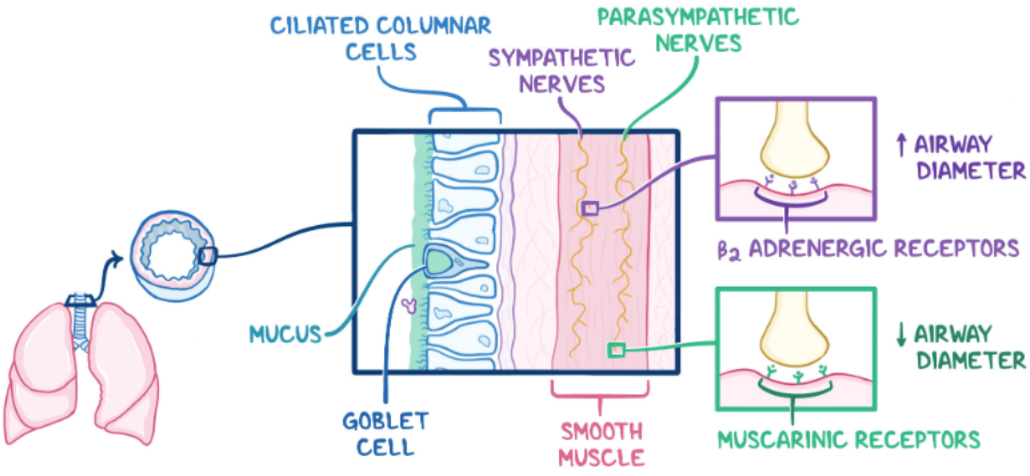


Figure 67.3 Section of tracheal wall showing its histology. Stimulation by sympathetic nerves dilates airways, stimulation by parasympathetic nerves constricts airways.

Histological changes as conducting tubes decrease

- Cartilage
  - Cartilage amount ↓ while elastic fibers ↑ (bronchioles contain no cartilage)
- Epithelium
  - Mucosal epithelium changes from pseudostratified columnar → columnar → cuboidal
  - Goblet cells, cilia ↓ (completely absent in bronchioles)
- Smooth muscle ↑

Bronchioles

- Narrow airways after first three bronchial generations
- *Terminal bronchioles*: last part of terminal bronchioles, end of conducting zone
- *Respiratory bronchioles*: distal to terminal bronchioles, first part of respiratory zone
- Terminal bronchiole → respiratory bronchiole → alveolar ducts → alveolar sac → alveoli

Alveoli

- Alveolar wall
  - Composed of a single simple squamous epithelium layer
- Elastic fibers surround alveoli → allow lung expansion during inspiration, recoil during expiration
  - *Type I pneumocytes*: primary gas exchange site; oxygen–carbon dioxide exchange occurs between alveolar gas, pulmonary capillary blood; thin walls, large alveoli surface-area maximizes gas exchange diffusion capabilities
  - *Type II pneumocytes*: secrete surfactant (↓ surface tension within alveoli → eases expansion, prevents collapsing
- Alveolar macrophages phagocytize particles inside lungs → conducting bronchioles → mucociliary escalator
- Respiratory membrane
  - Capillary, alveolar walls; basement membranes
- Alveolar pores connect adjacent alveoli
- Blood supply
  - Pulmonary capillary networks

Lungs

- Main respiration organs
- Right lung
  - *Three lobes*: upper, middle, lower lobe
- Left lung
  - *Two lobes*: upper, lower lobe
- Base of lungs rest on diaphragm
- *Pleura*: double-layered serosa covering lungs, pleural fluid lining pleural cavity between two layers
  - *Parietal pleura*: outer layer adherent to thoracic wall, superior surface of diaphragm
  - *Visceral pleura*: inner layer adherent to external lung surface

- Pulmonary circulation
  - Pulmonary veins (anterior to main bronchi) bring oxygen-rich blood to lungs from heart
  - Pulmonary arteries bring oxygen-poor systemic venous blood for oxygenation
  - Low-pressure, high-volume circulation
- Bronchial circulation
  - *Bronchial arteries*: provide oxygenated systemic blood to lung tissue
  - *Bronchial veins*: drain deoxygenated venous blood from lungs (with pulmonary veins)
  - High-pressure, low-volume circulation
- Innervation
  - Pulmonary plexus
  - Parasympathetic motor causes bronchoconstriction
  - Sympathetic motor causes bronchodilation
  - Visceral sensory
  - Diaphragm innervated by phrenic nerve

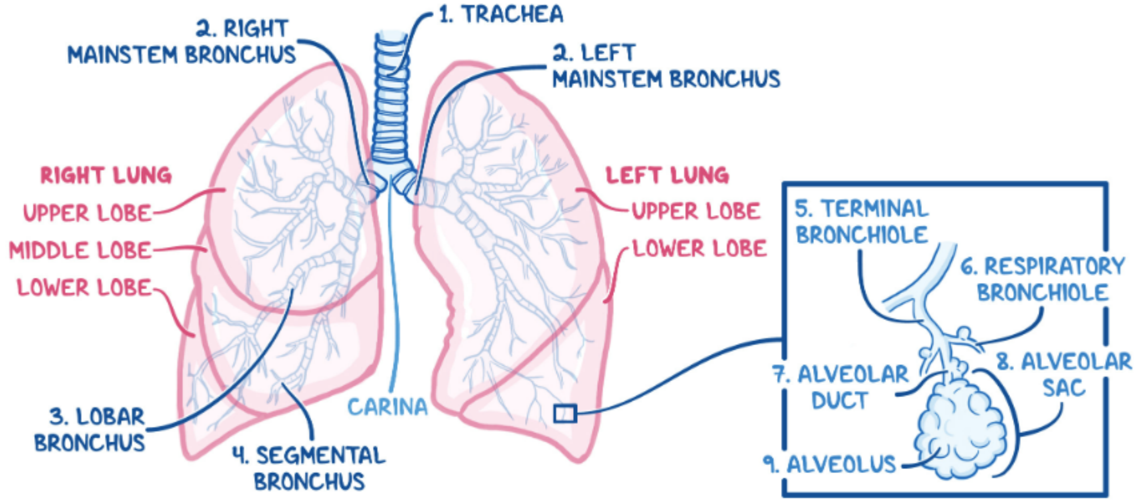


Figure 67.4 Trachea and lung anatomy. Numbered labels show sequence of airflow going into the airways from (trachea to alveoli).

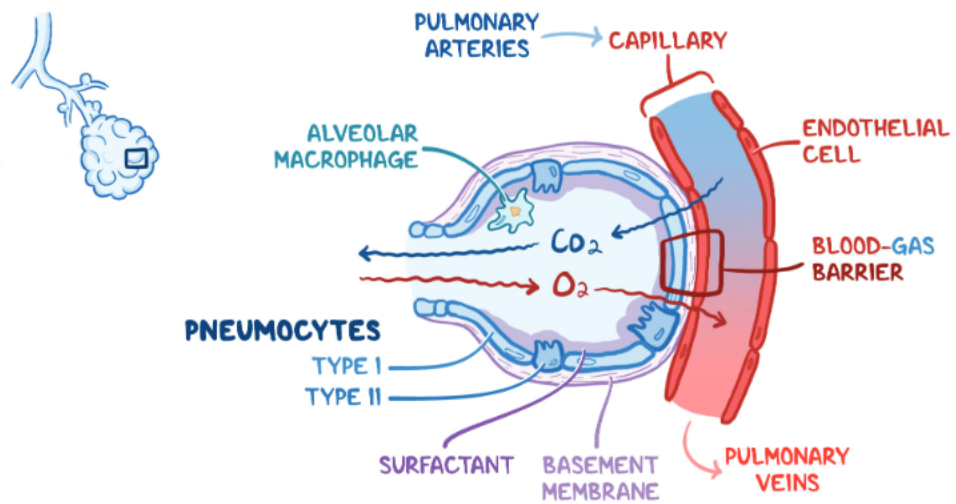
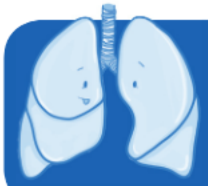


Figure 67.5 Alveolus structure. Gas exchange occurs at the blood-gas barrier. De-oxygenated blood from pulmonary arteries are oxygenated then sent to pulmonary veins.

VENTILATION

- *Ventilation (breathing)*: moving air in, out of lungs
- Oxygen pathway
  - Air inhaled through nostrils → nasal cavity → pharynx → larynx → trachea → mainstem bronchus → conducting bronchioles → terminal bronchioles → respiratory bronchioles → alveolar duct → alveoli → capillary → body
  - Carbon dioxide moves in reverse
- Airflow from atmosphere to lungs
  - Higher pressure → lower pressure
- Muscle movement creates pressure gradient
  - *Primary respiration muscles*: diaphragm, external intercostals, scalenes
  - *Forceful breathing*: other muscles recruited
- *Airflow resistance*: function of respiratory passage diameter
- *Passive inhalation*: negative pressure inside body generated → moves air into lungs
  - Diaphragm contracts downwards, chest muscles pull ribs outward → ↑ intrathoracic volume → ↓ intrathoracic pressure → air moved into lungs (air flows down pressure gradient)
- *Passive exhalation*: ↑ intrathoracic pressure generated → moves air out of lungs
  - Diaphragm relaxes (returns to resting position), external intercostal muscles relax, thoracic cage recoils → elastic lung recoil → ↓ intrathoracic volume → ↑ intrathoracic pressure → air pushed out of lungs



NOTES
BREATHING MECHANICS

LUNG VOLUMES & CAPACITIES

osms.it/lung-volumes-capacities

- *Spirometry:* spirometer used to measure air volume moving in, out of lungs
- *Static lung volumes:* volumes not involved in airflow rate
- *Capacities:* combination of > one lung volume

Volume variations

- Related to age, sex, body size, posture
- Tidal volume (V_T)
  - 500mL
  - Air volume inspired, expired during quiet breathing
- Inspiratory reserve volume
  - Maximum volume inhaled air above V_T = 3L
- Expiratory reserve volume
  - Maximum expired air volume below V_T = 1.2L
- Residual volume (RV)
  - Air remaining in lungs after forced expiration = 1.2L (not measured by spirometry)
- Functional residual capacity (FRC)
  - Expiratory reserve volume (ERV) + RV = 2.4L
- VT + inspiratory reserve volume = 3.5L
- Vital capacity (V_C)
  - V_T + inspiratory reserve volume (IRV) + ERV = 4.7L
- Total lung capacity (TLC)
  - Combination of all lung capacities = 5.9L

MEASURING FRC

Helium dilution method

- Helium placed in spirometer → inhaled
- Helium concentration in lungs equalizes with amount of helium placed in spirometer (helium insoluble in blood) after few breaths
- Total helium mass measured in spirometer = FRC

Body plethysmograph method

- Application of Boyle's law (P X V = k)
- Person sits inside plethysmograph (airtight box) → breathes in/out through mouthpiece → measures air pressure in mouth
- Mouthpiece closed after expiring V_T; as person attempts to breathe FRC calculated using measurements of alveolar pressure, lung volume, pressure changes within plethysmograph

ANATOMIC & PHYSIOLOGIC DEAD SPACE

osms.it/anatomic-physiologic-dead-space

- *Dead space:* air volume enters airways, lungs; no gas exchange occurs

ANATOMIC DEAD SPACE

- Air inaccessible to body for gas exchange (due to anatomical structure)
- Air contained in conducting zone (nose → terminal bronchioles)
- Conduit for air movement in/out of lungs; warms, humidifies air; removes debris, pathogens
- Volume = 150mL (⅓ of tidal volume)

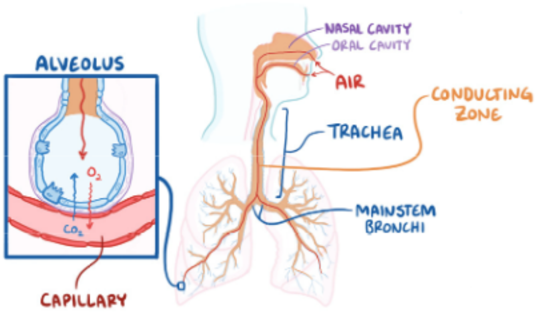


Figure 68.1 The volume of air contained in the conducting zone is called anatomic dead space because no gas exchange occurs here; therefore, no oxygen can be extracted from this air.

PHYSIOLOGIC DEAD SPACE

- Air physiologically inaccessible to body for gas exchange
- *Composition:* anatomic dead space + dead space in respiratory zone (respiratory bronchioles, alveolar duct, alveolar sac, alveoli) that does not partake in gas exchange
  - *Ventilation/perfusion defect:* alveoli ventilated, not well perfused (alveolar dead space)
- Volume = approx. 0 (in healthy adult)
  - Anatomic dead space = physiologic dead space

$$V_T = V_D + V_A$$

  - V_T = tidal volume
  - V_D = physiological dead space volume
  - V_A = air volume present in functioning alveoli

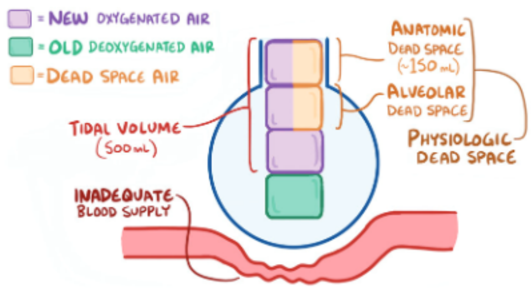


Figure 68.2 The green block represents residual air from the previous inhalation that participated in gas exchange. The purple blocks represent new oxygenated tidal volume inhaled during the current breath. Some of this new air also ends up being dead space air ("alveolar dead space") due to an inadequate blood supply to the alveolus.

Physiological dead space volume (Bohr equation)

- Assumptions
  - Environmental air CO_2 = 0 (actual amount ≅ 0.04%)
  - Dead space CO_2 contribution = 0
  - All CO_2 in exhaled air comes from functioning alveoli
- V_D = V_T x arterial CO_2 partial pressure ($PaCO_2$) - expired CO_2 partial pressure ($PeCO_2$) ÷ $PaCO_2$

$$V_D = V_T \times \frac{Pa_{CO_2} - Pe_{CO_2}}{Pa_{CO_2}}$$

VENTILATION

osms.it/ventilation

- Air movement between environment, lungs
- *Ventilation rates:* measure air volume moving in/out of lungs over period of time

MINUTE VENTILATION (V_E)

- V_E = amount of air moved in/out of lungs in one minute; does not factor in physiological dead space

$$V_E = (VT) \times (\text{Respiratory Rate/RR})$$
$$V_E = 500\text{mL} \times 15/\text{minute} = 7.5\text{L/minute}$$

ALVEOLAR VENTILATION (V_A)

- V_A = V_E corrected for physiological dead space

$$V_A = (VT - VD) \times RR$$
$$V_A = (500\text{ mL} - 150\text{mL}) \times 15 = 5.2\text{L/minute}$$

- V_A without measuring dead space
    - V_A = volume of CO_2 (V_{CO2}) ÷ fraction CO_2 (F_{CO2})

$$VA = (V_{CO2}) / (F_{CO2})$$

- *Partial pressure:* proportional to fractional concentration of that gas in mixture; based on constant K
    - Assumes gases are saturated with water vapor (normal body temperature, sea-level atmospheric pressure)
    - CO_2 partial pressure in alveolar air: $P_{CO2} = F_{CO2} \times K$
    - Alveolar ventilation equation: $V_A = [(V_{CO2}) / (P_{CO2})] \times K$
    - Replacing P_{CO2} with $_{CO2}$ pressure in arterial blood (Pa_{CO2}) in alveolar equation
    - Inverse relationship between alveolar ventilation, CO_2 partial pressure in alveolar air, pulmonary arteries (e.g. ↑ air ventilating the alveoli → ↓ CO_2 in blood, vice versa)

$$V_A = \frac{V_{CO_2} \times K}{P_{ACO_2}}$$

ALVEOLAR GAS EQUATION

osms.it/alveolar-gas-equation

- Pressure in alveoli = atmospheric pressure (P_{atm}); air in alveoli contains water vapor
- Alveolar pressure (P_{atm}) = water vapor pressure (P_{vapor}) + gas mixture pressure → total alveolar pressure exerted from all gases minus water vapor = P_{atm} - P_{vapor}
- O_2 partial pressure dissolved in blood (P_{aO2}) = CO_2 partial pressure in alveoli (P_{ACO2}) ÷ by R (respiratory quotient)

$$P_{aO2} = (P_{ACO2}) / R$$

- Partial pressure of O_2 inside alveolus (P_{AO2}) = partial pressure of inspired oxygen (P_{iO2}) minus partial pressure of oxygen going into blood (P_{aO2})

Partial pressure: gas particle mixture

- Gas' partial pressure proportional to fractional gas concentration in mixture
- Fractional CO_2 concentration (F_{CO2}) = 0.3
  - Accounts for 30% of gas molecules (F_{CO2} x total pressure of gas mixture P_{gases})
- Fractional concentration of O_2 (F_{O2}) = 0.7
  - Accounts for remaining 70% (F_{O2} x total pressure of gas mixture P_{gases})
- Pressure exerted by O_2 > pressure exerted by CO_2 (proportional to fractional concentrations)
  - If P_{gases} = 20mmHg; partial pressure of O_2 = 14mmHg (0.7 x 20); partial pressure of CO_2 = 6mmHg (0.3 x 20)
  - Partial pressure of inspired air (P_{iO2}), fractional oxygen concentration in inspired air (F_{iO2}), accounting for water vapor

$$P_{iO2} = F_{iO2} \times (P_{atm} - P_{vapor})$$

Alveolar gas equation

- Relationship between O_2 partial pressure inside alveolus to CO_2 partial pressure in alveolus

$$P_{AO2} = [F_{iO2} \times (P_{atm} - P_{vapor})] - [(P_{ACO2}) / R]$$
$$P_{AO2} = 150 - (1.25 \times P_{ACO2})$$

  - F_{iO2} = 0.21 (normal air = 21% O_2)
  - Atmospheric pressure = 760mmHg
  - Water vapor pressure i = 47mmHg
  - R = 0.8

COMPLIANCE OF LUNGS & CHEST WALL

osms.it/compliance-lungs-chest-wall

- Compliance measures how changes in pressure → lung volume change
- *Lung, chest wall compliance:* inversely correlated with elastic, "snap back" properties (elastance)
  - Compliance = ΔV/ΔP
  - Elastance = ΔP/ΔV
- ↑ compliance → lungs easier to fill with air
  - *Forces promoting open alveoli:* compliance, transmural pressure gradient, surfactant
- ↓ compliance → lungs harder to fill with air
  - *Forces promoting collapse of alveoli:* elastic recoil/elastance, alveolar surface tension

COMBINED PRESSURE-VOLUME CURVES FOR THE LUNG & CHEST WALL

osms.it/pressure-vol_curves_lung_chest_wall

- Pressure-volume relationship is curvilinear
- Volume at FRC (zero airway pressure)
  - *Lung inward recoil:* balanced with chest wall's tendency to expand outward (e.g. at equilibrium with no tendency to collapse/expand)
- Volume > FRC
  - Positive transmural pressure
  - ↑ lung recoiling force
  - ↓ chest wall outward force
- Volume < FRC (forced expiration)
  - Negative transmural pressure
  - ↓ lung recoiling force
  - ↑ chest wall outward force
- Pressure-volume curves plotted on graph
  - *X-axis:* pressure
  - *Y axis:* volume
  - Slope of curve = compliance
- Curve flattens out when lung, chest wall compliance combined
- *Hysteresis:* compliance for inspiration, expiration are different → slopes will be different

ALVEOLAR SURFACE TENSION & SURFACTANT

osms.it/alveolar-surface-tension-surfactant

- Alveoli lined with fluid film; water tends to form spheres (e.g. drops)
  - Due to intrinsic surface tension (caused by attraction of water molecules to each other)
- Surface tension creates pressure → pulls alveoli closed → collapses into sphere → ↓ gas exchange
- *Law of Laplace:* pressure that promotes lungs' collapse is (1) directly proportional to surface tension, (2) inversely proportional to alveoli radius

$$P = 2T/r$$

  - P = pressure on alveolus
  - T = surface tension
  - r = alveolar radius
- Smaller alveolus (r = 1) → ↑ pressure
  - $P = 2 \times 50/1 = 100$
- Larger alveolus (r = 2) → ↓ pressure
  - $P = 2 \times 50/2 = 50$
- Alveoli are small (allows ↑ surface area relative to volume), so have ↑ collapsing pressure

SURFACTANT

- ↓ collapsing pressure in alveoli → ↑ gas exchange, ↑ lung compliance, ↓ work of breathing
  - Lipoprotein mixture primarily containing dipalmitoyl phosphatidylcholine (DPPC)
  - Synthesized by type II pneumocytes, coats inside of alveoli

- Contains both hydrophilic, hydrophobic group (amphipathic nature)—intermolecular forces produced by repelling hydrophobic groups, attracting hydrophilic groups → ↓ surface tension, collapsing pressure

AIRFLOW, PRESSURE, & RESISTANCE

osms.it/airflow-pressure-resistance

AIR FLOW & PRESSURE

- Airflow in lungs determined by Ohm's law
  - Air flow directly proportional to pressure difference between alveoli, mouth/nose; inversely proportional to airway resistance

$$Q = \Delta P/R$$

  - Q = air flow
  - ΔP = change in pressure
  - R = resistance
- Pressure gradient
  - Driving force for air flow
  - Diaphragm contracts during inspiration → creates pressure gradient (↑ lung volume, ↓ alveolar pressure) → air flows into lungs

RESISTANCE

Poiseuille's law

- Resistance in lungs determined by Poiseuille's law
  - Air flow directly proportional to resistance along airway

$$R = \frac{8nl}{\pi r^4}$$

  - R = resistance
  - n = gas viscosity
  - l = length of airway
  - $\pi r4$ = flow is related exponentially to airway's radius
- Highlights critical importance of airway diameter on airflow
  - E.g. if airway radius ↓ by a factor of 2 → ↑ resistance by 24 (16-fold)

Resistance changes

- Parasympathetic muscarinic receptor stimulation → bronchial smooth muscle constriction → ↓ airway diameter → ↓ airflow; sympathetic stimulation of β2 receptors → bronchial smooth muscle relaxation → ↑ airway diameter → ↑ airflow
- ↓ lung volume → ↑ resistance; ↑ lung volume → ↓ resistance
- ↑ viscosity (e.g. deep sea diving) → ↑ resistance; ↓ viscosity (e.g. inhaling helium) → ↓ resistance

BREATHING CYCLE

osms.it/breathing-cycle

- Normal, quiet breathing phases
  - Rest (period between breaths), inspiration, expiration
- Involves changes in air volume, intrapleural pressure, alveolar pressure
- Affected by respiratory system's resistance, compliance

Rest

- Alveolar pressure (P_{alv}) = atmospheric pressure (P_{atm}) = 0
- No air movement in/out of lungs
  - Due to pressure gradient's absence
- Air volume in lungs = FRV
- Intrapleural pressure = -0.5cm0.2in H_2O
  - Transmural pressure gradient (intrapleural pressure always less than alveolar pressure) keeps lungs inflated
- Diaphragm relaxed

Inspiration

- Active process (requires muscle activity)
- Diaphragm (major inspiratory muscle; innervated by phrenic nerve) contracts, moves downward; external intercostal muscles contract (innervated by intercostal nerves) contract, elevate ribs outward, upward → enlarge thoracic cavity → ↑ lung volume → ↓ pressure in lungs (P_{alv} = -1cm/0.39in H_2O)
  - *Boyle's law (P = k/V)*: gas pressure (P) in container (thorax, alveoli) at constant temperature (k) inversely proportional to volume (V)
- Pressure gradient causes air to flow into lungs until $P_{alv} = P_{atm}$ at inspiration's end
- Volume in lungs = FRC + VT
- Intrapleural pressure = -8cm/3.1in H_2O at expiration's end

Expiration

- Passive process
- Elastic forces of lungs compress alveolar air volume → ↑ pressure in lungs → $P_{alv} > P_{atm}$ → pressure gradient causes air to flow out of lungs until $P_{alv} = P_{atm}$ at inspiration's end
- Diaphragm, external intercostal muscles relax → ↓ thoracic cavity size → ↓ lung volume → ↑ pressure in lungs
- V_T expired → lung volume = FRC

NOTES
BREATHING REGULATION

BREATHING CONTROL

osms.it/breathing-control

WHAT IS BREATHING CONTROL?

- *Breathing (ventilation):* movement of gasses in, out of lungs
- Regulation maintains arterial partial pressures of O_2, CO_2 (PaO_2, $PaCO_2$)
- *Components:* brainstem respiratory centers; peripheral, central chemoreceptors; mechanoreceptors in lungs, muscles of respiration, joints

BRAINSTEM RESPIRATORY CENTERS

Dorsal respiratory group (DRG)

- Inspiratory center, located in dorsal medulla
- Sets basic rhythm of breathing
- Receives sensory input via cranial nerves (CN) IX, X from peripheral chemoreceptors, mechanoreceptors in lungs → sends motor output via phrenic nerve to stimulate contraction of diaphragm
  - DRG neurons generate repeating bursts of action potentials → period of quiescence
  - Bursts occur → action potential frequency "ramps up" → ↑ lung volume

Ventral respiratory group (VRG)

- Expiratory center, located in ventral medulla
- Inactive during basic, quiet breathing
- Provides high respiratory drive when ventilation needs to increase (e.g. exercise)

Pneumotaxic center

- Located in upper pons
- Limits inspiration by inhibiting DRG
- Limits tidal volume, increases respiratory rate
- Receives input from cerebral cortex

Apneustic center

- Located in lower pons
- Prolongs DRG inspiratory signal, diaphragm contraction → inspiratory gasps (apneusis)
- Associated with damage to pons/upper medulla

VOLUNTARY CONTROL

Cerebral cortex

- Sends commands to voluntarily override autonomic control of ventilation
- Hyperventilation
  - Voluntarily breathing at rate > that needed by metabolism
  - *Self-limiting:* hyperventilation → ↓ $PaCO_2$ (strongly inhibits autonomic respiratory centers, ventilation)
- Hypoventilation
  - Voluntarily breathing at rate insufficient for metabolism
  - *Self-limiting:* hypoventilation → ↓ PaO_2, ↑ $PaCO_2$

HYPOTHALAMIC CONTROL

- *Strong emotions, pain:* act via hypothalamus, limbic system → signal respiratory centers → modify respiratory rate, depth
- Rise in body temperature → ↑ respiratory rate
- Drop in body temperature → ↓ respiratory rate

PULMONARY CHEMORECEPTORS & MECHANORECEPTORS

osms.it/pulmonary-central-peripheral-chemoreceptors

CENTRAL CHEMORECEPTORS

- Located in ventral surface of medulla
- Sensitive to changes in H^+ indirectly by sensing acute changes in $PaCO_2$ (unable to cross blood-brain barrier)
  - ↑ $PaCO_2$ → conversion to carbonic acid (H_2CO_3) by enzyme carbonic anhydrase → dissociation into H^+, HCO_3^- → ↓ CSF pH (↑ CSF [H^+]) → stimulates central chemoreceptors → stimulates DRG → ↑ ventilation → ↓ $PaCO_2$ (40mmHg)
- Crucial minute-to-minute control
  - Match ventilation with metabolism by monitoring $PaCO_2$

PERIPHERAL CHEMORECEPTORS

- Located in carotid bodies at bifurcation (near aortic arch)
- Responds directly to changes in PaO_2, $PaCO_2$
  - Strongly stimulated in linear fashion when $PaO_2 < 60$mmHg
  - Weakly stimulated by ↑ $PaCO_2$
  - Carotid bodies only: stimulated by ↑ arterial [H^+]
- Afferents send information to DRG via CN IX, X → directs ventilatory response to hypoxemia, acidemia, alkalemia

MECHANORECEPTORS

Lung stretch receptors

- Located in airway smooth muscle
- Respond to lung inflation → termination of inspiration (Hering–Breuer inspiratory-inhibitory reflex)

Joint and muscle receptors

- Respond to bodily movement → ↑ respiratory rate

Irritant receptors

- Respond to noxious gasses; particulates via CN X → coughing, bronchoconstriction

Juxtacapillary (J) receptors

- Located in alveoli, near capillaries
- Respond to capillary engorgement → ↑ respiratory rate

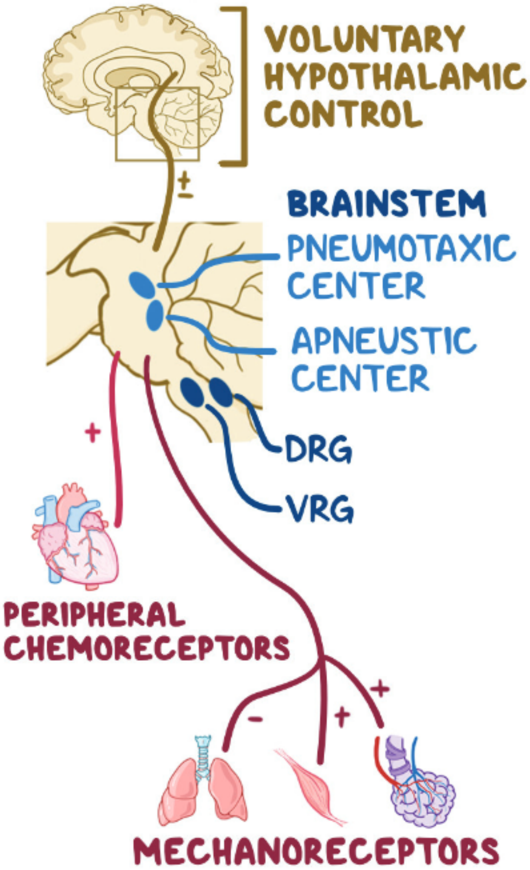
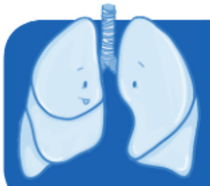


Figure 69.1 The brainstem is the respiratory center of the body. Many receptors throughout the body send signals to the brainstem so that it can regulate the breathing rate accordingly.



NOTES
GAS EXCHANGE

GAS EXCHANGE & LAWS

- Diffusion of oxygen (O_2), carbon dioxide (CO_2) in lungs, peripheral tissues
- Alveolar O_2 from inhaled gas → pulmonary capillary blood → circulation → tissue capillaries → cells
- CO_2 from cells → tissue capillaries → circulation → pulmonary capillary blood → CO_2 for exhalation from alveoli
- Gas exchange, gas behavior in solution is governed by fundamental physical gas properties → represented by gas laws

FORMS OF GAS IN SOLUTION

Dissolved gas

- All gas in solution are to some extent carried in a freely dissolved form
- For given partial pressure, the higher the solubility of a gas, the higher the concentration in solution
- In solution only dissolved gas molecules contribute to partial pressure
- Of the gases inspired as air, only nitrogen is exclusively carried in dissolved form

Bound gas

- O_2, CO_2, CO are bound to proteins in blood
- O_2, CO_2, CO can all bind to hemoglobin
- CO_2 also binds to plasma proteins

Chemically modified gas

- The ready back and forth conversion of CO_2 to bicarbonate (HCO_3^-) in presence of enzyme carbonic anhydrase allows CO_2 to contribute to gas equilibria despite chemical conversion
- Majority of CO_2 in blood carried as HCO_3^-

IDEAL (GENERAL) GAS LAW

osms.it/ideal-gas-law

- Relates multiple variables to describe state of a hypothetical "ideal gas" under various conditions
  - *Ideal gas:* theoretical gas composed of many randomly moving point particles whose only interactions are perfectly elastic collisions
  - All gas laws can be derived from general gas law
- PV = nRT
  - P = Pressure (millimeters of mercury (mmHg)
  - V = Volume (liters (L)
  - n = Moles (mol)
  - R = Gas constant (8.314 J/mol)
  - T = Temperature (Kelvin [K])
- *In gas phase:* body temperature, pressure (BTPS) used
  - T = 37°C/98.6°F/310K
  - P = Ambient pressure
  - Gas is saturated with water vapor (47mmHg)
- *In liquid phase/solution:* standard temperature, pressure (STPD) used
  - T = 0°C/32°F/273K
  - P = 760mmHg
  - Dry gas (no humidity)
- Ideal gas law can be used to interconvert between properties of same gas under BTPS, STPD conditions
  - E.g. gas volume (V_1) at BTPS → gas volume at STPD (V_2)

$$V_2 = V_1 \times \frac{T_1}{T_2} \times \frac{P_1 - P_{w1}}{P_2 - P_{w2}}$$

$$V_2 = V_1 \times \frac{273}{310} \times \frac{760 - 47}{760 - 0}$$

$$V_2 = V_1 \times 0.826$$

BOYLE'S LAW

osms.it/Boyles-law

- Describes how pressure of gas ↑ as container volume ↓
- $P_1V_1 = P_2V_2$
- For gas at given temperature, the product of pressure, volume is constant
- Inspiration → diaphragm contraction → ↑ lung volume
- If PV constant + lung volume ↑ → pressure ↓
- Pressure ↓ → disequilibrium between room, lung air pressures → air fills lungs to equalize pressure

DALTON'S LAW

osms.it/Daltons-law

- Total pressure exerted by gaseous mixture = sum of all partial pressures of gases in mixture → partial pressure of gas in gaseous mixture = pressure exerted by that gas if it occupied total volume of container
- $P_x = P_B \times F$
  - Px = partial pressure of gas (mmHg)
  - P_B = barometric pressure (mmHg)
  - F = fractional concentration of gas (no unit)
- Partial pressure = total pressure X fractional concentration of dry gas
- For humidified gases
  - $P_x = (P_B - P_{H2O}) \times F$
  - P_{H2O} = Water vapor pressure at 37°C/98.6°F (47mmHg)
  - If the sum of partial pressures in a mixture = total pressure of mixture → barometric pressure (P_B) is sum of the partial pressures of O_2, CO_2, N_2 (nitrogen), and H_2O
  - At barometric pressure (760 mmHg) composition of humidified air is O_2, 21%; N_2, 79%; CO_2, 0%
  - Within airways, air is humidified thus water vapor pressure is obligatory = to 47mmHg at 37°C/98.6°F

HENRY'S LAW

osms.it/Henrys-law

- For concentrations of dissolved gases
- When gas is in contact with liquid → gas dissolves in proportion to its partial pressure → greater concentration of a particular gas, in gas phase → more dissolves into solution at faster rate
    - $C_x = P_x$ x Solubility
    - C_x = concentration of dissolved gas (mL gas / 100mL blood)
    - Concentration of gas in solution only applies to dissolved gas that is free in solution
    - Concentration of gas in solution does not include any gas that is presently bound to any other dissolved substances (e.g. plasma proteins/ hemoglobin)
    - P_x = partial pressure of gas (mmHg)
    - Solubility = solubility of gas in blood (mL gas / 100mL blood per mmHg)
- Henry's law governs gases dissolved within solution (e.g. O_2, CO_2 dissolved in blood)
- To calculate gas concentration in liquid phase
    - Partial pressure of gas in gas phase → partial pressure in liquid phase → concentration in liquid
    - Partial pressure of gas in liquid phase (at equilibrium) = partial pressure of gas in gaseous phase
    - If alveolar air has PO_2 of 100mmHg → PO_2 of capillary blood that equilibrates with alveolar air = 100mmHg

HYPERBARIC CHAMBERS

- Hyperbaric chambers employ Henry's law
    - Contain O_2 gas pressurized to above 1 atm → greater than normal amounts of O_2 forced into the blood of the enclosed individual
    - Used to treat carbon monoxide poisoning, gas gangrene due to anaerobic organisms (cannot live in presence of high concentrations of O_2), improve oxygenation of skin grafts, etc.

FICK'S LAWS OF DIFFUSION

osms.it/Ficks-law-of-diffusion

- Describes diffusion of gases

$$V_x = \frac{DA\Delta P}{\Delta x}$$

- V_x = volume of gas transferred per unit time
- D = gas diffusion coefficient
- A = surface area
- ΔP = partial pressure difference of gas
- Δx = membrane thickness

- Driving force of gas diffusion is difference in partial pressures of gas (ΔP) across membrane (not the concentration difference)
    - If P_{O2} of alveolar air = 100mmHg
    - P_{O2} of mixed venous blood entering pulmonary capillary = 40mmHg
    - Driving force across membrane is 60mmHg (100mmHg - 40mmHg)
- Diffusion coefficient of gas (D) is a combination of usual diffusion coefficient (dependent on molecular weight) and gas solubility
- Diffusion coefficient dramatically affects

diffusion rate, e.g. diffusion coefficient for CO_2 is approximately 20x greater than that of O_2 → for a given partial pressure difference CO_2 would diffuse across the same membrane 20x faster than O_2

LUNG DIFFUSION CAPACITY (DL)

- A functional measurement which takes into account
  - Diffusion coefficient of gas used
  - Membrane surface area
  - Membrane thickness
  - Time required for gas to combine with proteins in pulmonary capillary blood (e.g. hemoglobin)
- Measured using carbon monoxide (CO) → CO transfer across alveolar-capillary barrier exclusively limited by diffusion process
- Lung diffusion capacity of carbon monoxide (DL_{CO}) is measured using a single breath
  - Individual breathes a mixture of gases with a low CO concentration → rate of CO disappearance is predictable in different disease states
  - Emphysema → destruction of alveoli → decreased surface area for gas exchange → decreased DL_{CO}
  - Fibrosis/pulmonary edema → increase in membrane thickness (via fluid accumulation in the case of edema) → decreased DL_{CO}
  - Anemia → reduced hemoglobin → reduced protein binding in a given time period → decreased DL_{CO}
  - Exercise → increased utilization of lung capacity, increased recruitment of pulmonary capillaries → increased DL_{CO}

GRAHAM'S LAW

osms.it/Grahams-law

- Diffusion rate of gas through porous membranes varies inversely with the square root of its density
- To compare rate of effusion (movement through porous membrane) of two gases → velocity of molecules determine the rate of spread
- Kinetic temperature in kelvin of a gas is directly proportional to average kinetic energy of gas molecules → at the same temperature, molecule of heavier gas will have a slower velocity than those of lighter gas
  - Kinetic energy = ½mv2
  - $\frac{1}{2}m_1v_1^2 = \frac{1}{2}m_2v_2^2$
  - $v_1^2 / v_2^2 = m_2 / m_1$
  - $v_1 / v_2 = \sqrt{(m_2 / m_1)}$
  - Which can be rewritten to give Graham's law

$$\frac{Rate_1}{Rate_2} = \sqrt{\frac{M_2}{M_1}}$$

GAS EXCHANGE IN THE LUNGS

osms.it/gas-exchange-in-lungs

PULMONARY GAS EXCHANGE

- AKA external respiration
- Pulmonary capillaries perfused with blood from right heart (deoxygenated)
- Gas exchange occurs between pulmonary capillary, alveolar gas
  - Room air → inspired air → humidified tracheal air → alveoli
  - O_2 diffuses from alveolar gas → pulmonary capillary blood
  - CO_2 diffuses from pulmonary capillary blood → alveolar gas
  - Blood exits the lungs → left heart → systemic circulation

Dry inspired air

- P_{O2} is approximately 160mmHg
  - Barometric pressure x fractional concentration of O_2 (21%)
  - P_{O2} = 760mmHg x 0.21
  - Assume no CO_2 in dry inspired air

Humidified tracheal air

- P_{O2} of humidified tracheal air is 150mmHg
  - Air is fully saturated with water vapor → "dilution" of partial pressures → calculations must correct for water vapor pressure (subtracted from barometric pressure)
  - At 37°C/98.6°F, P_{H2O} is 47mmHg
  - P_{O2} = (760mmHg − 47mmHg) x 0.21
  - Assume no CO_2 in humidified inspired air

Alveolar air

- Pressures of alveolar gas designated "PA"
- Alveolar gas exchange in lungs sees a drop in O_2 partial pressure, increase in CO_2 partial pressure
- PA_{O2} = 100mmHg
- PA_{CO2} = 40mmHg
- Amount of these gases entering/leaving alveoli correspond to physiological body needs (i.e. O_2 consumption, CO_2 production)

Pulmonary capillaries

- Blood entering pulmonary capillaries is mixed venous blood
- Tissues (metabolic activity alters composition of blood) → venous vasculature → right heart → pulmonary circulation
- P_{O2} = 40mmHg
- P_{CO2} = 46mmHg

Systemic arterial blood (oxygenated)

- Gas partial pressures of systemic arterial blood designated "Pa"
- In a healthy individual, diffusion of gas across alveolar, capillary membrane is so rapid that we can assume equilibrium is achieved between alveolar gases, pulmonary capillaries → P_{O2} and P_{CO2} of blood leaving pulmonary capillaries = alveolar air
- $PA_{O2} = Pa_{O2}$ = 100mmHg
- $PA_{CO2} = Pa_{CO2}$ = 40mmHg
- This blood enters systemic circulation to eventually return to lungs

Physiological shunt

- Small fraction of pulmonary blood flow bypasses alveoli → physiological shunt → blood not arterialized → systemic blood has slightly lower P_{O2} than alveolar air
- Shunting occurs due to
  - Coronary venous blood, drains directly into left ventricle
  - Bronchial blood flow
- Shunting may be increased in various pathologies → ventilation-perfusion defects/mismatches
- As shunt size increases → alveolar gas, pulmonary capillary blood do not equilibrate → blood is not fully arterialized
- *A-a difference:* difference in P_{O2} between alveolar gas (A), systemic arterial blood (a)
  - Physiological shunting → negligible/small differences
  - Pathology → notably increased difference

FACTORS AFFECTING EXTERNAL RESPIRATION

Thickness of respiratory membrane

- In healthy lungs, respiratory membrane → 0.5–1 micrometer thick
- Presence of small amounts of fluid (left heart failure, pneumonia) → significant loss of efficiency, equilibration time dramatically increases → the 0.75 seconds blood cells spend in transit through pulmonary circulation may not be sufficient

Surface area of respiratory membrane

- Greater surface area of respiratory membrane → greater amount of gas exchange
- Healthy adult male lungs have surface area of $90m^2$
- Pulmonary diseases (e.g. emphysema) → walls of alveoli break down → alveolar chambers enlarge → loss of surface area
- Tumors/pneumonia → prevent gas from occupying all available lung → loss of surface area

Partial pressure gradients and gas solubilities

- Partial pressures of O_2, CO_2 drive diffusion of these gases across respiratory membrane
- Steep O_2 partial pressure gradient exists
  - PO_2 of deoxygenated blood in pulmonary arteries = 40mmHg
  - PO_2 of 104mmHg in alveoli
  - O_2 diffuses rapidly from alveoli into pulmonary capillary blood
- O_2 equilibrium (PO_2 of 104mmHg on both sides of respiratory membrane) occurs in around 0.25 seconds of transit through lungs (about ⅓ of the time available)
- CO_2 has smaller gradient → 5mmHg (45mmHg vs 40mmHg), although pressure gradient for O_2 is much steeper than for CO_2, CO_2 is 20x more soluble in plasma, alveolar fluid than O2 → equal amounts of gas exchanged

Ventilation-perfusion coupling

- *Ventilation:* amount of gas reaching alveoli
- *Perfusion:* amount of blood flow in pulmonary capillaries
- These are regulated by local autoregulatory mechanisms → continuously respond to local conditions → some control in blood flow around lungs
- Arteriolar diameter controlled by P_{O2}
  - If alveolar ventilation is inadequate → blood taking O_2 away faster than ventilation can replenish it → low local P_{O2} → terminal arteriole restriction → blood redirected to respiratory areas with high P_{O2}, oxygen pickup more efficient
  - In alveoli where ventilation is maximal → high P_{O2} → pulmonary arteriole dilation → blood flow into pulmonary arterioles increases
  - Pulmonary vascular muscle autoregulation is opposite of that in systemic circulation
- Bronchiolar diameter controlled by P_{CO2}
  - Bronchioles connecting areas where PA_{CO2} high → dilation → allows CO_2 to be eliminated from body
  - Those with low CO_2 → constrict
- Independent autoregulation of arterioles, bronchioles → matched perfusion, ventilation
- Ventilation-perfusion matching is imperfect
  - Gravity → regional variation in blood, air flow (apices have greater ventilation but lesser perfusion, bases have greater perfusion, lesser ventilation)
  - Occasionally alveolar ducts may be plugged with mucus → unventilated areas

INTERNAL RESPIRATION

- Capillary gas exchange in body tissue
- Partial pressures, diffusion gradients are reversed from lungs however physical laws governing the exchanges remain identical
- Cells in body continuously use O_2, produce CO_2
  - PO_2 always lower in tissue than arterial blood (40mmHg vs 100mmHg) → O_2 moves rapidly from blood → tissues until equilibrated
  - CO_2 moves rapidly down its pressure gradient (P_{CO2} of 40mmHg in fresh blood arriving at capillary beds beds vs. P_{CO2} of 45mmHg in tissues) → venous blood → right heart

- Gas exchange at tissue level driven by partial pressures, occurs via simple diffusion

DIFFUSION-LIMITED & PERFUSION-LIMITED GAS EXCHANGE

osms.it/diffusion-limited-perfusion-limited-gas-exchange

Diffusion-limited gas exchange

- Diffusion is limiting factor determining total amount of gas transported across alveolar-capillary barrier
- As long as partial pressure gradient is maintained, diffusion continues
  - Gas readily diffuses across permeable membrane
  - Blood flow away from alveoli/chemical binding → partial pressure of gas on systemic end does not rise → partial pressure maintenance
  - Given a sufficiently long capillary bed diffusion will continue along entire length as equilibrium is not achieved
- Examples include
  - CO across alveolar-pulmonary capillary barrier
  - Oxygen during strenuous exercise/ emphysema/fibrosis

Perfusion-limited gas exchange

- Perfusion (blood flow) is the limiting factor determining total amount of gas transported across alveolar-capillary barrier
- Increasing blood flow → increasing amount gas transported; examples include
  - Nitrous oxide (N_2O): not bound in blood → entirely free in solution; PA_{N2O} is constant, Pa_{N2O} = zero at start of capillary → initial large A-a difference → because no N_2O binds to any other components of blood, all of it remains free in solution → partial pressure builds rapidly → rapid equilibration, most of capillary length does not participate in gas exchange; new blood must be supplied to partake in further gas exchange with alveolar N_2O → "perfusion-limited gas exchange"
  - O_2 at rest
  - CO_2

Limitations of O_2 transport

- Under physiological conditions O_2 transport into pulmonary capillaries → perfusion-limited
- Diseased or abnormal conditions → diffusion-limited
- Perfusion-limited O_2 transport
  - PA_{O2} is constant = 100mmHg
  - At beginning of capillary Pa_{O2} = 40mmHg (mixed venous blood) → large partial pressure gradient → drives diffusion
  - As O_2 diffuses into pulmonary capillary blood → increase in Pa_{O2}
  - Hemoglobin binds O_2 → resists increase in Pa_{O2} → initially gradient is maintained; eventually equilibrium is achieved → perfusion-limitation
  - Therefore pulmonary blood flow determines net O_2 transfer (changes in pulmonary blood flow will affect net O_2 transfer)

Diffusion-limited O_2 transport

- Fibrosis → thickening of alveolar walls → increased diffusion distance for O_2 (decreases DL) → slowed rate of diffusion → prevents equilibration → partial pressure gradient maintained along length of capillary
- Increasing capillary length allows for more time for equilibrium to occur → diffusion-limitation

O_2 transport at high altitude

- High altitude reduces barometric pressure → reduced partial pressures
- Reductions in Pa_{O2} → reduce oxygen amount available to diffuse into blood → reduced rate of equilibration at capillary → more time required for gas exchange, lower peak oxygen concentration reached once equilibrated

NOTES
GAS TRANSPORT

OXYGEN BINDING CAPACITY & OXYGEN CONTENT

osms.it/oxygen-binding-capacity-oxygen-content

MEASURES OF OXYGEN AVAILABILITY

O_2 binding capacity

- Maximum amount of O_2 bound to hemoglobin when 100% saturated (per blood volume)
  - More hemoglobin → more oxygen (per blood volume)
- Measurement
  - Expose blood to air with high P_{O2} → complete hemoglobin saturation
  - Hemoglobin's oxygen affinity → 1g of hemoglobin A binds 1.34mL of O_2
  - Normal hemoglobin A concentration in blood → 15g/100mL
  - O_2 binding capacity = hemoglobin concentration × hemoglobin's affinity for oxygen
- *Example:* O_2 binding capacity = 15g/100mL × 1.34mL O_2/g hemoglobin = 20.1mL O_2/100mL blood

Oxygen content (CaO_2)

- Oxygen (mL) per 100mL of blood
- CaO_2 = O_2 binding capacity × % saturation + oxygen dissolved in solution
  - Correction for dissolved O_2 → solubility of O_2 in blood → 0.003mL O_2/100mL blood per mmHg
- CaO_2 = hemoglobin concentration (g/100mL blood) × hemoglobin oxygen affinity (mL O_2/g) × SaO_2 (arterial oxygen saturation) + partial pressure of oxygen (mmHg) × solubility of O_2 in blood (mL O_2/blood/mmHg)
- CaO_2 (ml O_2/100mL blood) = ([Hb] × 1.34 × SaO_2) + (PaO_2 × 0.003)

O_2 DELIVERY TO TISSUES

- Dependent on blood flow (determined by cardiac output), blood's oxygen content
- O_2 delivery = cardiac output × oxygen content

OXYGEN TRANSPORT

- Majority of oxygen in blood bound to hemoglobin, remainder dissolved in solution

Dissolved O_2

- Free in solution (1.5% of total blood O_2 content)
- Only free O_2 contributes to partial pressure → drives O_2 diffusion
- O_2 solubility in blood = 0.003mL O_2/100mL blood per mmHg → at normal PaO_2 of 100mmHg → concentration of dissolved O_2 is 0.3mL O_2/100mL blood
- Normal consumption of O_2 = 250mL O_2/minute
- Only dissolved O_2 delivered to tissues (cardiac output 5L/min) × dissolved O_2 concentration → 15mL O_2/min → incompatible with life
- Hemoglobin increases amount of O_2 carried by blood

Hemoglobin bound

- Hemoglobin → greater concentrations of O_2 carried to tissues by blood
- 98.5% of O_2 in blood bound to hemoglobin

- Four subunits of hemoglobin molecule
  - *Each subunit contains heme moiety:* iron-binding porphyrin, polypeptide chain (alpha/beta)
  - *Adult hemoglobin subunits ($\alpha_2\beta_2$):* two alpha chains, two beta chains → each contains one iron molecule (Fe^{2+}) → binds one O_2 molecule → four molecules of O_2 per molecule of hemoglobin → oxyhemoglobin
  - Deoxygenated hemoglobin → deoxyhemoglobin

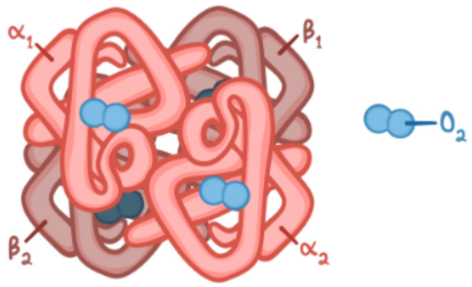


Figure 71.1 Each of the four hemoglobin subunits contains a heme group capable of binding one oxygen molecule.

- Heme binds oxygen in lungs → oxyhemoglobin
  - Oxygen diffuses from alveoli → across single cell thick alveolar walls → diffuses into blood → through red blood cell (RBC) membrane → interacts with heme → oxyhemoglobin (bright red blood)
- Oxygen binding to hemoglobin → conformational shift in heme structure → ↑ oxygen binding affinity → sigmoidal (S-shaped) oxygen-binding affinity/ dissociation curve
- *At tissue level:* association process reversed
  - O_2 released → deoxyhemoglobin (dark red blood)
  - 20% of dissolved CO_2 → binds with globin amino acids (not heme group) of deoxyhemoglobin → carbaminohemoglobin

Fetal oxygen transport

- Fetal blood requires higher affinity for oxygen to facilitate movement of O_2 from maternal to fetal blood
- Fetal variant hemoglobin (hemoglobin F)
  - Contains two alpha chains, two gamma chains ($\alpha_2\gamma_2$) → greater affinity for oxygen

OXYGEN-HEMOGLOBIN DISSOCIATION CURVE

osms.it/oxygen-hemoglobin_dissociation_curve

- Proportion of saturated hemoglobin plotted against partial pressure of oxygen
- Illustrates how blood carries, releases oxygen as partial pressures vary
  - *Hemoglobin:* primary oxygen transporter in blood
  - Amount of oxygen bound to hemoglobin at any given time determined by environmental partial pressure of oxygen (high in lungs, lower in tissue capillary beds) → hemoglobin binds to oxygen in lungs, releases at tissue level
  - *Oxyhemoglobin dissociation curve:* determined by hemoglobin affinity for oxygen; rate hemoglobin acquires, releases oxygen into surrounding fluid; plots SO_2 against PO_2

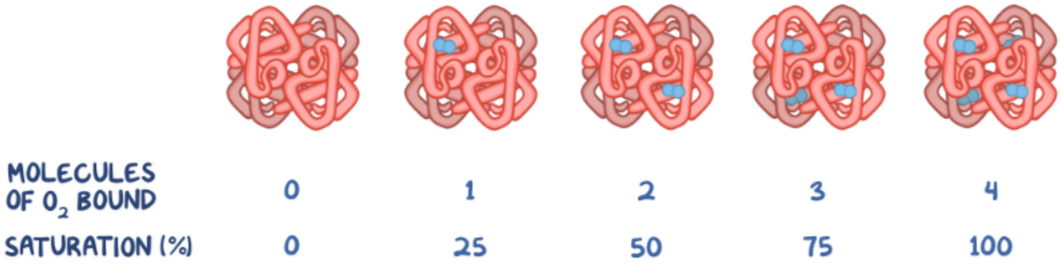


Figure 71.2 Each hemoglobin molecule can bind four O_2 molecules, but each hemoglobin isn't always 100% saturated, or bound, by O_2. A hemoglobin molecule with no O_2 bound (0% saturation) is called deoxyhemoglobin.

SIGMOIDAL SHAPE

- Oxyhemoglobin dissociation curve is sigmoidal
  - Positive cooperativity → each successive oxygen molecule binding to heme group → ↑ affinity
  - Approaches maximum saturation limit → few binding sites remain → little additional binding possible → curve levels off → large ↑ in oxygen partial pressure → no effect on hemoglobin saturation beyond saturation point
  - Partial pressures ↓ at tissue level → oxygen release → with each successive oxygen molecule release, subsequent release eases → rapid oxygen unloading at low partial pressures

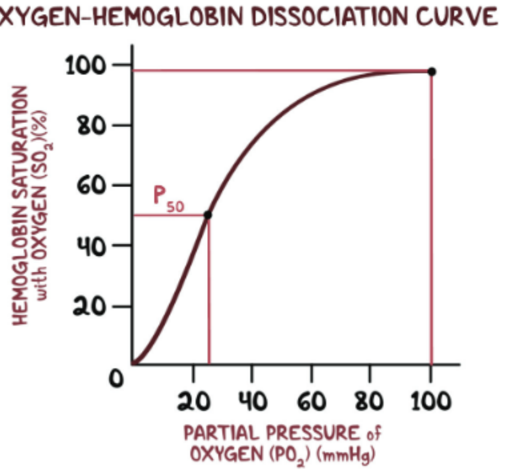


Figure 71.3 The oxygen-hemoglobin dissociation curve. O_2 saturation is influenced by the PO_2 of the blood. P_{50} indicates the partial pressure at which hemoglobin proteins are 50% saturated.

P_{50}

- P_{50}: partial pressure of oxygen in blood when hemoglobin 50% saturated (e.g. 26.6mmHg)
- Conventional measure of hemoglobin affinity for oxygen
- Physiological/disease processes may shift dissociation curve to left/right, alter P_{50}
  - Left shift → lower P_{50} → ↑ oxygen affinity
  - Right shift → raised P_{50} → ↓ oxygen affinity

RIGHT SHIFT

- Right shift → lower oxygen affinity → 50% saturation occurs at higher PO_2 → oxygen unloading

↑ PCO_2, ↓ pH

- ↑ metabolic activity of tissues → ↑ CO_2 → ↑ H^+ concentration → ↓ pH → ↓ hemoglobin oxygen affinity → oxygen unloading in metabolically active tissues
- Effect of PCO_2, pH on oxygen-hemoglobin dissociation curve → Bohr effect

↑ temperature

- Very metabolically active tissue (e.g. active muscle → ↑ heat production → ↓ hemoglobin oxygen affinity)

↑ 2,3-diphosphoglycerate (2,3-DPG) concentration

- 2,3-DPG (glycolysis byproduct) → binds deoxyhemoglobin beta chains → ↓ oxygen affinity → binds to hemoglobin beta chains → oxygen unloading
- 2,3-DPG production ↑ under hypoxic conditions (e.g. living at high altitude) →

hypoxemia → 2,3-DPG production in red blood cells → greater oxygen delivery to tissues

LEFT SHIFT

- Left shift → higher oxygen affinity → 50% saturation occurs at lower PO_2 → impairs oxygen unloading

↓ PCO_2, ↑ pH

- ↓ tissue metabolism → ↓ CO_2 production → ↓ H^+ concentration → ↑ pH → left shift → O_2 tightly bound to hemoglobin

↓ temperature

- ↓ tissue metabolism → ↓ heat production → ↓ O_2 unloading

↓ 2,3-DPG concentration

- ↓ tissue metabolism → ↓ 2,3-DPG concentration → ↓ O_2 unloading

Hemoglobin F

- Alternate molecular structure → ↑ oxygen affinity → left shift
- 2,3-DPG doesn't bind strongly to HbF gamma chains

Carbon monoxide (CO)

- Causes left shift, ↓ maximum saturation possible (curve levels off at lower PO_2)
- CO binds to hemoglobin with 250x affinity of O_2 (at partial pressure; 1/250 O_2, = O_2; CO bound to hemoglobin) → forms carboxyhemoglobin (longer-living molecule than oxyhemoglobin)
- CO binding to heme → confirmation shift → ↑ remaining heme molecules' affinity for oxygen (reducing oxygen release efficiency) → CO poisoning reduces blood's absolute oxygen-carrying capacity, impairs oxygen release → hypoxic injury

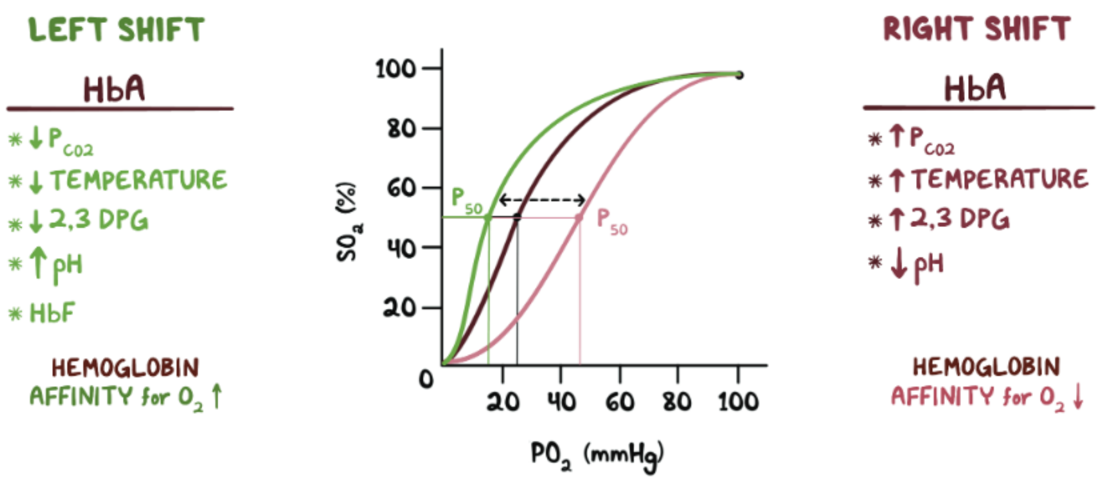


Figure 71.4 Summary of factors that can shift the oxygen-hemoglobin dissociation curve to the left (↑ hemoglobin's affinity for O_2) and to the right (↓ hemoglobin's affinity for O_2).

ERYTHROPOIETIN (EPO)

osms.it/erythropoietin

- Glycoprotein cytokine secreted by kidney (cellular hypoxia response) → stimulates erythropoiesis → RBCs

RENAL INDUCTION OF EPO SYNTHESIS

- ↓ O_2 delivery to kidneys (↓ hemoglobin concentration/PaO_2) → increased production of alpha subunit of hypoxia-inducible factor 1 (HIF1)
- Hypoxia-inducible factor 1-alpha (HIF1A) → acts on fibroblasts in renal cortex, medulla → upregulation of EPO messenger RNA (mRNA) → increased EPO synthesis
- EPO → promotes proerythroblast differentiation → mature to form erythrocytes (maturation not EPO-dependent)

RENAL SENSING OF HYPOXIA

- To effectively regulate EPO secretion, kidneys must distinguish between following:

Decreased blood flow

- → ↓ O_2 availability
  - ↓ renal blood flow → ↓ glomerular filtration → ↓ sodium (Na^+) filtration/reabsorption → ↓ O_2 consumption (Na^+ resorption closely linked to O_2 consumption in kidney)
  - O_2 delivery, consumption remain matched → EPO production not triggered

Decreased arterial blood O_2 content

- → ↓ O_2 availability
  - Renal blood flow remains normal → normal glomerular filtration → normal Na^+ filtration/reabsorption → reduced oxygen availability for given metabolic demand → stimulus for EPO secretion

CARBON DIOXIDE TRANSPORT IN BLOOD

osms.it/carbon-dioxide-transport-in-blood

- Carried as dissolved carbon dioxide (CO_2), carbaminohemoglobin (bound to hemoglobin), bicarbonate (HCO_3^-)

DISSOLVED CO_2

- Small fraction of CO_2 dissolved in blood (similar to oxygen)
- *Henry's law:* CO_2 concentration in blood = partial pressure x solubility of CO_2
- *Solubility:* 0.07mL CO_2/100mL blood per mmHg
- *Partial pressure:* 40mmHg
- Concentration = 2.8mL CO_2/100mL blood (5% of total CO_2 content of blood)

CARBAMINOHEMOGLOBIN

- CO_2 binds to terminal amino groups on proteins (e.g. albumin, hemoglobin)
- CO_2 bound to hemoglobin → carbaminohemoglobin (3% of total blood CO_2)
  - CO_2 binding to hemoglobin at different site than oxygen → conformational shift of protein structure → ↓ oxygen affinity

→ right shift in dissociation curve
  - Haldane effect: less O_2 bound to hemoglobin → ↑ CO_2 affinity

BICARBONATE

- 90% of CO_2 in blood
- *Tissue level:* CO_2 produced by aerobic metabolism → driven by partial pressure gradient → CO_2 diffuses across cell membrane, capillary wall → enters RBCs

RBC blood pH regulation

- RBCs regulate blood pH via interaction with CO_2 in blood
- RBCs contain enzyme, carbonic anhydrase → catalyzes conversion of CO_2, water → carbonic acid (also catalyzes reverse reaction)
- Carbonic acid dissociates into bicarbonate, hydrogen ion in blood
  - $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$
  - Mass action drives reaction to right as tissues continuously supply CO_2
- H_2CO_3 dissociates → H^+, HCO_3^-
- H^+ remains in RBCs → buffered by deoxyhemoglobin
  - If H^+ remains free in solution → acidifies RBCs, venous blood → H^+ must be buffered
  - H^+ buffered by deoxyhemoglobin, carried in venous blood (deoxyhemoglobin more efficient buffer than oxyhemoglobin)
  - H^+ production favors oxyhemoglobin conversion → deoxyhemoglobin (Bohr effect)
- HCO_3^- transported into plasma (exchanged for chloride)
  - Band 3 protein facilitates anion exchange of Cl^- for HCO_3^- (chloride shift)
  - HCO_3^- carried in plasma to lungs

Respiratory system blood pH regulation

- Respiratory system further regulates blood pH
  - Controls CO_2 elimination rate → CO_2 elimination ↑ pH by shifting equation to left
  - RBCs, carbonic anhydrase allow rapid reaction in lungs → reverse processes in blood at tissue level

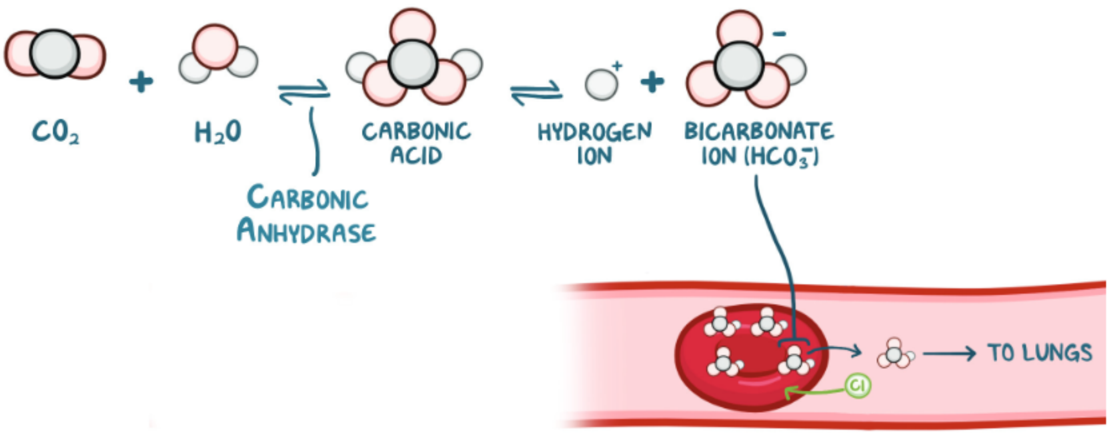


Figure 71.5 CO_2 transport in the form of bicarbonate. CO_2 undergoes a chemical reaction with H_2O to form carbonic acid, which then dissociates into hydrogen ions and bicarbonate ions. This reaction can occur in the plasma, but is sped up in red blood cells by the presence of carbonic anhydrase enzymes. Ionic exchange of bicarbonate ions and chloride occurs via facilitated diffusion to ensure charges stay balanced. Bicarbonate then travels to the lungs in the plasma.

REGULATION OF PULMONARY BLOOD FLOW

osms.it/pulmonary-blood-flow-regulation

- Regulated by altering arteriole resistance → controlled by arteriolar smooth muscle tone
- Regulatory changes mediated by local vasoactive substance concentrations

PULMONARY VASOACTIVE SUBSTANCES & STATES

Nitric oxide (NO)

- Retains similar function on pulmonary vascular beds (compared to systemic) → vasodilation
- Nitric oxide (NO) synthase inhibition → hypoxic vasoconstriction enhancement
- Inhaled NO → reduction in/prevention of hypoxic vasoconstriction

Thromboxane A_2

- Product of arachidonic acid metabolism via cyclooxygenase pathway (macrocytes, leukocytes, endothelial cells)
- Lung injury → potent vasoconstrictor of pulmonary arterioles, veins

Prostaglandin I_2 (prostacyclin)

- Product of arachidonic acid metabolism via cyclooxygenase pathway (endothelium)
- Potent local vasodilator

Leukotrienes

- Product of arachidonic acid metabolism via lipoxygenase pathway
- Potent airway constrictor

LUNG VOLUME

- Pulmonary blood vessels → alveolar capillaries that surround alveoli, extra-alveolar vessels which do not (arteries, veins)

Increased lung volume

- Crushes alveolar capillaries → ↑ resistance to blood flow
- Intrapleural pressure becomes more negative (↓ resistance) → pulls open extra alveolar vessels
- *Total pulmonary vascular resistance:* sum of alveolar, extra-alveolar resistance → increased lung volume effect dependent on larger effect
  - Low lung volumes (extra-alveolar vessels dominate) → ↑ volume → extra-alveolar vessels pulled open → ↓ resistance
  - High lung volume (alveolar capillaries dominate) → ↑ lung volume → alveolar vessels crushed, sharp ↑ resistance

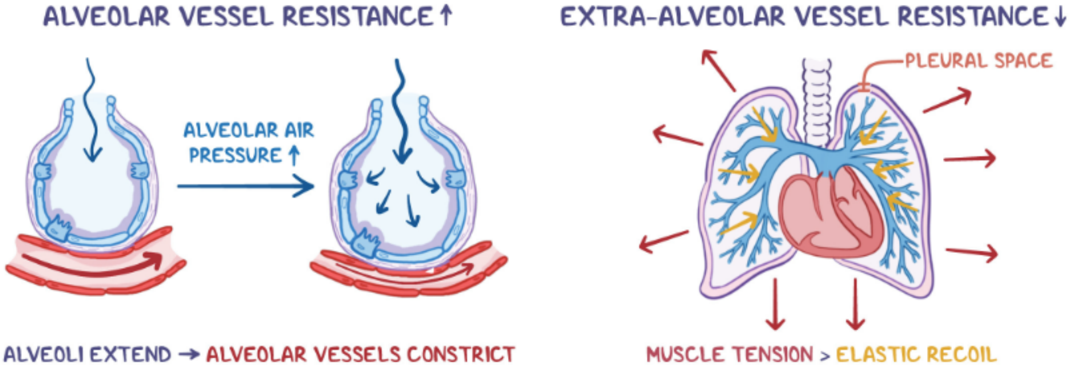


Figure 71.6 Blood vessel resistance associated with increased lung volume.

ZONES OF PULMONARY BLOOD FLOW

osms.it/zones-of-pulmonary-blood-flow

POSITIONAL EFFECT

- Supine gravitational effect largely uniform
- Upright distribution of blood flow (perfusion), ventilation throughout lungs not uniform
- Blood flow favors gravity-dependent lung regions → ↑ pulmonary arterial hydrostatic pressure moving inferiorly → blood flow in inferior (basal) regions > superior (apical) regions
- Ventilation favors apices → ventilation ↓ with move towards bases of lungs

LUNG ZONES

- Lungs divided into three vertical sections (based on pressure differences between compartments)

Zone I

- *Unobserved in healthy lung:* pulmonary arterial pressure (P_a) > alveolar pressure (P_A) in all parts of lung
- P_A generally = atmospheric pressure; can be overcome by low-pressure lung circulation
- Positive pressure ventilation → $P_A > P_a$ in apices of lung → blood vessels collapse → physiological dead space (ventilated, not perfused)

Zone II

- $P_a > P_A >$ pulmonary venous pressure (P_V)
- Capillary compression not problematic
- Perfusion driven by difference between P_a, P_A (not P_a, P_V; as in systemic vascular beds)

Zone III

- Majority of healthy lung volume
- No external resistance to blood flow
- Flow determined by P_a - P_V (both exceed P_A)

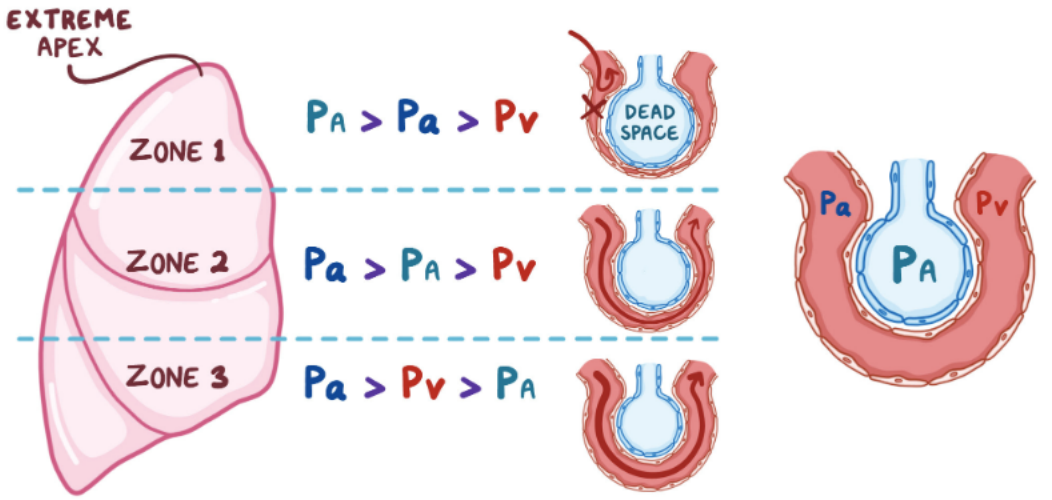


Figure 71.7 Relationships between P_A, P_a, and P_v in the three lung zones.

PULMONARY SHUNTS

osms.it/pulmonary-shunts

- Shunts occur when blood flow redirected from expected route, bypassing circulatory conduit

PHYSIOLOGICAL SHUNTS (ANATOMICALLY NORMAL)

- *Bronchial blood flow:* fraction of pulmonary blood which bypasses alveoli to supply bronchi
- *Coronary blood flow:* thebesian venous network allows for alternative myocardium drainage directly into left ventricle (not reoxygenated)

LEFT-TO-RIGHT SHUNTS

- More common
- Blood shunted from left to right heart
  - Due to septal defects (e.g. trauma, patent ductus arteriosus)
- Blood intended for systemic circulation directly circulated back to lungs → pulmonary blood flow exceeds systemic blood flow → fraction of blood does reach systemic circulation fully oxygenated → no hypoxia

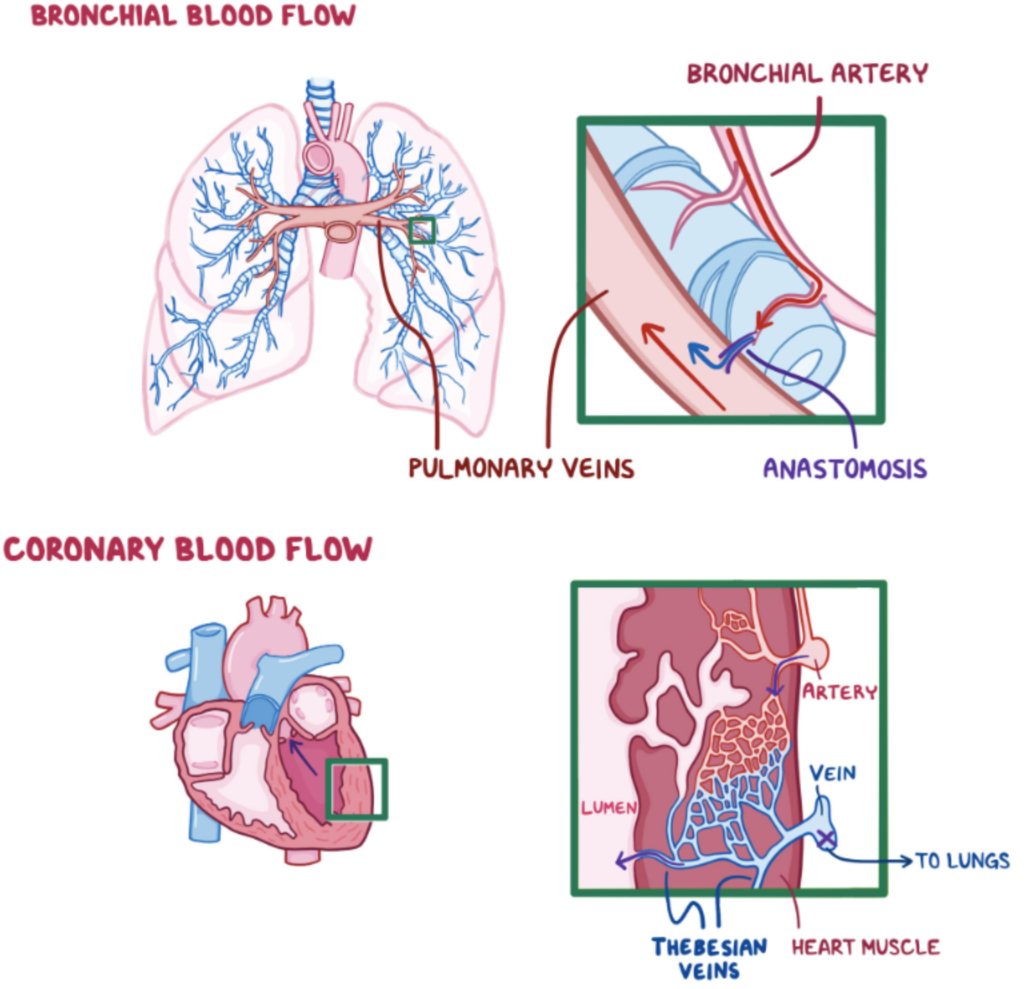


Figure 71.8 Physiologic shunts.

RIGHT-TO-LEFT SHUNTS

- Defect in wall between right, left sides of heart → blood shunted from right to left side of heart
- Allows for large cardiac output fraction to be shunted (approx. 50%) → bypasses lungs → oxygenated blood diluted with shunted deoxygenated blood → hypoxemia
- Not responsive to high P_{O2} gas treatment → complete pulmonary blood saturation doesn't improve shunted blood oxygenation
- Causes minimal Pa_{CO2} change → central chemoreceptors responsive to small Pa_{CO2} increases (shunted blood not available for gas exchange) → ↑ ventilation rate → extra CO_2 expired
- Central O_2 receptors significantly less sensitive than CO_2 receptors → only ↑ ventilation once Pa_{O2} < 60mmHg

Shunt fraction equation

- Oxygenation bypass of venous blood in lung capillaries
- $Q_S/Q_T = (C_{CO2} - C_{AO2})/(C_{CO2} - C_{VO2})$
- Q_S: blood flow through right-to-left shunt (L/min)
- Q_T: cardiac output (L/min)
- C_{CO2}: oxygen content of nonshunted pulmonary capillary blood
- C_{aO2}: oxygen content of systemic arterial blood
- C_{VO2}: oxygen content of venous blood

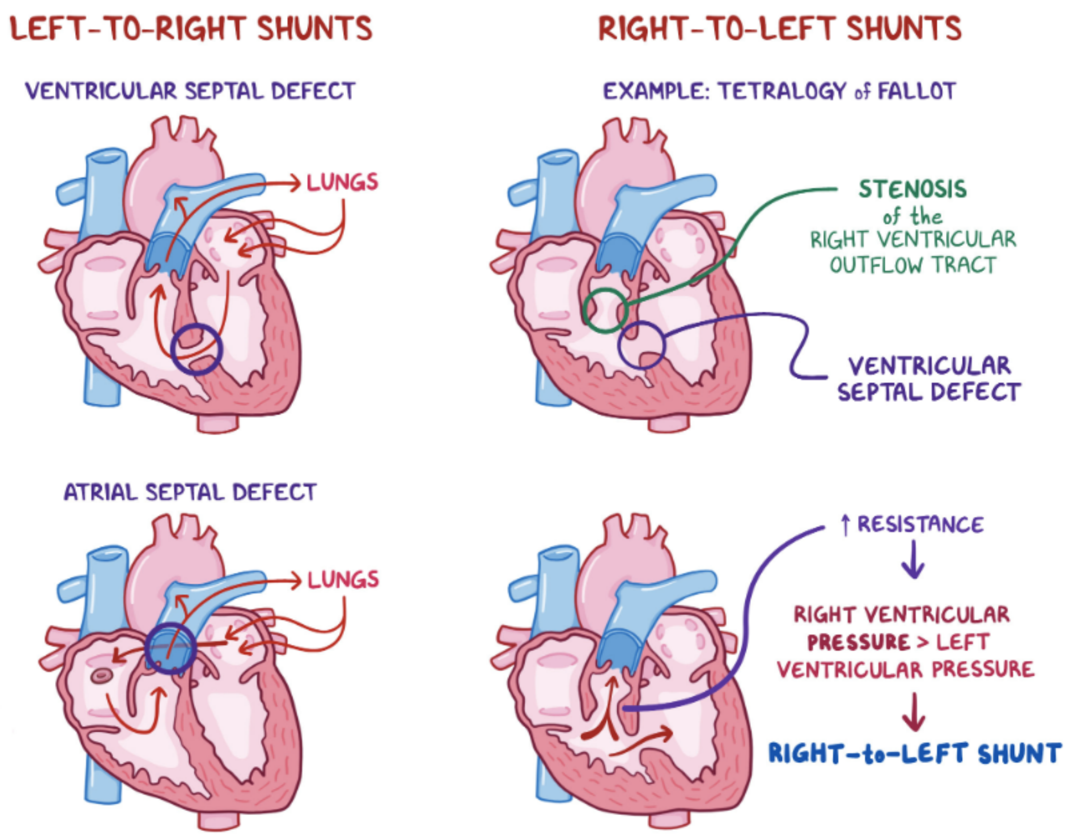


Figure 71.9 Pathologic shunts occurring in the left-to-right (more common) and right-to-left directions.

VENTILATION PERFUSION RATIOS & V Q MISMATCH

osms.it/ventilation-perfusion-ratios-V-Q-mismatch

- Ratio of amount of air to amount of blood reaching alveoli per minute ($\dot{V}/\dot{Q}$ ratio)

IDEAL SCENARIO

- Oxygen provided saturates blood fully → ratio of 1

NORMAL SCENARIO

- Average across entire lung → ratio of 0.8 (apex higher, bases lower)
- Normal breathing rate, tidal volume, cardiac output

DEFECTS

- Mismatching between ventilation, perfusion → abnormal gas exchange

Dead space

- Ventilation of lung regions not perfused
- No gas exchange (no blood to facilitate gas exchange)
- Alveolar gas same composition as humidified inspired air (PA_{O2} = 150mmHg, PA_{CO2} = 0)
- Pulmonary embolism

High $\dot{V}/\dot{Q}$

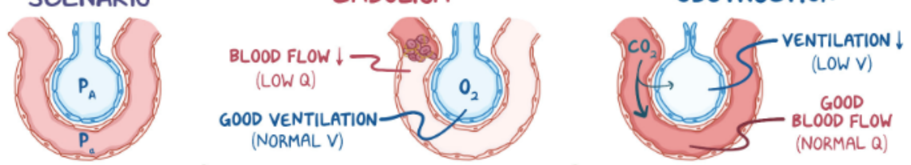
- High ventilation relative to perfusion (ventilation wasted)
- Usually due to ↓ blood flow (limited blood flow → limited gas exchange)
- Relatively high ventilation → pulmonary capillary blood with high P_{O2}, low P_{CO2}
- Emphysema

Low $\dot{V}/\dot{Q}$

- Low ventilation relative to perfusion (perfusion wasted)
- Usually due to ↓ ventilation → pulmonary capillary blood with low P_{O2}, high P_{CO2}
- Asthma, chronic bronchitis, pulmonary edema, etc.

Right-to-left shunt

- Perfusion of lung regions not ventilated
- No gas exchange occurs (no gas available to exchange)
- Same blood composition as mixed venous blood (Pa_{O2} = 40mmHg, Pa_{CO2} = 46mmHg)
- Airway obstruction, right-to-left cardiac shunts, etc.



	NORMAL SCENARIO	PULMONARY EMBOLISM	AIRWAY OBSTRUCTION
V/Q	NORMAL (0.8)	HIGH (can equal ∞)	LOW (can equal zero)
Pa_{O_2}	95 mmHg	N/A	↓ to 40 mmHg
Pa_{CO_2}	40 mmHg	N/A	↑ to 40 mmHg
PA_{O_2}	100 mmHg	150 mmHg	N/A
PA_{CO_2}	40 mmHg	0 mmHg	N/A

Figure 71.10 Normal $\dot{V}/\dot{Q}$, P_a, and P_A compared to pulmonary embolism and airway obstruction.

HYPOXEMIA & HYPOXIA

osms.it/hypoxemia-and-hypoxia

HYPOXEMIA

- Decrease in arterial Pa_{O2}

High altitude

- Barometric pressure is decreased → decrease in P_{O2} of inspired air → decreased PA_{O2}
- Equilibration of alveolar air, pulmonary capillary blood (normal)
- Systemic arterial blood achieves same (lower) P_{O2} of alveolar air
- Normal alveolar–arterial (A–a) gradient
- High altitude breathing supplemental O_2 → raised inspired P_{O2} → raised PA_{O2} → raised Pa_{O2}

Hypoventilation

- Less inspired fresh air → decrease in PA_{O2}
- Normal equilibration → pulmonary capillary blood achieves same (lower) PA_{O2} as A–a gradient
- *Hyperventilation:* breathing supplemental O_2 → raised PA_{O2} → raised Pa_{O2}

Diffusion defects (fibrosis, pulmonary edema)

- Increased diffusion distance/decreased surface area → impaired equilibration
- Normal PA_{O2}, decreased Pa_{O2} → ↑ A–a gradient
- Breathing supplemental O_2 → raised PA_{O2} → increased driving force for diffusion → raised Pa_{O2}

Ventilation/perfusion mismatches

- Regions of well-ventilated (high PA_{O2}), poorly-ventilated (low PA_{O2}), well-perfused, poorly-perfused lung
- Poor perfusion to well-ventilated areas, adequate perfusion to areas poorly ventilated → low Pa_{O2}
- Supplemental oxygen → raised PA_{O2} in poorly-ventilated areas with adequate perfusion → increase in Pa_{O2}
- ↑ A–a gradient

COMMON HYPOXEMIA CAUSES/THEIR EFFECT ON GAS EXCHANGE

CAUSE	PaO_2	A–a GRADIENT	SUPPLEMENTAL O_2 BENEFICIAL?
HIGH ALTITUDE	↓	Normal	Yes
HYPOVENTILATION	↓	Normal	Yes
DIFFUSION DEFECT	↓	↑	Yes
VENTILATION/PERFUSION MISMATCH	↓	↑	Yes
RIGHT-TO-LEFT-SHUNT	↓	↑	↑ shunt severity → ↓ effect

Right-to-left shunts (right-to-left cardiac shunts, intrapulmonary shunts)

- Shunted blood completely bypasses alveoli, cannot equilibrate
- Shunted blood mixes with, "dilutes" blood that did pass through alveoli → ↓ Pa_{O2} (even if PA_{O2} normal)
- ↑ A–a gradient
- Limited supplemental O_2 effect → raises PA_{O2}, Pa_{O2} of nonshunted blood, does not address underlying shunted blood/ oxygenated blood mixing → larger shunt, less effective supplemental O_2

HYPOXIA

- ↓ O_2 delivery to/utilization by tissues
- O_2 delivery → determined by cardiac output, O_2 content of blood
- ↓ cardiac output/localized blood flow → hypoxia
- Hypoxemia (any cause) → ↓ Pa_{O2} → ↓ hemoglobin saturation → ↓ oxyhemoglobin concentration in blood → ↓ oxygen delivery to tissues → hypoxia
- Anemia (↓ hemoglobin concentration) → ↓ oxyhemoglobin concentration in blood → decreased oxygen delivery to tissues → hypoxia
- Carbon monoxide poisoning → irreversible binding with hemoglobin → ↓ oxyhemoglobin concentration in blood → ↓ oxygen delivery to tissues → hypoxia
- Cyanide poisoning → interferes with O_2 utilization on cellular level

HYPOXIC VASOCONSTRICTION

- Alveolar partial pressure of oxygen (PA_{O2}) major factor controlling pulmonary blood flow
- ↓ PA_{O2} → vasoconstriction (opposite to systemic vasculature where ↓ in Pa_{O2} → vasodilation)
  - Vasoconstriction in response to poor oxygenation ensures blood flow coupled to areas of good ventilation → optimal gas exchange
  - In localized lung disease, areas of poorly-ventilated, diseased lung circumvented → blood directed towards healthy lung

COMMON HYPOXIA CAUSES/ARTERIAL OXYGENATION STATUS

CAUSE	MECHANISM	PaO2
↓ CARDIAC OUTPUT	↓ blood flow	Equilibrated
HYPOXEMIA	↓ PaO2 ↓ O2 saturation of hemoglobin ↓ O2 content of blood	↓
ANEMIA	↓ hemoglobin concentration ↓ O2 concentration of blood	Equilibrated
CARBON MONOXIDE POISONING	↓ O2 concentration of blood Left shift of O2-hemoglobin curve	Equilibrated
CYANIDE POISONING	↓ O2 utilization of blood	Equilibrated

Alveolar P_{O2} direct action on vascular smooth muscle → hypoxic vasoconstriction

- Pulmonary microcirculation surrounds alveoli
- O_2 highly lipid soluble → permeable across cell membranes
- Normal PA_{O2} (100mmHg), O_2 diffuses from alveoli → arteriolar smooth muscle → maintains relaxation, dilation of arterioles
- PA_{O2} decreases (70–100mmHg) → vascular smooth muscle sense change (hypoxia) → vasoconstriction → ↓ pulmonary blood flow to region
  - Vasoconstriction mechanism likely due to hypoxia → vascular smooth muscle depolarization → voltage-gated calcium channels open → calcium enters smooth muscle → contraction

HIGH ALTITUDE & HYPOXIC VASOCONSTRICTION

- Entire lung exposed to ↓ PA_{O2} (e.g. high altitudes) → global ↑ in pulmonary arteriolar resistance → ↑ pulmonary vascular resistance
- Chronic ↑ pulmonary vascular resistance → ↑ right heart afterload → right heart hypertrophy

FETAL HYPOXIC VASOCONSTRICTION

- Fetal circulation must acquire oxygen from maternal circulation via placenta → significantly lower Pa_{O2} → fetal lung vasoconstriction → reduction of blood flow to lungs (15% of cardiac output)
- At birth low pressure placenta circuit removed → ↑ systemic blood pressure → first breath after birth → ↑ PA_{O2} → 100mmHg → ↓ hypoxic vasoconstriction → ↓ pulmonary vascular resistance → pulmonary blood flow begins to normalize

NOTES
NORMAL VARIATIONS

PULMONARY CHANGES DURING EXERCISE

osms.it/pulmonary_changes_during_exercise

RESPIRATORY RESPONSE TO EXERCISE

- Exercise → muscle workload increase → consumption of significant O_2 amounts, above baseline production of CO_2, lactic acid
- Increased O_2 demand → hyperpnea (ventilation increases 10–20x to compensate)
- Hyperpnea vs. hyperventilation
    - *Hyperpnea:* aims to maintain homeostasis → blood O_2 ,CO_2 levels remain relatively constant
    - *Hyperventilation:* excessive ventilation, blowing off too much CO_2 → low P_{CO2}, respiratory alkalosis
- Exercise-induced ventilation not initially prompted by alterations in blood gases (rising P_{CO2} , declining P_{O2}, pH)
- Ventilation increases abruptly as exercise begins due to neural factors
    - Psychological stimuli (conscious exercise anticipation)
    - Simultaneous cortical motor activation of skeletal muscle, respiratory centers
    - Proprioceptors moving muscles, tendons, joints → stimulate respiratory centers
    - Initial neural regulation → early compensation to exercise as opposed to waiting for change in blood values
- Initial abrupt increase in ventilation is followed by gradual increase (reflective of lung CO_2 delivery rate) → eventually, steady state of ventilation appropriate for intensity achieved
- Exercise cessation → initial small abrupt decline in ventilation (higher neurological stimulation ends) → followed by gradual decrease to pre-exercise respiratory rate (gradual decrease in CO_2 flow to lungs)

PULMONARY CIRCULATORY RESPONSE

- Cardiac output increases to meet tissue O_2 demand → increased right heart output → increased blood flow through pulmonary circulation → increased blood return to left heart → increased output to systemic circulation → increased O_2 tissue delivery
- Exercise → pulmonary resistance decrease → perfusion of more pulmonary capillary beds → more even distribution of pulmonary perfusion, ventilation → improved V/Q ratio (decreased physiological dead space) → increased gas exchange efficiency

HEMATOLOGICAL RESPONSE

Bohr effect

- Hemoglobin's oxygen binding affinity is inversely related to acidity, carbon dioxide concentration
    - Exercise → increased tissue P_{CO2}, decreased tissue pH, increased temperature → right shift of O_2-hemoglobin dissociation curve → decreased affinity of hemoglobin for O_2 → greater unloading of oxygen to exercising muscle

Regulation of blood gases during exercise

- Arterial P_{CO2}, P_{O2} remain nearly constant during exercise
- Venous P_{CO2}, P_{O2} may change significantly during exercise
  - Ventilation increases sufficiently to blow off all excess CO_2, maintain arterial homeostasis

Anaerobic respiration

- Leads to rise in lactic acid levels
- Not due to inadequate respiratory function
- Alveolar ventilation, pulmonary perfusion remain well matched during exercise → hemoglobin fully saturated
- Cardiac output limitation/limits of skeletal muscle to utilize oxygen → rising lactic acid

RESPIRATORY RESPONSE TO EXERCISE OVERVIEW

	RESPONSE
VENTILATION RATE	↑
PHYSIOLOGIC DEAD SPACE	↓
V/Q RATIO	More equal distribution throughout lungs
PULMONARY BLOOD FLOW, CARDIAC OUTPUT	↑
O_2 CONSUMPTION	↑
CO_2 CONSUMPTION	↑
ARTERIAL P_{O2}, P_{CO2}	No change
ARTERIAL pH	Light exercise: no change

PULMONARY CHANGES AT HIGH ALTITUDE & ALTITUDE SICKNESS

osms.it/pulmonary_changes_high_altitude_altitude_sickness

RESPIRATORY RESPONSE TO ALTITUDE

- Humans typically live at altitudes between sea level and 2400m/7800ft
- Altitudes > 2400m/7800ft → lower overall atmospheric pressure → lower P_{O2} → hemoglobin less saturated at baseline
  - At rest at sea level hemoglobin typically unloads 20–25% O_2 content on a single trip through the circulatory system
  - Significant functional reserve allows for survival due to further hemoglobin unloading when poorly saturated

ACCLIMATIZATION

- Long-term, slow steady move from sea level to higher altitude → respiratory, hematopoietic adaptation
- Decrease in arterial P_{O2} → peripheral chemoreceptors more responsive to increases in P_{CO2} → chemoreceptors stimulate medullary inspiratory center → increased breathing rate

Initial (fast) adaptation

- Some changes occur immediately, others over course of days
- Pulmonary
  - Minute ventilation → 2–3L/min higher than sea level
  - Increased ventilation → decreased arterial CO_2 (<40mmHg) → respiratory alkalosis → increased blood pH → inhibition of central, peripheral chemoreceptors → offset increase in ventilation rate (initial effect)
  - As adaptation occurs → HCO_3^- excretion increases → HCO_3^- concentration in cerebrospinal fluid (CSF) decreases → CSF pH decreases toward normal → increased ventilation rate resumes
  - Respiratory alkalosis as result of rapid ascent to high altitude managed with carbonic anhydrase inhibitors → increased HCO_3^- excretion → mild compensatory metabolic acidosis
- Hematological
  - Increase in 2,3-bisphosphoglyceric acid (2,3-BPG) concentration → hemoglobin affinity for O_2 reduced → increased unloading of O_2 at tissue level (also decreases efficiency of oxygen loading in lungs)
- Cardiac
  - Increased heart rate
  - *Right heart hypertrophy:* low P_{O2} alveolar gas → pulmonary vasculature vasoconstriction → increase in pulmonary vascular resistance → increased right heart strain → right ventricular hypertrophy
- Oxygen conservation
  - Non-essential body functions suppressed → reduction in food digestion efficiency (decreased circulation in favor of perfusing more important organs)

Late (slow) acclimatization

- Occurs over weeks to months
- *Hematological:* hypoxia → kidneys produce more erythropoietin → stimulates bone marrow production of red blood cells → total O_2 carrying capacity of blood increased
  - Essential compensation for living at altitude
  - Increases blood viscosity → greater blood flow resistance → greater heart workload
  - *Full acclimatization:* increase in red blood cell plateaus
- Effect on complete blood count parameters
  - *Total red cells:* ↑
  - *Hemoglobin:* ↑
  - *Hematocrit:* ↑

- *Mean corpuscular volume:* unchanged
- *Mean corpuscular hemoglobin concentration:* ↑

Exercise at altitude

- Adaptations normally serve to achieve homeostasis at rest → unless fully acclimatized intense physical activity → homeostasis loss → severe hypoxia
- This transient intentional hypoxia can be exploited by athletes → further adaptive changes to altitude → blood with greater oxygen carrying capacity → improved performance at lower altitude
- Late phase acclimatization of skeletal muscle includes: increased capillary concentration, increased myoglobin amount, increased mitochondria number, increased aerobic metabolism enzyme concentration

PHYSIOLOGICAL ACCLIMATIZATION TO HIGH ALTITUDE OVERVIEW

	RESPONSE
ALVEOLAR P_{O_2}	↓ (lower barometric pressure → lower atmospheric P_{O_2})
ARTERIAL P_{O_2}	↓ (hypoxemia)
ARTERIAL pH	↑ (respiratory alkalosis due to hyperventilation)
HEMOGLOBIN CONCENTRATION	↑ red blood cell concentration
2,3-DPG CONCENTRATION	↑
MUSCLE METABOLISM	↑ efficiency of aerobic metabolism
O_2-HEMOGLOBIN DISSOCIATION CURVE	Right shift (more oxygen unloaded to tissues)
PULMONARY ARTERIAL PRESSURE	↑ (secondary to increased pulmonary vascular resistance)
PULMONARY VASCULAR RESISTANCE	↑ (vasoconstriction)
VENTILATION RATE	↑

ACUTE MOUNTAIN SICKNESS

- AKA altitude sickness
- Commonly associated with altitudes above 2400m/7800ft
  - Minor symptoms may occur at as low as 1500m/5000ft
  - *Death zone:* 5500m/18000ft, altitude considered incompatible with human life; acclimatization not possible
- Caused by sudden transition to altitude without sufficient acclimatization → low atmospheric pressure → low P_{O2} → hypoxia
- Contributing factors
  - Rate of ascent
  - Rate of water vapor loss from lungs
  - Activity level
- Sudden increase in altitude without taking time to acclimatize

Symptoms

- Headache, shortness of breath, nausea, dizziness, peripheral edema

Complications

- Severe complications of high altitude can be fatal
- High altitude pulmonary edema (HAPE)
  - Low atmospheric pressure → decreased oxygen partial pressures, poor oxygenation → increased pulmonary arterial, capillary pressures, idiopathic increase in permeability of vascular endothelium → fluid extravasation → pulmonary edema
- High altitude cerebral edema (HACE)
  - Hypoxia → increased cerebral microvascular permeability, failure of cellular ion pumps → vasogenic, cytotoxic edema

Treatment

- Supplemental oxygen/immediate descent