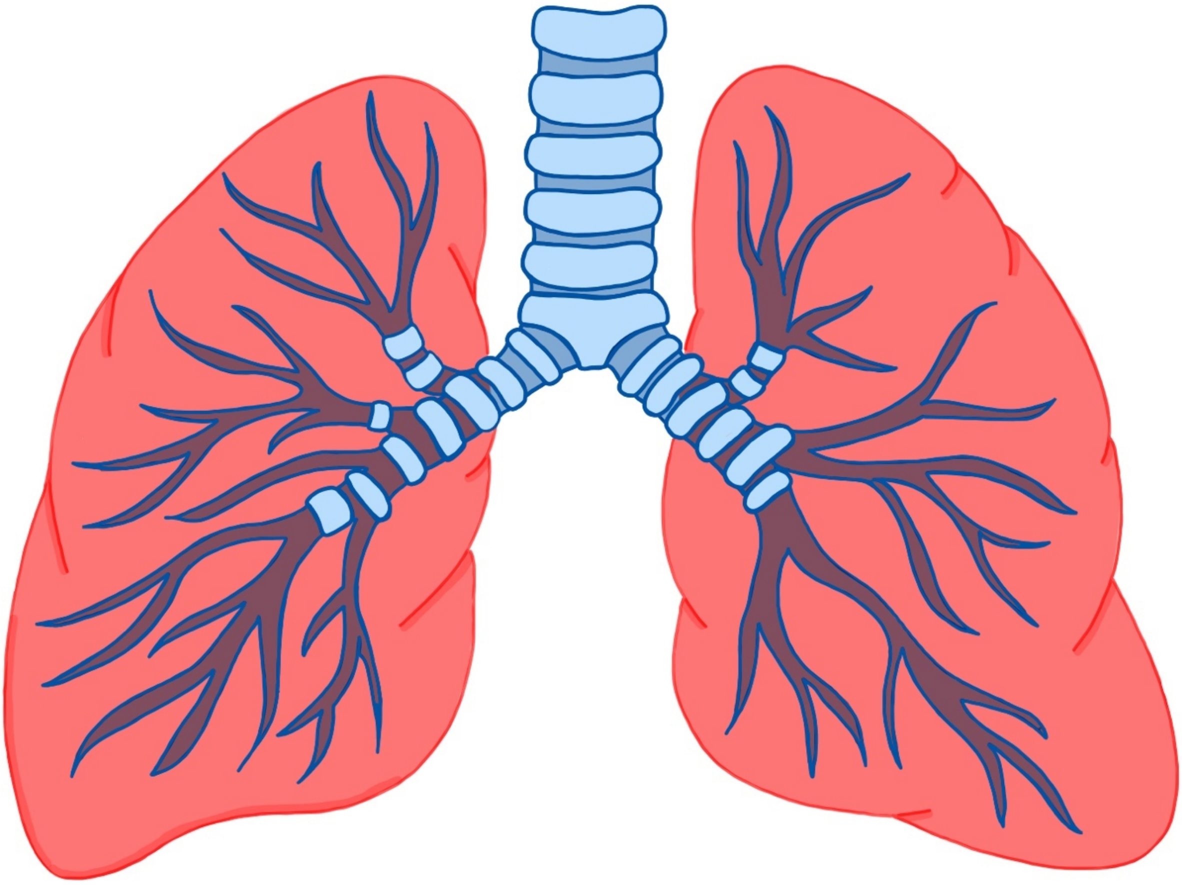

RESPIRATORY PHYSIOLOGY

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Section 1 – Mechanics of Ventilation

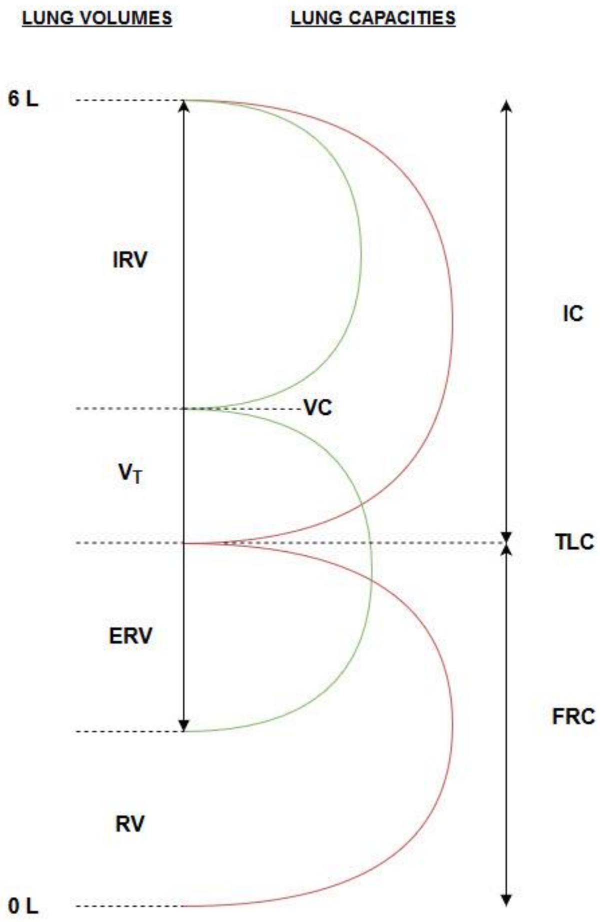
1.0 – Lung Volumes and Capacities

I. Lung volumes

- Measured by spirometry (*exception*: RV)
- 4 types
- Tidal volume (V_T), inspiratory reserve volume (IRV), expiratory reserve volume (ERV) and residual volume (RV)

II. Lung capacities

- Calculated from the lung volumes ($\geq$ 2 lung volumes)
- 4 types
- Inspiratory capacity (IC), vital capacity (VC), functional residual capacity (FRC) and total lung capacity (TLC)



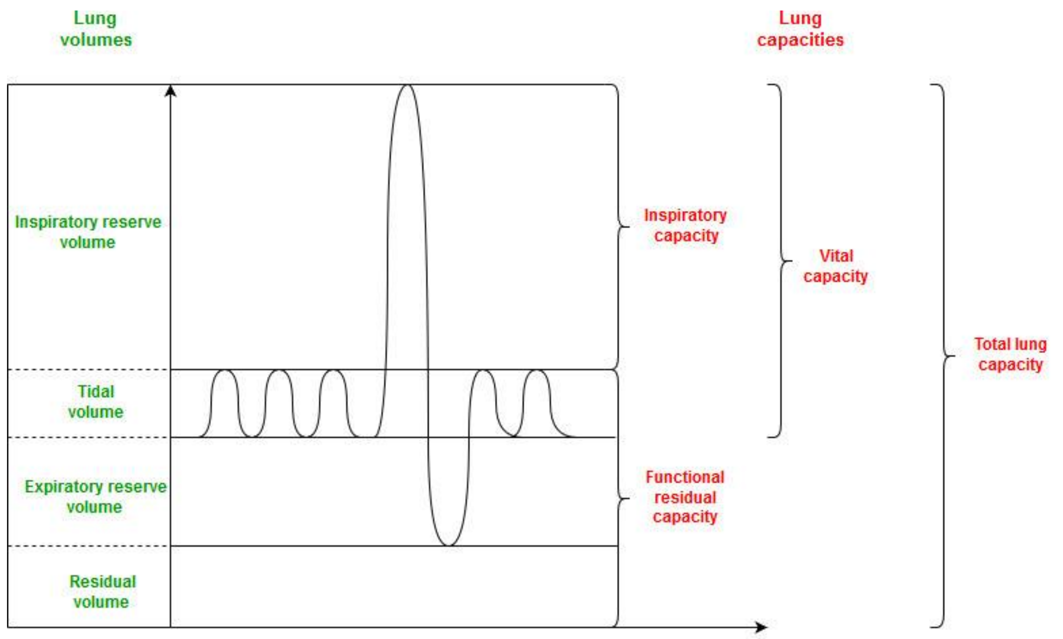
III. Summary

Term	Definition	Value
Tidal volume (V_T)	Amount of air inspired or expired during *quiet* ventilation	0,5 L
Inspiratory reserve volume (IRV)	The maximal amount of air that can be inspired with *effort* at the end of a normal inspiration	3 L
Expiratory reserve volume (ERV)	The maximal amount of air that can be expired with *effort* at the end of a normal expiration	1,2 L
Inspiratory capacity (IC)	Maximal inhalation after normal expiration	3,5 L
Vital capacity (VC)[1]	Maximal expiration after maximal inspiration	4,7 L
Residual volume (RV)[2]	Volume remaining in the lungs after maximal expiration	1,2 L
Functional residual capacity (FRC)[3]	Volume remaining in the lungs after normal expiration	2,4 L

[1] Vital capacity (VC) and forced vital capacity (FVC) have the same value, but the process of measurement is different. When measuring VC, the patient takes a full inspiration and blows out the air in a slow maneuver. When measuring FVC, the patient takes a full inspiration and blows out the air in a forceful maneuver.

[2] If we did not have any residual volume, the lungs would collapse.

[3] Equilibrium volume of the lung.



1.1 – Ventilation

1.1.1 – Definition

- Refers to the movement of air between the atmosphere and the lungs through the process of inspiration and expiration
- It must be distinguished from *respiration*

Ventilation	Respiration
Mechanical	Ventilation + diffusion + perfusion

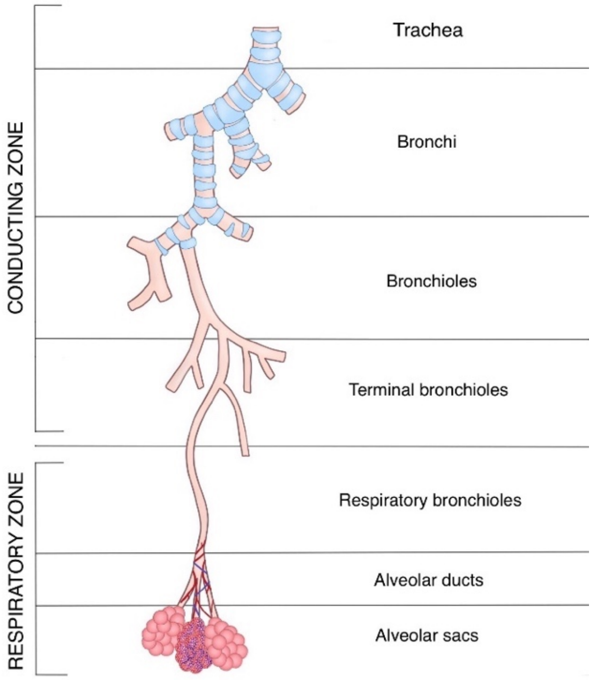
1.1.2 – Structure of the Respiratory System

I. Conducting zone

- Composed of the airways (*trachea*, *bronchus*, *bronchioles* and *terminal bronchioles*)
- Does not participate in gas exchange

II. Respiratory zone

- Composed of the lungs (*respiratory bronchioles*, *alveolar ducts* and *alveolar sacs*)
- Participates in gas exchange



1.1.3 – Minute Ventilation (V_M)

I. Definition

- Refers to the total volume of gas that enters the respiratory system per minute

II. Equation

$$V_M = (CZ + RZ) \times RR$$

- V_M = Minute ventilation (mL/min)
- **CZ** = Air in the conducting zone (mL)
- **RZ** = Air in the respiratory zone (mL)
- **RR** = Respiratory rate (breaths/min)

III. Calculation

$$V_M = (CZ + RZ) \times RR$$
$$= V_T \times RR$$
$$= 500 \text{ mL} \times 15/\text{min}$$
$$= 7{,}500 \text{ mL/min}$$

1.1.4 - Alveolar Ventilation (V_A)

I. Definition

- Refers to the volume of gas that reaches the alveoli per minute

II. Equation

$$V_A = (V_T - V_D) \times RR$$

- V_A = Alveolar ventilation (mL/min)
- V_T = Tidal volume (mL)
- V_D = Dead space (mL)
- **RR** = Respiratory rate (breaths/min)

III. Calculation

$$V_A = (V_T - V_D) \times RR$$
$$= (500\ mL - 150\ mL) \times 15/min$$
$$= 350\ mL \times 15/min$$
$$= \underline{\underline{5{,}250\ mL/min}}$$

1.1.5 – Dead Space

I. Definition

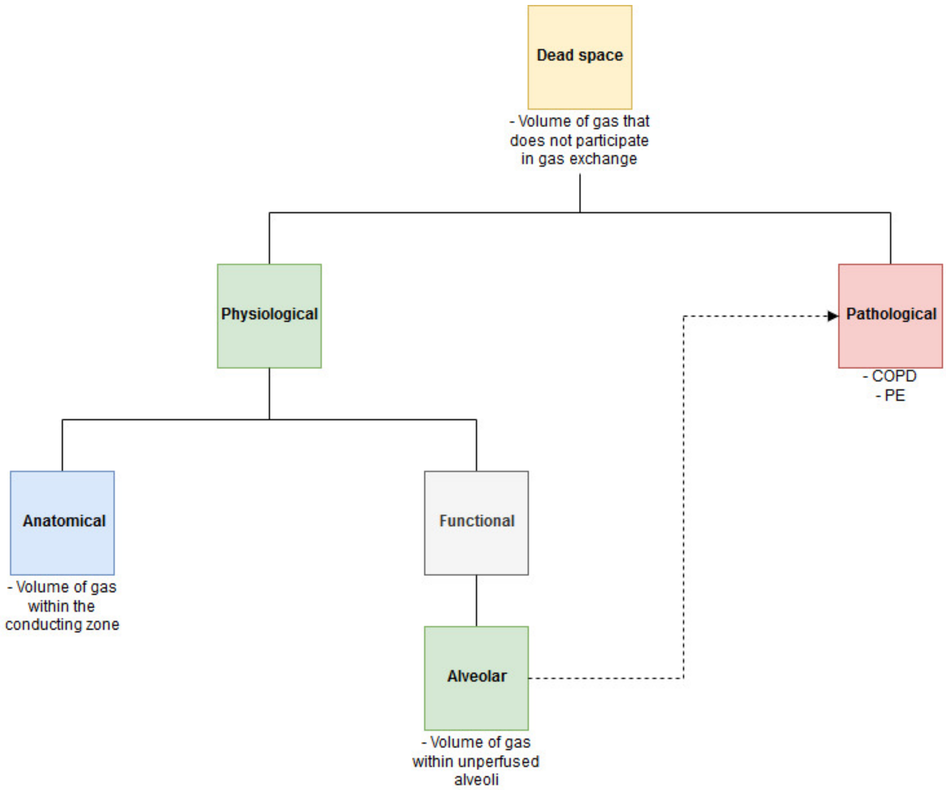
- Refers to the volume of gas that does not participate in gas exchange
- It may be considered as "*wasted ventilation*"
- Divided into physiological- and pathological dead space

II. Physiological dead space

- Composed of anatomical- and alveolar dead space
- **Anatomical dead space**: Volume of gas within the conducting zone
- **Alveolar dead space**: Volume of gas within unperfused alveoli
- The ratio of the physiological dead space to the tidal volume is ≈1/3

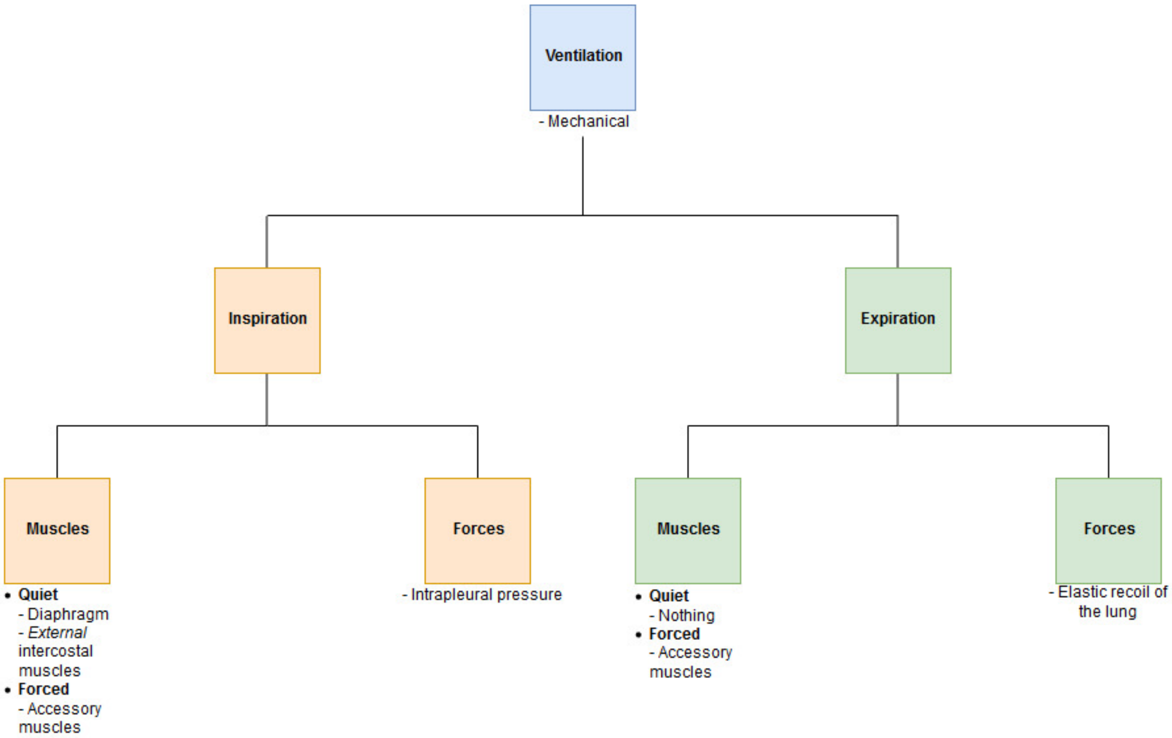
III. Pathological dead space

- Chronic obstructive pulmonary disease (COPD)
- Pulmonary embolism (PE)



1.2 – Mechanics of Ventilation

1.2.1 – Overview



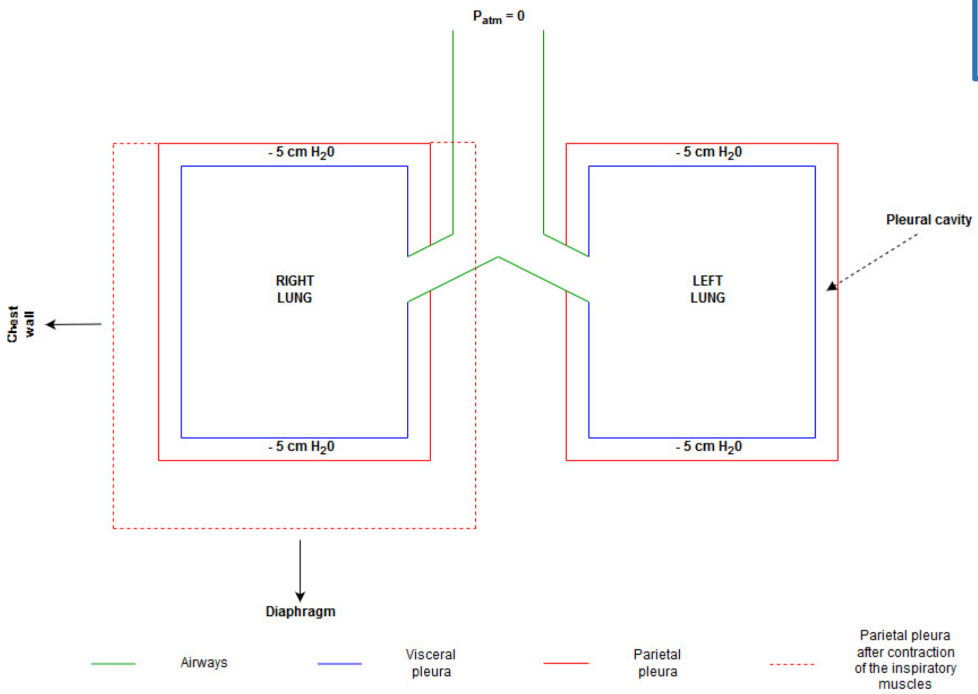
1.2.2 – Inspiration

I. Muscles

	***Quiet* inspiration**		***Forced* inspiration**
Diaphragm	- Major muscle - Contraction of the diaphragm → downward displacement - Increases the vertical diameter of the thoracic cavity	**Sternocleidomastoid**	- Contraction of the sternocleidomastoid → elevation of the sternum - Increases the anteroposterior diameter of the thoracic cavity
***External* intercostal muscles**	- Minor muscle - Contraction of the external intercostal muscles → ribs are lifted up and out - Increases the anteroposterior - and horizontal diameter of the thoracic cavity	**Scalene muscles**	- Contraction of the scalene muscles → elevation of the upper ribs - Increases the anteroposterior diameter of the thoracic cavity

Note: Inspiration is an <u>active</u> process (*regardless of whether it is quiet or forced*)

1 cm H_2O = 0.74 mmHg



II. Forces

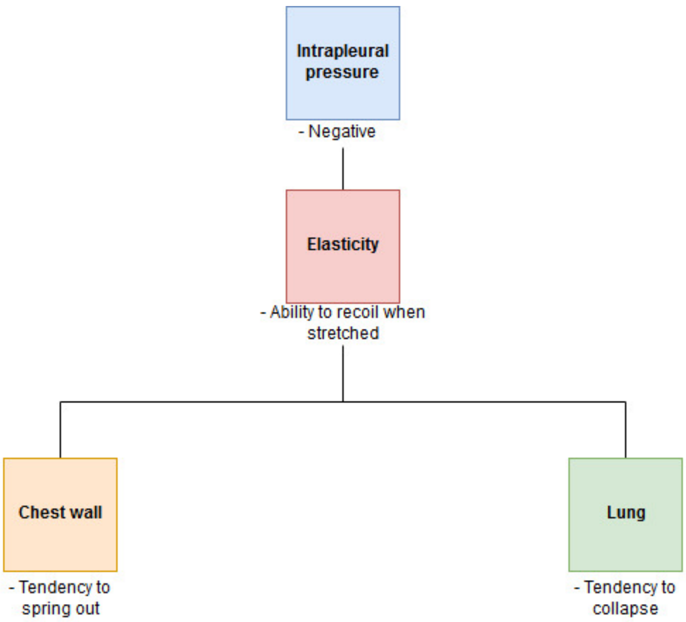
1. Intrapleural pressure

- Represents the pressure in the pleural cavity
- Subatmospheric (*negative*)
- Expanding force

Boyles law

$$P \propto \frac{1}{V}$$

- **P** = Pressure (mmHg)
- **V** = Volume (mL)



$$P_L = (P_A) - (P_{pl})$$

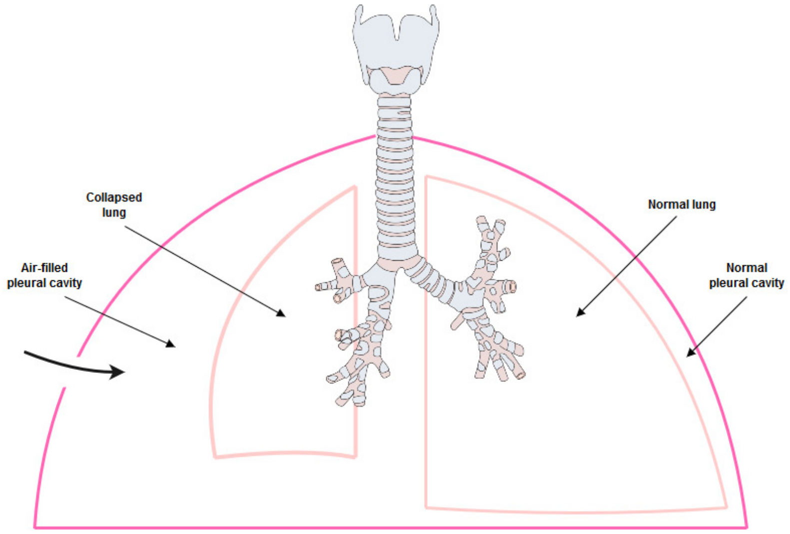
- P_L = Transpulmonary pressure (cm H_20)
- P_A = Alveolar pressure (cm H_20)
- P_{pl} = Intrapleural pressure (cm H_20)

III. Clinical correlation

CLINICAL CORRELATION

Pneumothorax
- When a sharp object penetrates the chest wall and punctures the intrapleural space – a connection is created between the atmosphere and the pleural space
- Air flows into the pleural cavity along the pressure gradient until the intrapleural pressure equals the atmospheric pressure
- There are two important clinical consequences of a pneumothorax;

1. **Collapsed lung**
2. **Expansion of the chest wall**

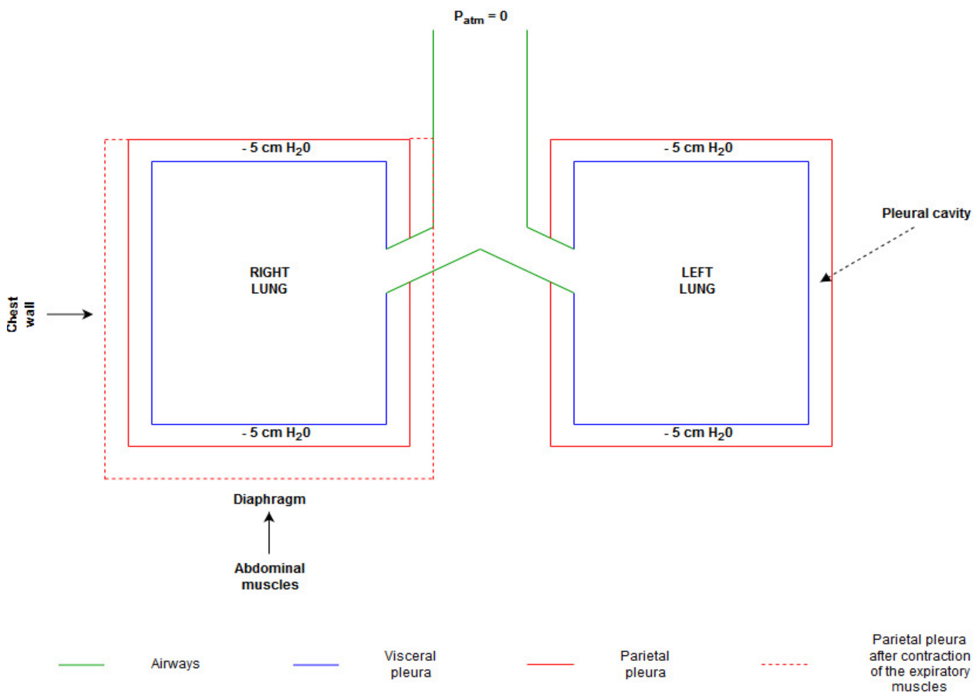


1.2.3 – Expiration

I. Muscles

***Quiet* expiration**		***Forced* expiration**
	Abdominal muscles	- Major muscle - Contraction of the abdominal muscles → upward displacement of the diaphragm - Decreases the vertical diameter of the thoracic cavity
	***Internal* intercostal muscles**	- Minor muscle - Contraction of the *internal* intercostal muscles → ribs are pulled down and in - Decreases the anteroposterior- and horizontal diameter of the thoracic cavity

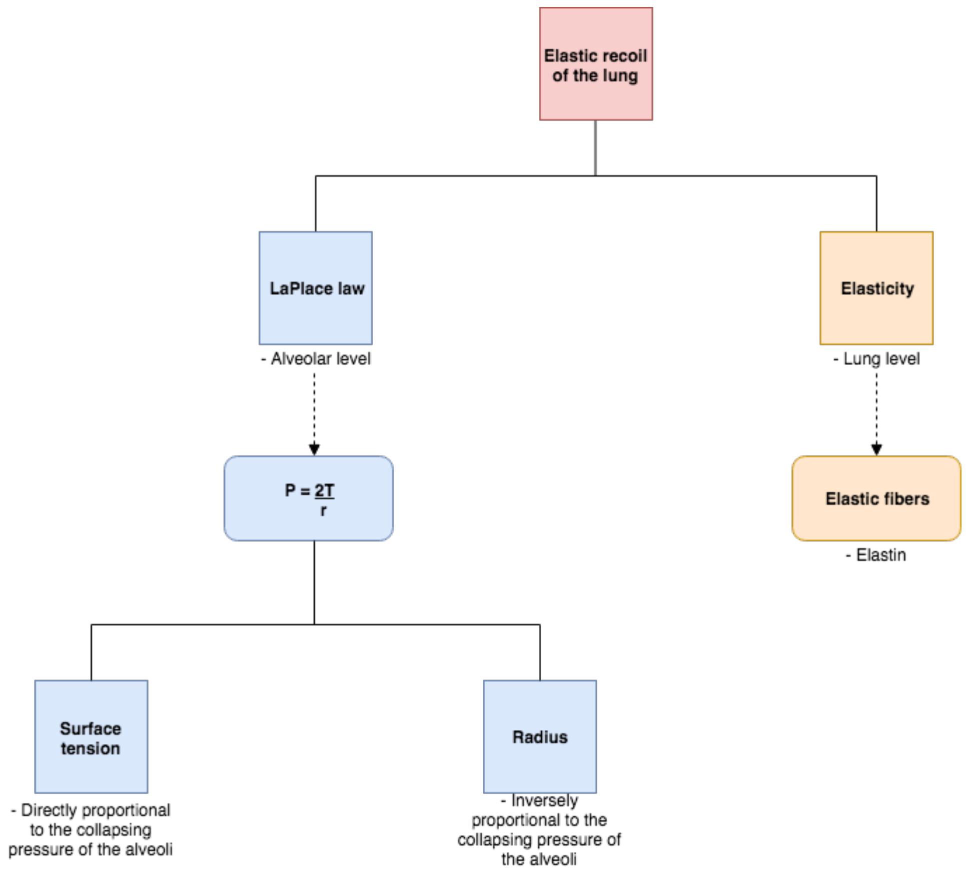
Note: Quiet expiration is a passive process, while *forced* expiration is an active process



II. Forces

1. Elastic recoil of the lung

- Represents the tension in the wall of the lung
- It is determined by LaPlace law and the inherent elasticity of the lung
- Collapsing force



III. Clinical correlation

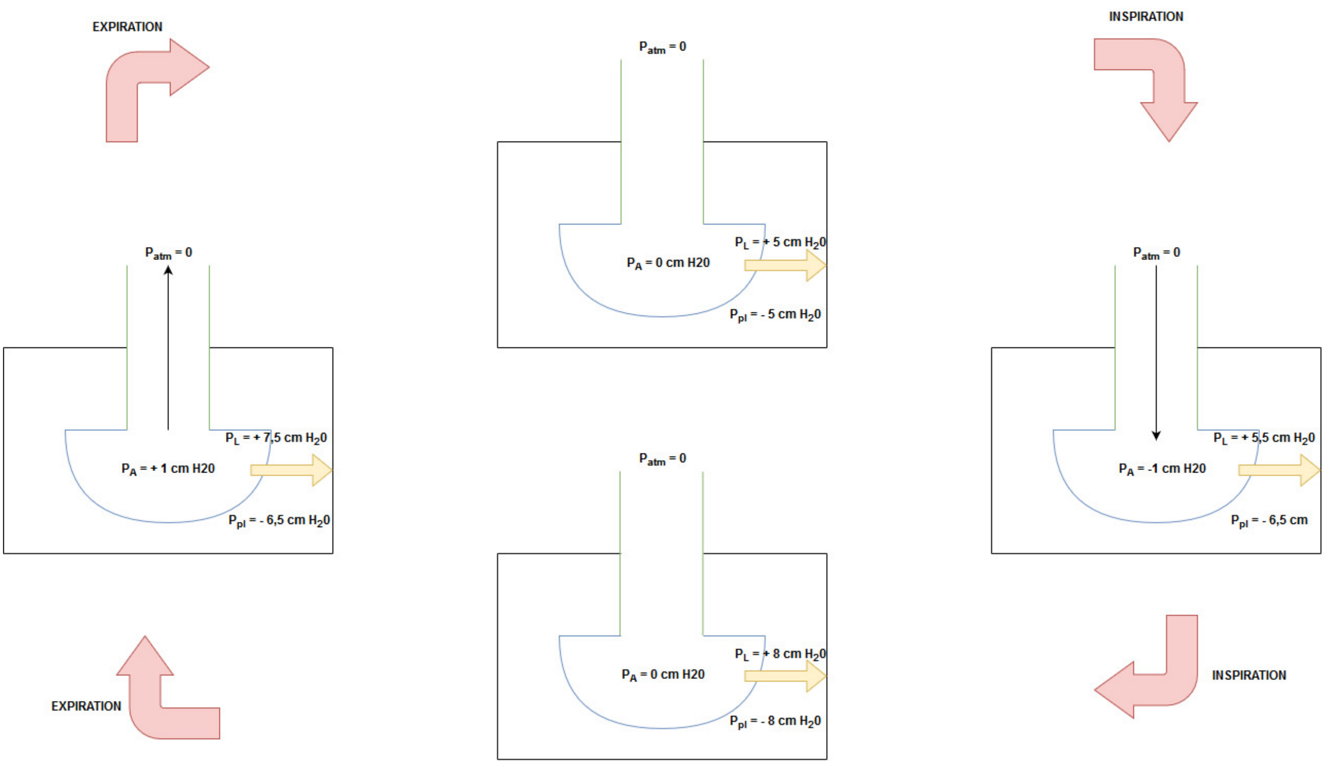
<u>CLINICAL CORRELATION</u>

Respiratory distress syndrome (RDS)

- Surfactant is synthesized by type II pneumocytes
- The most important constituent of surfactant is dipalmitoylphosphatidylcholine (DPPC)
- The production of surfactant occurs between 24th and 34th week of gestation
- Infants born before 24th week of gestation → *never* have surfactant
- Infants born between 24th and 34th week of gestation → *uncertain* surfactant status
- Lack of surfactant produces the following consequences;

1. **Increased surface tension**
   - Collapse of alveoli
2. **Unopposed LaPlace Law**
   - Collapse of small alveoli

1.2.4 – Ventilatory Cycle



1.2.5 – Clinical Correlations

	Restrictive lung disease	Obstructive lung disease
Pathophysiology	- Fibrosis of lung tissue → ↓compliance	- Destruction of elastic fibers → ↓elasticity → ↑compliance
Definition	- Any pathology that interferes with the ability to develop negative P_A	- Any pathology that interferes with the ability to develop positive P_A
Main problem	- Inspiration	- Expiration
Examples	- Pulmonary fibrosis (IPF)	- Chronic obstructive pulmonary disease (COPD) - Asthma

1.3 – Test Yourself

1) Select the correct statement(s) regarding lung volumes and capacities

a) Tidal volume is the amount of air inspired or expired during *forced* ventilation

b) IRV and ERV are used during *quiet* ventilation

c) VC and FVC have different values

d) The amount of air remaining in the lungs after normal expiration is called FRC and has a value of 2,4 L

e) None of the above

2) Which are the only lung volumes and capacities NOT measurable with spirometry? (tip: draw the mneumonic "m and M")

a) RV, FRC and VC

b) RV, VC and TLC

c) RV, FRC and TLC

d) All of the lung volumes and capacities are technically measurable with spirometry

e) It depends on the patient

3) What is/are the correct formula(s) for calculation of lung capacities.

a) VC = V_T + IRV + ERV

b) TLC = VC + RV

c) TLC = FRC + IC

d) A and C are correct

e) All of the above

4) Select the correct statement regarding ventilation.

a) Alveolar ventilation is greater than minute ventilation

b) The conducting zone may sometimes participate in gas exchange

c) The respiratory zone is composed of terminal bronchioles, respiratory bronchioles, alveolar ducts and alveolar sacs

d) In all cases, the quantity of the physiological dead space is around 1/3 of the tidal volume

e) None of the above

5) What is the difference between ventilation and respiration?

a) There is no difference between ventilation and respiration

b) Ventilation refers to the mechanical aspect of breathing

c) Respiration refers to everything from the mechanical aspect of breathing to the usage of oxygen in oxidative phosphorylation

d) B and C are correct

e) None of the above

6) Select the correct statement regarding the muscles of ventilation.

a) Contraction of the internal intercostal muscles increases the anteroposterior- and horizontal diameter of the thoracic cavity

b) Inspiration is always an active process

c) In some individuals, quiet expiration might be an active process

d) A and B are correct

e) None of the above

7) Select the correct statement regarding intrapleural pressure.

a) The normal value of the intrapleural pressure in a resting adult is - 5 cm H_20

b) The negative value is created by the lung and the chest wall pulling on the parietal- and visceral pleural, respectively

c) The intrapleural pressure may become positive in a pneumothorax

d) A and C are correct

e) All of the above

8) Select the correct statement regarding elastic recoil of the lung.

a) Elastic recoil is determined by LaPlace law and the inherent compliance of the lung

b) Surfactant is produced by type I pneumocytes

c) The major function of surfactant is to destroy the elastic fibers of the lung

d) When elastic recoil is greater than the intrapleural pressure, the lung will collapse

e) None of the above

9) At which point during the ventilatory cycle is the highest flow of air into the alveoli?

a) Beginning of inspiration

b) Middle of inspiration

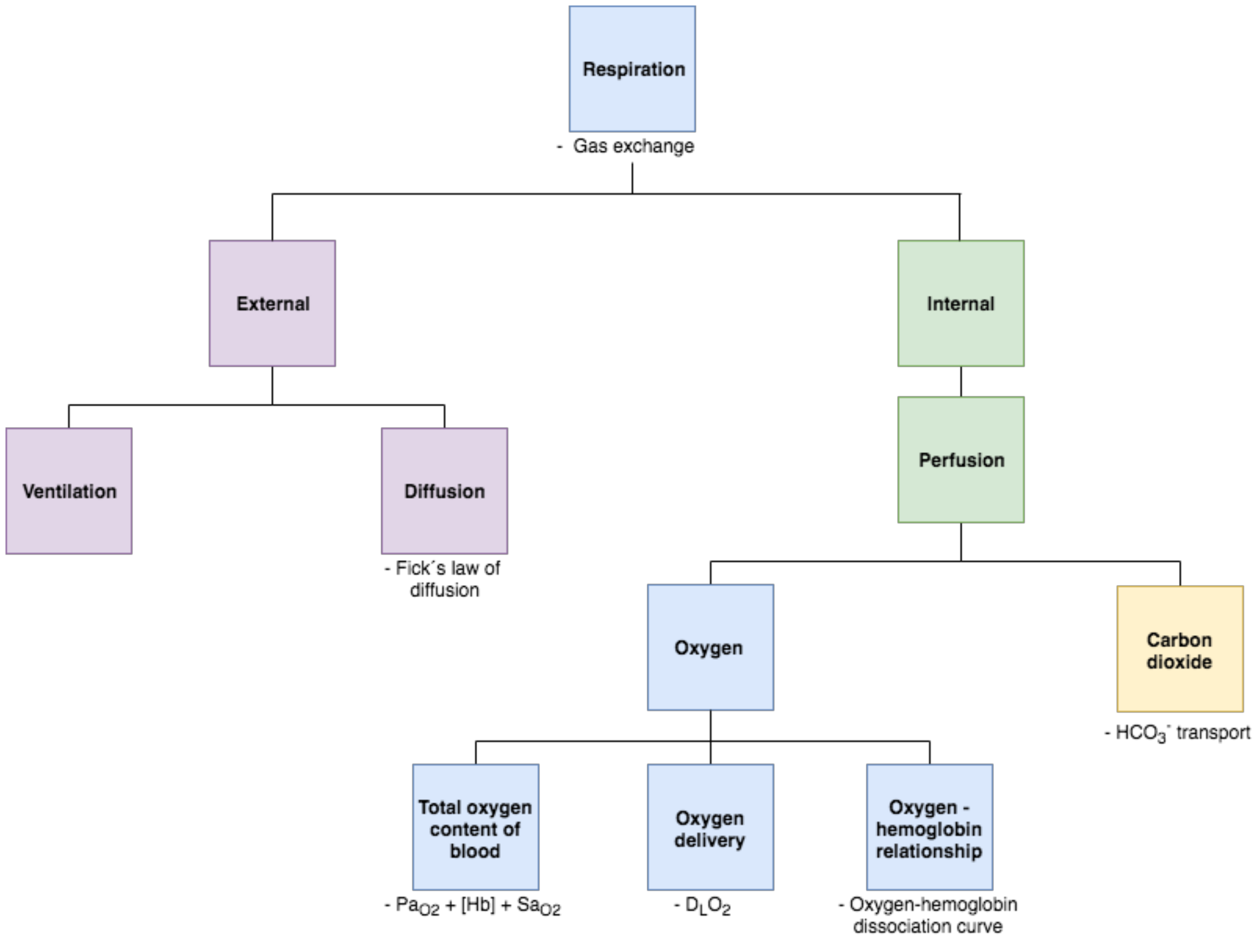
c) End of inspiration

d) The air flow is equally high during the whole inspiratory phase

e) A and B are correct

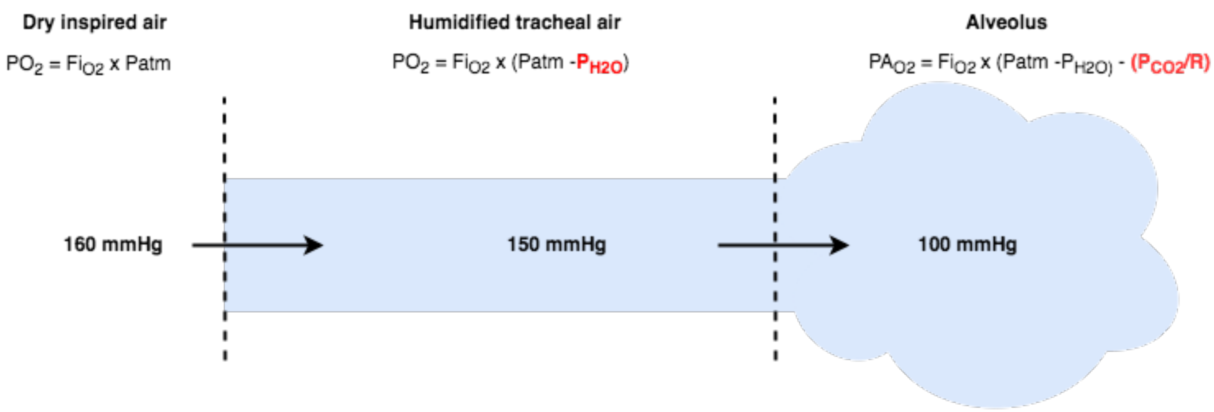
Section 2 – Respiration

2.0 – Overview



2.1 – External Respiration

2.1.1 – Ventilation



I. Dry inspired air

- The amount of oxygen in dry inspired air is determined by the fraction of inspired oxygen (Fi_{O2}) and the atmospheric pressure (P_{atm})

$$P_{O2} = Fi_{O2} \times Patm$$
$$= (0.21 \times 760) \text{ mmHg}$$
$$= 160 \text{ mmHg}$$

CLINICAL CORRELATION

Q: "How does supplementation of oxygen increase the partial pressure of oxygen present in the alveoli?"

A: Oxygen supplementation will increase the Fi_{O2}. For example, 1L/min of oxygen increases the Fi_{O2} from 21% to 25%.

II. Humidified tracheal air

- The presence of water in the respiratory tract will dilute the oxygen

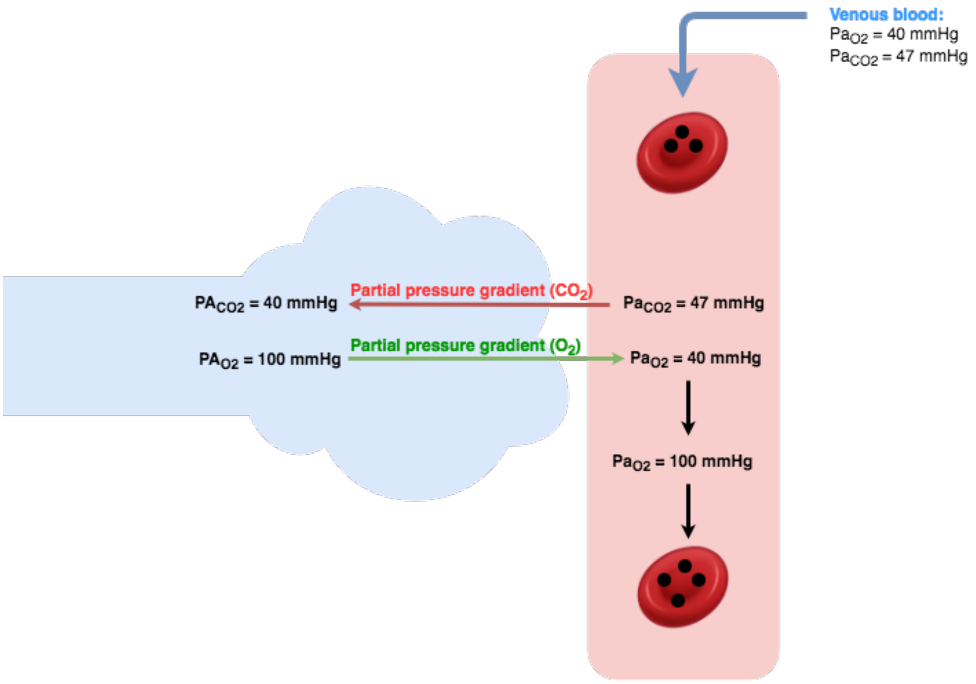
$$P_{O2} = Fi_{O2} \times (Patm - P_{H2O})$$
$$Pi = 0.21 \times (760 - 47)$$
$$= 150 \text{ mmHg}$$

III. Alveolar air

- Gives the **alveolar gas equation**
- The partial pressure of oxygen decreases because carbon dioxide has the ability to displace oxygen

$$PA_{O2} = Pi - P_{CO2}/R$$
$$= 0.21 \times (760 - 47) - (40/1)$$
$$= 100 \text{ mmHg}$$

2.1.2 – Diffusion



RULES OF PARTIAL PRESSURE GRADIENTS

- Gases always diffuse from an area of higher partial pressure to an area of lower partial pressure

- Only **dissolved gases** can contribute in the partial pressure gradient

I. Oxygen

- **Partial pressure gradient:** The partial pressure of oxygen in the alveoli (PA_{O2}) is higher than the partial pressure of oxygen in the pulmonary venous blood (Pa_{O2}). Oxygen will therefore diffuse from the alveoli to the pulmonary capillary
- **Equilibrium:** diffusion of oxygen continues until the partial pressure in the pulmonary capillary equals the partial pressure in the alveolus
- **Hemoglobin uploading:** the dissolved oxygen uploads on hemoglobin after equilibrium is reached

II. Carbon dioxide

- **Partial pressure gradient:** The partial pressure of carbon dioxide in the pulmonary venous blood (Pa_{CO2}) is higher than the partial pressure of carbon dioxide in the alveolus (PA_{CO2}). Therefore, carbon dioxide will diffuse from the capillary and into the alveolus
- **Equilibrium:** Diffusion of carbon dioxide continues until the partial pressure in the pulmonary capillary equals the partial pressure in the alveolus

$$PA_{CO2} = \frac{\text{Metabolism}}{V_A}$$

	PA_{O2}	PA_{CO2}
Directly proportional to	Pa_{O2}	Pa_{CO2}
Main determinants	- P_{atm} - Fi_{O2}	- V_A[1] - Metabolism

2.1.3 – Fick´s Law of Diffusion

I. Definition

- Describes the rate of diffusion of a gas across a permeable membrane (e.g., how fast a gas will diffuse from the alveoli and into the pulmonary capillary)

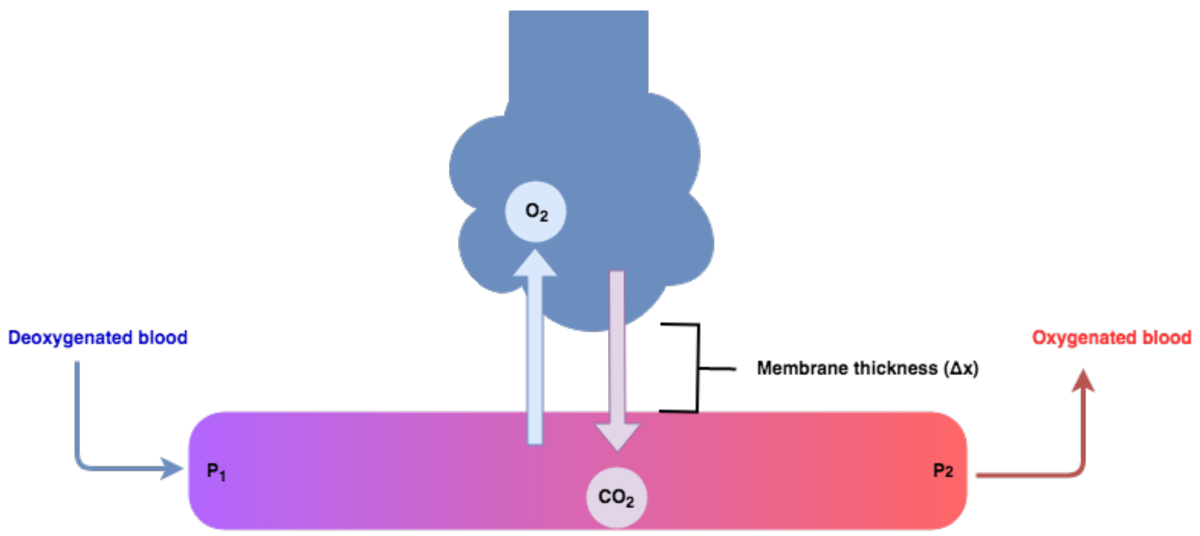
II. Factors determining rate of diffusion

Lung variables	Abbreviation	Comment
Surface area	A	Determined by the number of alveoli
Membrane thickness	Δx	Interstitial space

Gas variables	Abbreviation	Comment
Solubility	S	$CO > CO_2 >> O_2$
Partial pressure gradient	ΔP	$(P_1 - P_2)$

III. Equation

$$D = \frac{A \times \Delta P \times S}{\Delta x} \longrightarrow D = \Delta P \times S$$



IV. Examples

1. "Which gas will diffuse first, CO_2 or O_2?"

- In order to evaluate the rate of diffusion for CO_2 and O_2, one must compare the partial pressure gradient and the solubility of both gases

$$D = \Delta P \times S$$

Partial pressure gradients:
$\Delta P_{CO2} = (47 - 40) = 7$ mmHg
$\Delta P_{O2} = (100 - 40) = 60$ mmHg

Solubility:
$CO > CO_2 >> O_2$

- CO_2 will diffuse first due to a much larger solubility, even though it has a smaller pressure gradient

2. "Emphysema is a chronic obstructive lung disease which leads to destruction of the alveoli. How will this affect the diffusion of O_2 and CO_2 across the alveoli?"

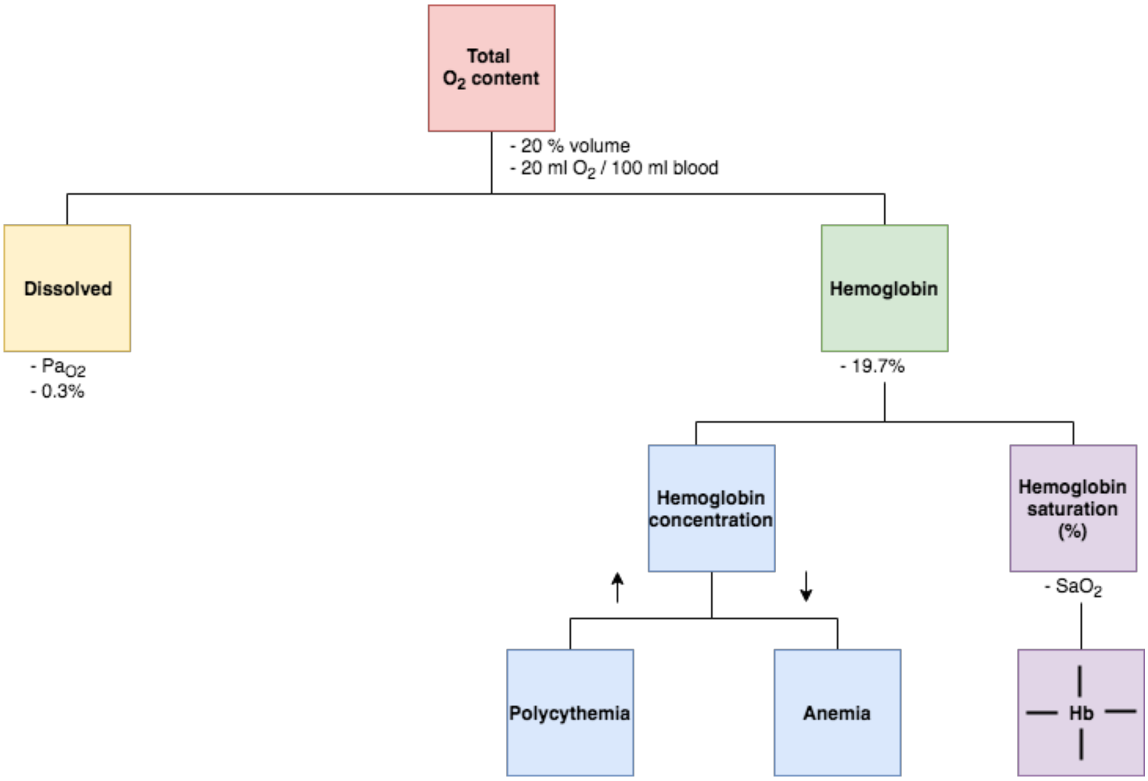
- Destruction of the alveoli will decrease the surface area of the lung

$$\downarrow D = \frac{\downarrow A \times \Delta P \times S}{\Delta x}$$

- Decreased surface area will impair the diffusion of both O_2 and CO_2
- Less O_2 will be able to diffuse from the alveoli into the blood → hypoxemia
- Less CO_2 will be able to diffuse from the blood into the alveoli → CO_2 builds up in the blood → hypercapnia

2.2 – Internal Respiration – Oxygen

2.2.1 – Total Oxygen Content



I. Dissolved oxygen

- Only form of oxygen which produces a partial pressure
- Not bound to hemoglobin

II. Hemoglobin

- Majority of circulating oxygen is bound to hemoglobin
- The amount of oxygen carried by hemoglobin is dependent on two variables

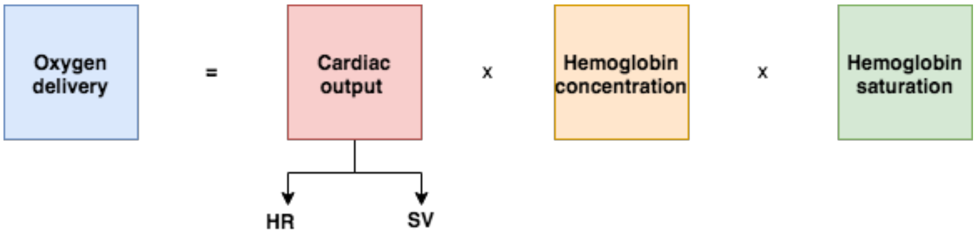
1. Concentration

- **Normal values:** 12-17 g/dL
- Hemoglobin concentration below the normal range is referred to as **anemia**
- Hemoglobin concentration above the normal range is referred to as **polycythemia**

2. Saturation

- A single molecule of hemoglobin can bind four oxygen molecules
- Hemoglobin is 100% saturated when four oxygen molecules are attached
- **Positive cooperativity:** When hemoglobin binds the first oxygen molecule, the next oxygen molecule will bind more easily

2.2.2 – Oxygen Delivery (D_LO_2)

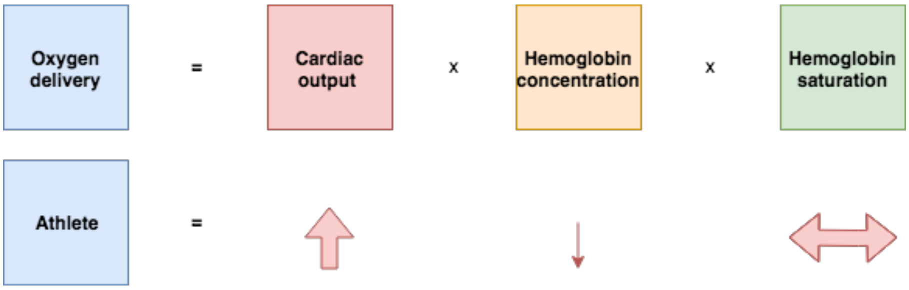


I. Definition

- Oxygen delivery to the tissues is determined by the blood flow (*cardiac output*) and the total oxygen content of blood

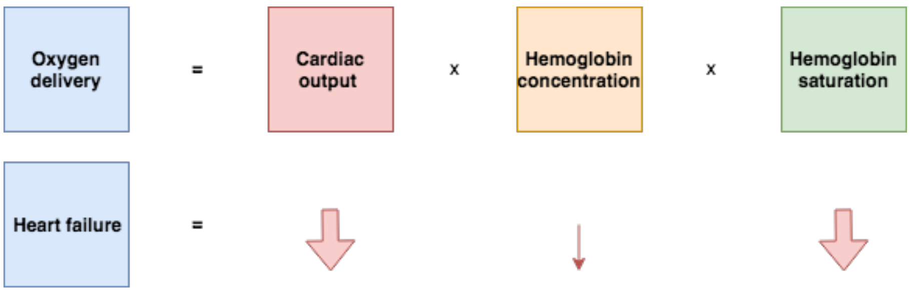
II. Clinical correlations

1. "How will a mild anemia affect the oxygen delivery in an young athlete?"



- Small drops in the hemoglobin concentration will be compensated by increasing the cardiac output
- Larger drops in hemoglobin is required for developing symptoms
- Oxygen delivery to the tissues will be maintained

2. "How will a mild anemia affect the oxygen delivery in an old patient with heart failure and chronic obstructive lung disease?"



- Small drops in the hemoglobin concentration will not be compensated by increasing the cardiac output
- Small drops in hemoglobin concentration is enough to cause symptoms
- Oxygen delivery to the tissues will worsen

2.2.4 – Oxygen-Hemoglobin Relationship

I. Affinity of hemoglobin to oxygen

- Under normal circumstances, the number of oxygen molecules unloaded from hemoglobin is determined by the amount of dissolved oxygen in the blood

1. **High amount of dissolved oxygen**
   - Blood is fully saturated with oxygen
   - The affinity of hemoglobin to oxygen is high
   - Unloading of oxygen from hemoglobin will be prevented

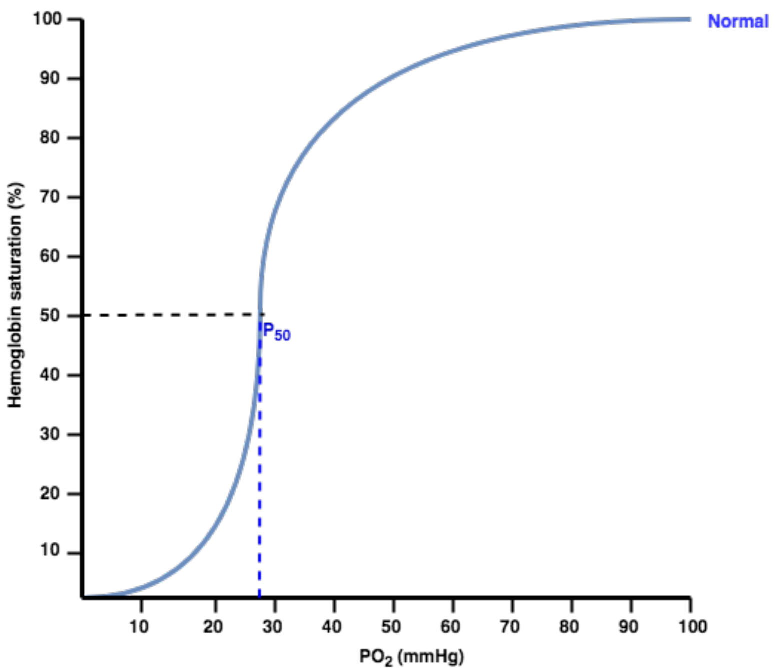
2. **Low amount of dissolved oxygen**
   - Blood is poorly saturated with oxygen
   - The affinity of hemoglobin to oxygen is low
   - Unloading of oxygen from hemoglobin will be favored

II. P_{50}

- Is the partial pressure of oxygen in blood (Pa_{O2}) at which hemoglobin is 50% saturated (25 mmHg)

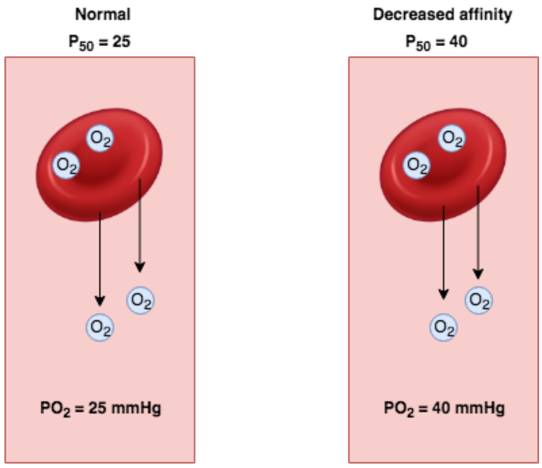
Pa_{O2}(mmHg)	Saturation (%)
100	> 96
40	75
25	**50**

III. Oxygen-hemoglobin dissociation curve



1. Decreased affinity of hemoglobin to oxygen

- Oxygen is less tightly bound to hemoglobin
- Hemoglobin will release more oxygen molecules at higher amounts of dissolved oxygen
- P_{50} is increased → curve shifted to the **right**
- **Example:** Muscle

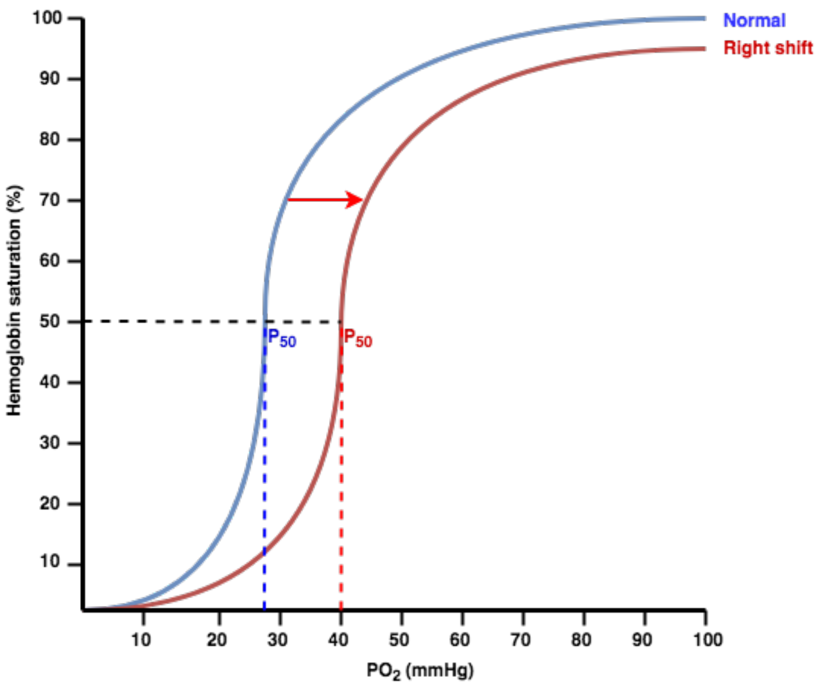


MNEUMONIC – RIGHT SHIFT

ACE BATs right handed:

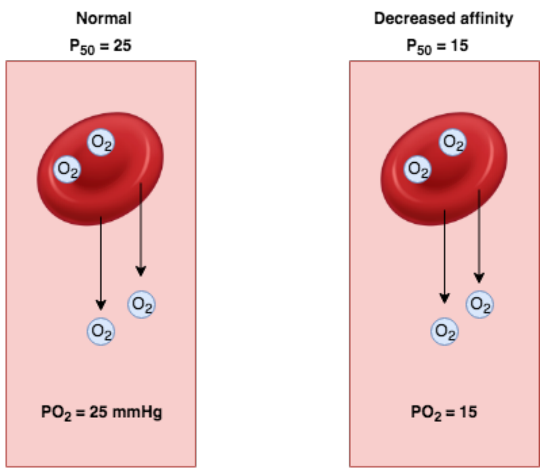
A – Acid
C – CO_2
E – Exercise
B – 2,3 **B**PG
A – **A**ltitude
T – **T**emperature

Variable	Comments
Increased P_{CO2} **Increased H^+**	- Bohr effect - Increased metabolic activity - Increased oxygen demand
Increased temperature	- Increased metabolic activity - Increased heat production - Increased oxygen demand
Increased 2,3 - BPG	- Product of RBC glycolysis - Increased metabolic activity - Increased oxygen demand

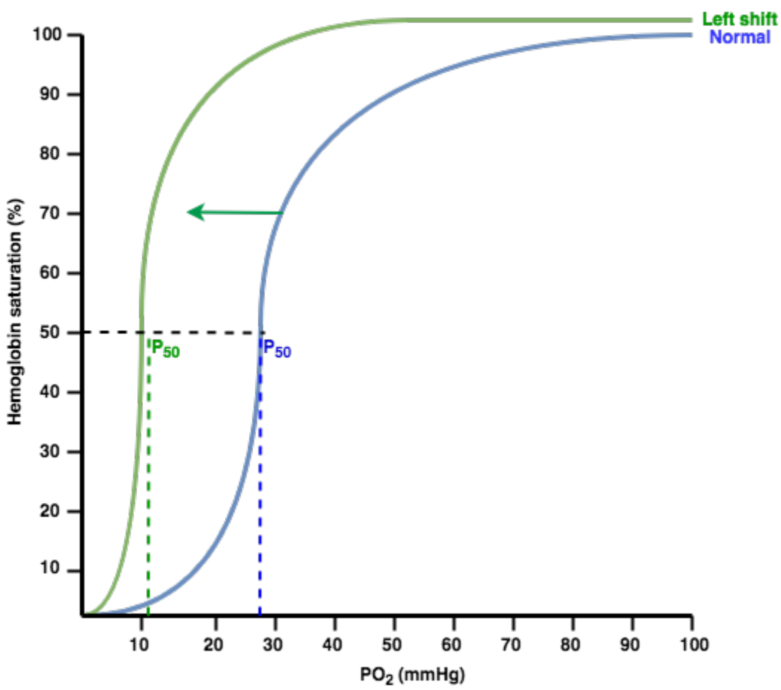


2. Increased affinity of hemoglobin to oxygen

- Oxygen is more tightly bound to hemoglobin
- Hemoglobin will release less oxygen molecules at lower amounts of dissolved oxygen
- P_{50} is decreased → curve shifted to the **left**
- **Example:** Pulmonary circulation after gas exchange

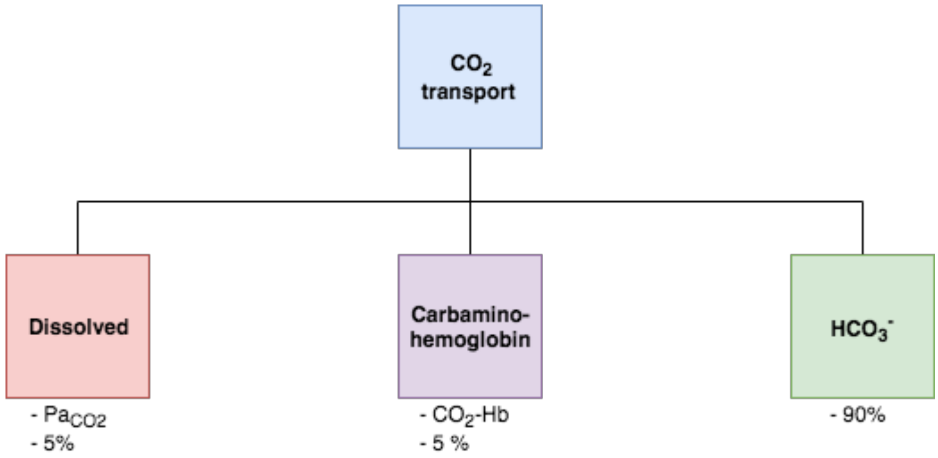


Variable	Comment
Decreased P_{CO2} **Decreased H^+**	- Decreased metabolic activity - Decreased oxygen demand
Decreased temperature	- Decreased metabolic activity - Decreased heat production - Decreased oxygen demand
Decreased 2,3 - BPG	- Decreased tissue metabolism - Decreased oxygen demand

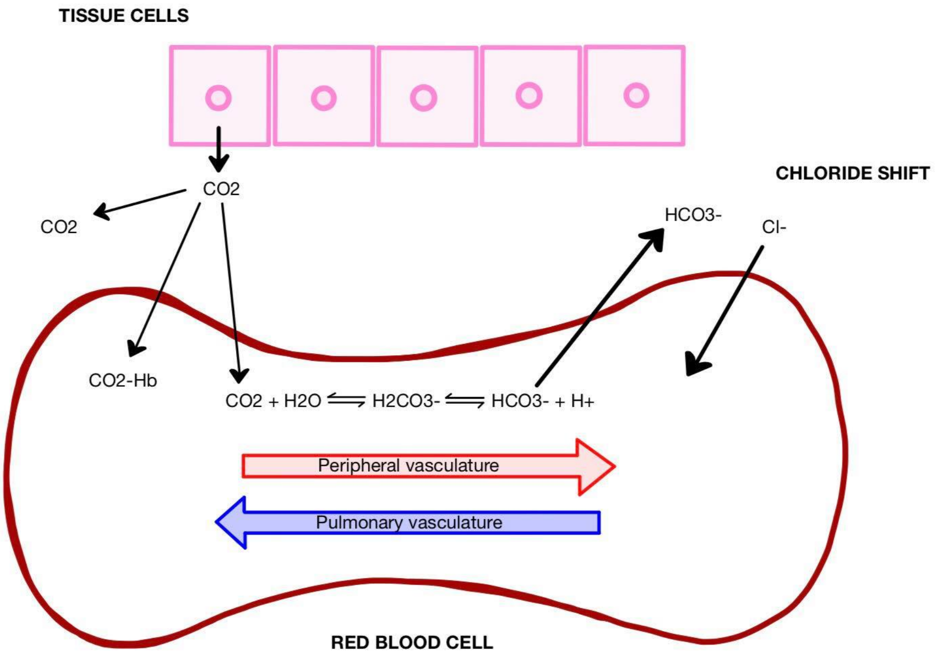


2.3 – Internal Respiration – Carbon Dioxide

2.3.1 – Overview



2.3.2 – HCO_3 transport



I. **Peripheral vasculature**
   - Due to the high amounts of CO_2 coming from the tissues, the reaction is shifted to towards HCO_3 production
   - CO_2 produced by tissue metabolism diffuses out of the tissues and into the red blood cell
   - CO_2 combines with H_2O to produce H_2CO_3, which dissociates into H^+ and HCO_3
   - HCO_3 is transported out of the RBC in exchange for Cl^- (*chloride shift*)

II. The pulmonary vasculature

- Due to the low amounts of CO_2 in the pulmonary vasculature, the reaction is shifted towards CO_2 production
- HCO_3^- will diffuse into the RBC in exchange for Cl^-
- HCO_3^- combines with H^+ to produce H_2CO_3, which is converted into CO_2 and H_2O
- CO_2 will diffuse out of the RBC and into the alveolus

2.4 – Test Yourself

1. Which factor(s) are the main determinants of the partial pressure of oxygen in the alveolus?

a) PA_{CO2}
b) Fi_{O2}
c) P_{atm}
d) P_{H2O}
e) B and D
f) B and C

2) Which of the following equations best describes the amount of oxygen present in the alveolus?

a) $PA_{O2} = Fi_{O2} \times (P_{atm} – P_{H20}) - (P_{CO2}/R)$
b) $Pa_{O2} = Fi_{O2} \times (P_{atm} – P_{H20}) - (P_{CO2}/R)$
c) $PA_{O2} = Fi_{O2} \times (P_{atm} – P_{H20})$
d) $PA_{O2} = Fi_{O2} \times (P_{atm} – P_{H20}) \times (P_{CO2}/R)$

3) What are the effects of supplemental oxygen?

a) It increases the P_{atm}
b) It increases the Fi_{O2}
c) Administration of 1 L/min of oxygen will increase the Fi_{O2} to 25%
d) Administration of 1 L/min of oxygen will increase the P_{atm} to 25%
e) A and D
f) B and C

4) Select the correct statement(s) regarding oxygen transport from the alveolus to the pulmonary capillary.

a) The direction of diffusion is determined by the partial pressure gradient
b) Gases will diffuse from an area of lower partial pressure to an area of higher partial pressure
c) Oxygen uploads directly on to hemoglobin during diffusion into the pulmonary capillary
d) Only gases bound to hemoglobin can participate in the partial pressure gradient
e) A and C
f) A and D

5) Select the correct statement(s) regarding Fick´s law of diffusion.

a) It describes how fast a gas will diffuse across a semipermeable membrane
b) It is dependent on surface area of the lung and size of the interstitial space
c) Pathologies which result in destruction of alveoli will decrease the diffusion rate of gases
d) It is dependent on the solubility and surface area of gases
e) A, B and C
f) B and C

6) Which of the following gases is most soluble?

a) Oxygen
b) Carbon dioxide
c) Carbon monoxide
d) Nitrogen

7) Select the correct statement(s) regarding the total oxygen content of blood.
a) The majority of oxygen is dissolved in blood
b) The majority of oxygen is bound to hemoglobin
c) The total oxygen content is determined by dissolved oxygen, hemoglobin saturation and hemoglobin concentration
d) The total oxygen content is determined by dissolved oxygen, hemoglobin saturation, hemoglobin concentration and cardiac output
e) B and C
f) B and D

8) "A young athlete comes to your office for her yearly checkup. She tells you that she has no complaints and is otherwise feeling healthy. As a part of the checkup, you take a blood sample to determine the hemoglobin level of the patient. When the results come back you see that her hemoglobin level is slightly decreased. Select the correct statement(s) regarding the oxygen delivery and symptoms in this patient."
a) The oxygen delivery will be decreased
b) Oxygen delivery will be maintained due to the ability of young patients to increase their hemoglobin production
c) Oxygen delivery will be maintained due to the ability of young patients to compensate by increasing their cardiac output
d) The patient may have no other signs of anemia than a slight increase in heart rate
e) The patient will be pale
f) B and E
g) C and D

9) Select the correctly matched pairs.
a) ↑ CO_2 – Right shift
b) ↓ Temperature – Right shift
c) ↑ pH – Left shift
d) Bohr effect – Left shift
e) ↑H^+ – Right shift
f) ↓ 2,3 BPG – Left shift

10) Select the correct statement(s) regarding the P_{50} value.
a) It is the partial pressure of oxygen at which hemoglobin is 50% saturated
b) It is the partial pressure of carbon dioxide at which hemoglobin is 50% saturated
c) It is increased with right shifts
d) It is increased with left shifts
e) A and C
f) A and D

11) In the transport of CO_2 from the tissues to the lungs; which of the following occurs in venous blood?
a) Conversion of CO_2 and H_2O to H^+ and HCO_3 in red blood cells
b) Shifting of HCO_3 into the RBCs from plasma in exchange for Cl^-
c) Binding of HCO_3 to hemoglobin
d) Conversion of HCO_3 and H^+ to CO_2 and H_2O

12) Most of the CO_2 transported in the blood is:

a) Dissolved in plasma (Pa_{CO2})

b) In the form of carbaminohemoglobin

c) Transported as HCO_3^-

d) Combined with chloride

13) Select the correct statement(s) regarding CO_2 transport in the lung.

a) There is conversion of CO_2 and H_2O to H^+ and HCO_3^- in red blood cells

b) There is conversion of HCO_3^- and H^+ to CO_2 and H_2O in red blood cells

c) The chloride concentration in the red blood cell decreases

d) The chloride concentration in the red blood cell increases

e) B and C

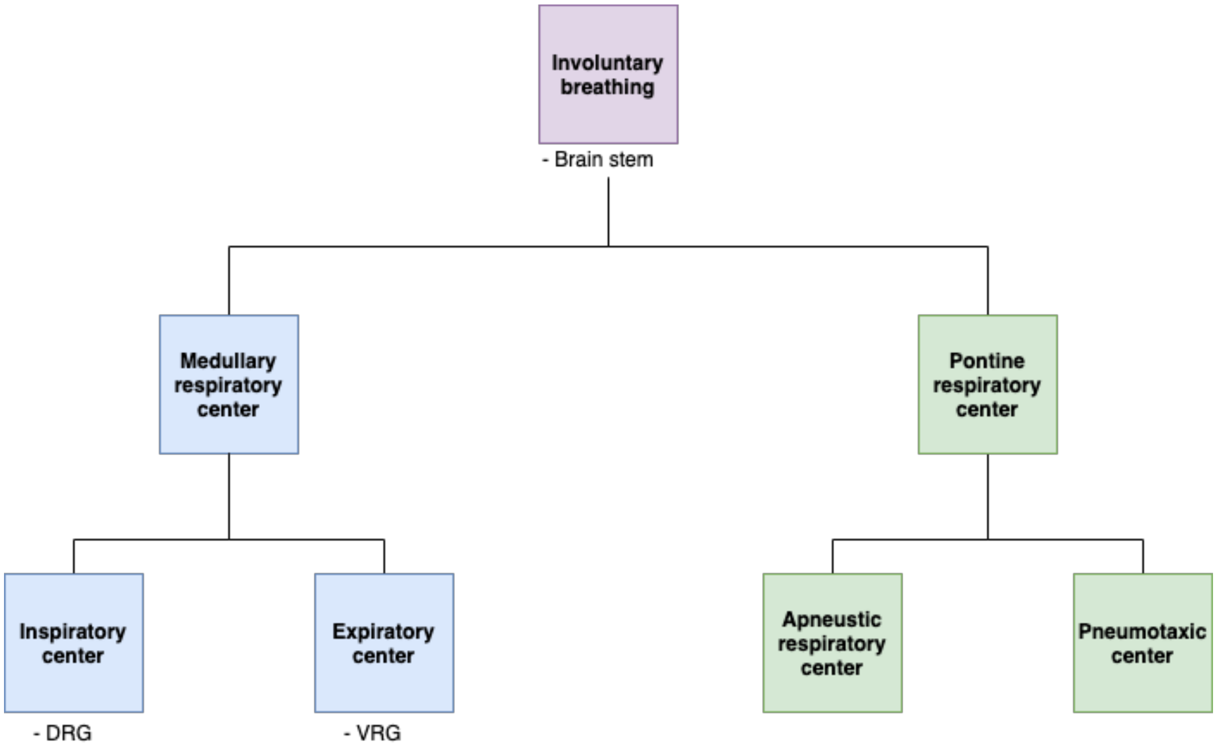
f) B and D

Section 3 – Control of Breathing

3.0 – Involuntary Breathing

- Involuntary breathing is controlled by specific centers located in the **brain stem**

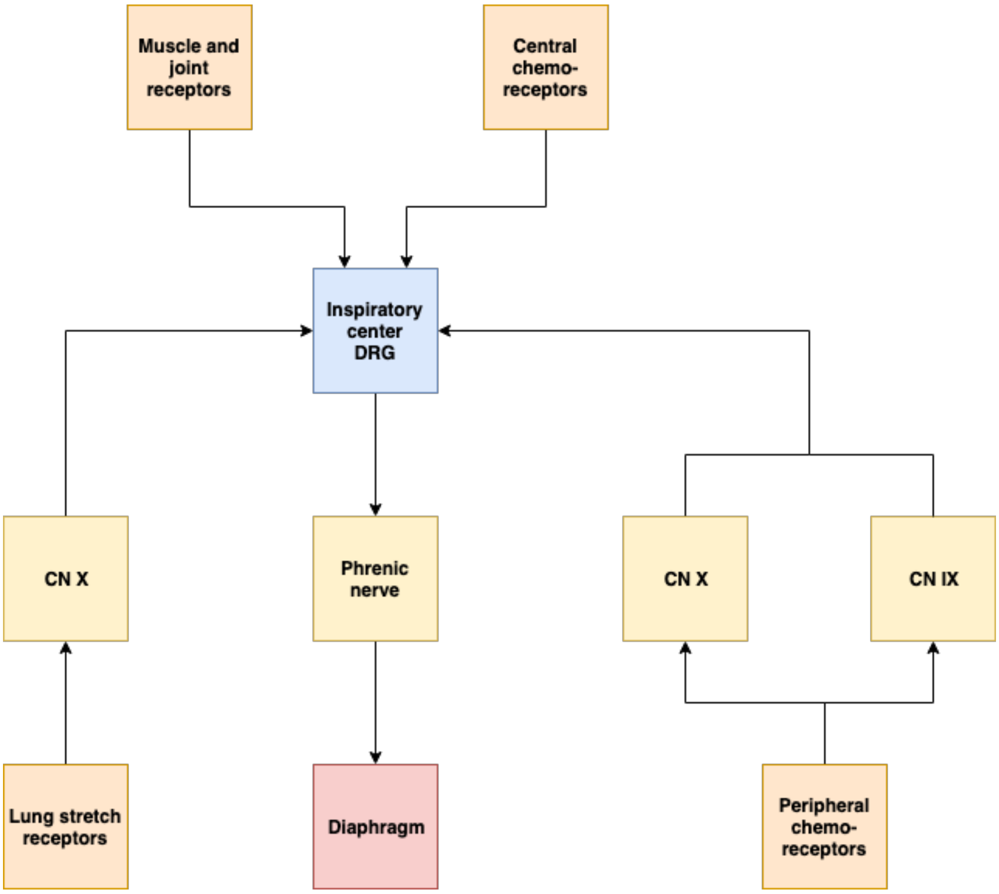
3.0.1 – Overview



3.0.2 – The Medullary Respiratory Center

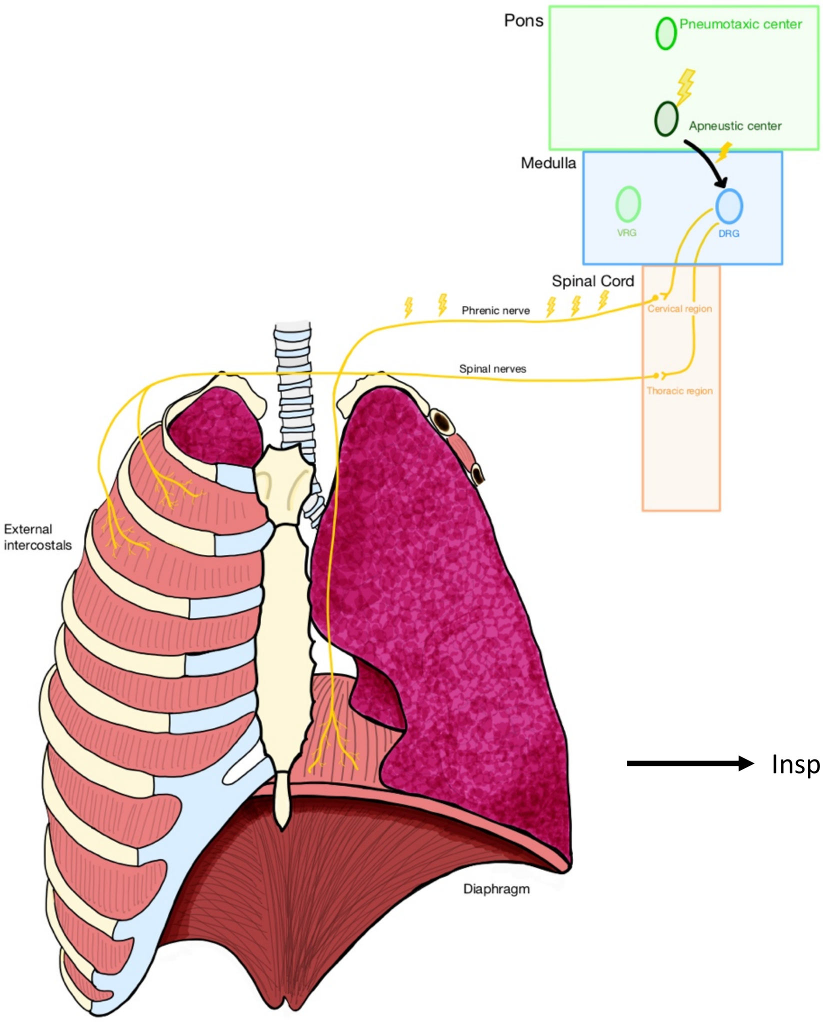
I. Inspiratory center

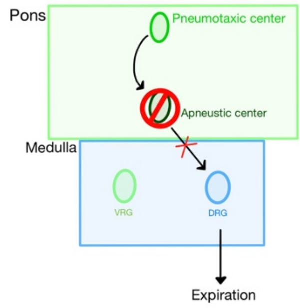
- Located in the dorsal respiratory group (DRG)
- The DRG is active only during inspiration and maintains the rate of normal, quiet breathing
- Receives sensory input from peripheral chemoreceptors
- Sends motor output to the diaphragm signaling contraction
- The posterior neurons of the DRG receives information from the Hering-Breuer reflex → inhibition of inspiration
- The DRG is inhibited by the pneumotaxic center



II. The expiratory center

- Located in the ventral respiratory group (VRG)
- The VRG is made up from neurons of the nucleus ambiguous, nucleus retroambiguus, and the **Pre-Bötzinger complex** (inspiratory and expiratory neurons)
- The Pre-Bötzinger complex is important in rhythmic respiration
- Inactive during normal quiet breathing
- Active during vigorous breathing, like exercise, signaling contraction of expiratory muscles
- The VRG sends inhibitory impulses to the apneustic center





→ Inspiration

3.0.3 – The Pontine Respiratory Center

I. Apneustic center

- Located in the lower pons
- Stimulates the DRG → increased depth of inspiration by sending action potentials via the phrenic nerve to the inspiratory muscles

II. Pneumotaxic center

- Located in the upper pons
- Inhibits the apneustic center → turning off inspiration and activating passive expiration allowing for an even transition from inspiration to expiration

CLINICAL CORRELATION

Q: "A patient presents at the emergency ward gasping for breath. Physical examination of the patient reveals prolonged deep inspiration followed by a brief and insufficient expiration. What part of the brain is damaged?"

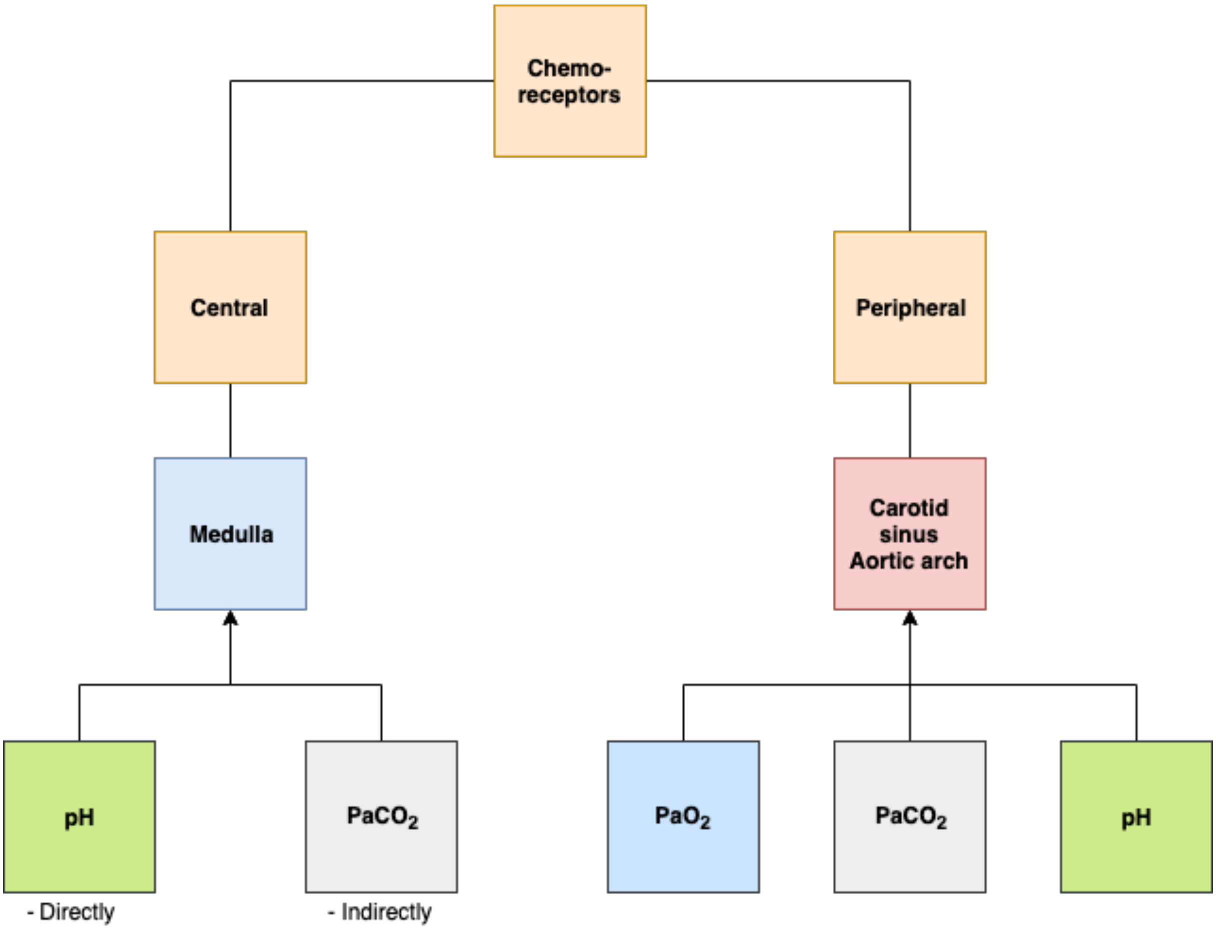
A: The patient is presenting with symptoms of **apneusis**, indicating damage to the upper pons and the pneumotaxic center.

Damage to the pneumotaxic center leads to loss of inhibition of the apneustic center, resulting in continuous inspiration.

3.1 – Chemoreceptors

3.1.1 – Overview

- Chemoreceptors detect changes in Pa_{O2}, Pa_{CO2}, and arterial pH and send this sensory information to the brain stem.



3.1.2 – Peripheral Chemoreceptors

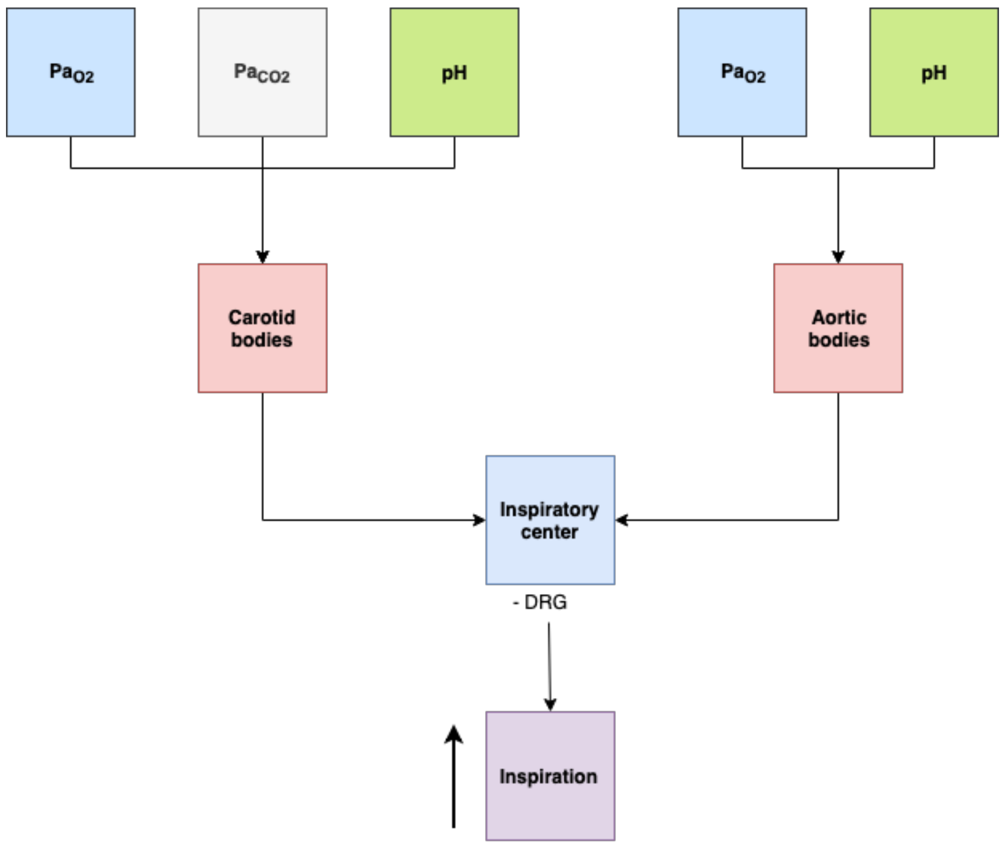
- The goal of the peripheral chemoreceptors is to detect any changes in Pa_{O2}, Pa_{CO2} or arterial pH
- Stimulation leads to an increase in respiratory rate

I. The carotid bodies

- Located in the bifurcation of the common carotid arteries
- Stimulated by decreased Pa_{O2} (< 60 mmHg), increased Pa_{CO2} and decreased arterial pH
- The peripheral chemoreceptors of the carotid bodies can also be called the **glomus type I cells**

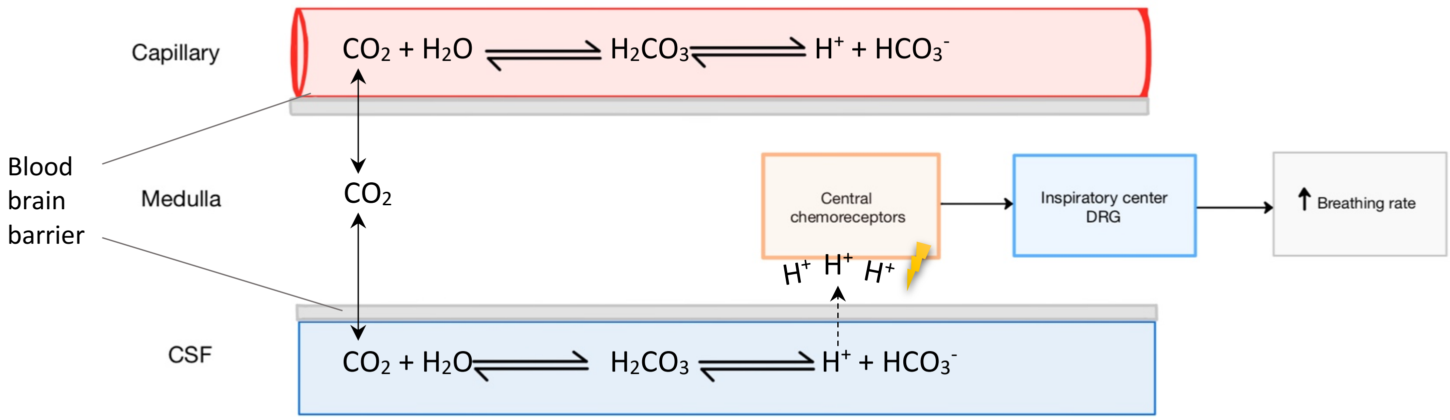
II. The aortic bodies

- Located in the aortic arch
- Stimulated by decreased Pa_{O2} and increased Pa_{CO2}



3.1.3 – Central Chemoreceptors

- Located on the ventral surface of the medulla
- The main drive of normal ventilation
- Increased Pa_{CO2} → increased H^+ in cerebrospinal fluid (CSF) → decreased pH in CSF
- Central chemoreceptors detect decreased pH in CSF → stimulation of the inspiratory center that increases respiratory rate to get rid of excess CO_2



<u>CLINICAL CORRELATION</u>

Q: "A patient is admitted to the hospital after overdosing on morphine. He is presenting with hypoventilation and a Pa_{O2} of 55 mmHg. To increase the Pa_{O2} you give the patient oxygen. Suddenly your patient stops breathing. What happened?"

A: - Morphine, an opioid, inhibits the central chemoreceptors and causes hypoventilation (decreased respiratory rate)
- Hypoventilation leads to increased Pa_{CO2} and decreased Pa_{O2}.
- Since morphine inhibits the central chemoreceptors, they will not respond to the increased Pa_{CO2}.
- When Pa_{O2} drops below 60 mmHg the peripheral chemoreceptors are activated, increasing the respiratory rate to increase Pa_{O2}.
- Treatment with oxygen rapidly rises Pa_{O2} above 60 mmHg and there is no longer stimulation of the peripheral chemoreceptors. Now both central and peripheral chemoreceptors are inhibited, and the patient stops breathing.

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3.2 – Other Receptors

	Lung stretch receptors	Joint and muscle receptors	Irritant receptors	Juxtacapillary[2] receptors
Type	Mechanoreceptor	Mechanoreceptor	Rapidly adapting receptors	Sensory nerve endings
Location	Airway smooth muscle	Joints and muscles	Between airway epithelial cells	Alveolar walls
Stimulation	Distension of the lungs	Movement of limbs during exercise	Noxious chemicals and particles	- ↑ Blood volume - ↑ Interstitial fluid volume
Effect on respiratory rate	↓	↑	↑	↑
Reflexes	Hering-Breuer reflex		Coughing reflex[1]	

[1]Caused by constriction of bronchial smooth muscle

[2]Juxta means close to/near; juxtacapillaries = close to capillaries, they are also called pulmonary **C-fiber receptors**

I. Hering-Breuer reflex

- Activated by stretch receptors in the wall of bronchi and bronchioles, when tidal volume > 1.5 liters (3 times that of normal V_T)
- It functions to protect the lungs from overinflation
- <u>**Effects:**</u> Turns off inspiration and prolongs expiratory time

II. Juxtacapillary receptors (C-fibers)

- Stimulation of C-fibers leads to rapid shallow breathing, bronchoconstriction, apnea and muscle relaxation

<u>CLINICAL CORRELATION</u>

Left-sided heart failure
Blood backs up into the pulmonary circulation

↓

↑ Blood volume

↓

J receptors (C-fibers)

↓

Rapid shallow breathing
and
dyspnea
(shortness of breath)

3.3 – Voluntary Breathing

I. Definition

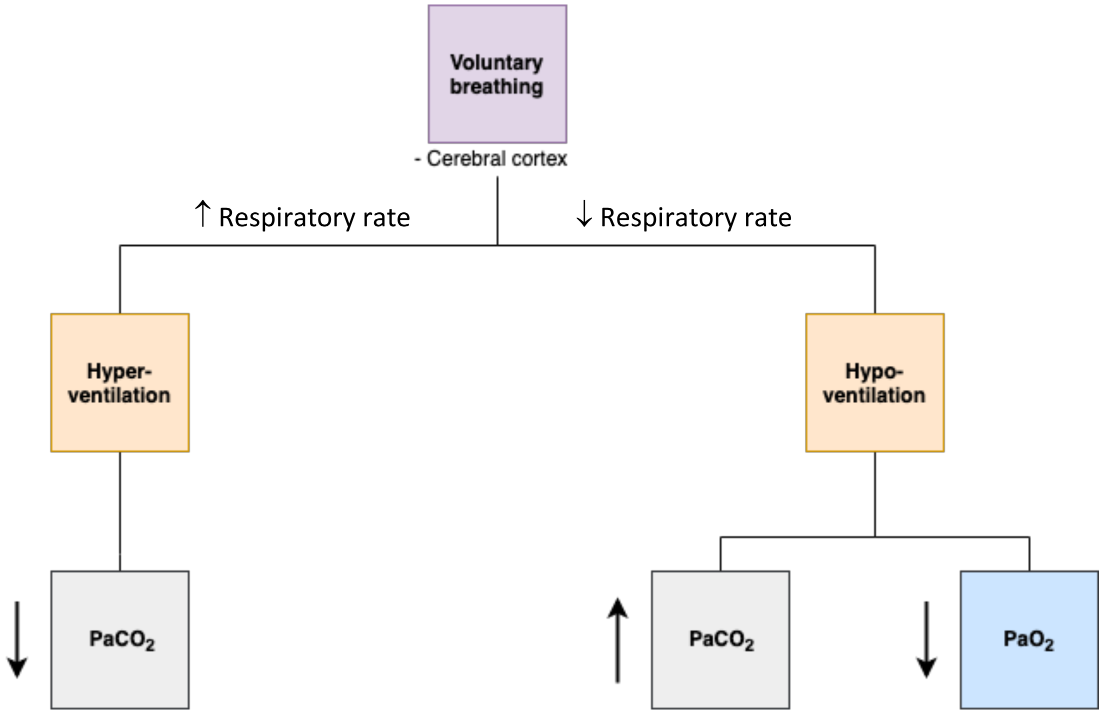
- The cerebral cortex can override the brain stem by sending impulses to the respiratory motor neurons via the **cortical spinal tract** activating impulses innervating muscles of inspiration.

II. Hypoventilation

- **Definition:** Respiratory rate below 12
- Decreased respiratory rate → increased Pa_{CO2} → decreased arterial pH, respiratory acidosis

III. Hyperventilation

- **Definition:** Respiratory rate above 20
- Increased respiratory rate → decreased Pa_{CO2} → increased arterial pH, respiratory alkalosis



3.4 – Test Yourself

1) Connect the correct center with its location in the brain stem.

Expiratory center	Upper pons
Apneustic center	Medulla - VRG
Inspiratory center	Medulla - DRG
Pneumotaxic center	Lower pons

2) Which of the following does NOT stimulate the inspiratory center?

a) Muscle and joint receptors
b) Pneumotaxic center
c) Glomus type I cells
d) Central chemoreceptors

3) Which medullary center contains both inspiratory and expiratory neurons?

a) The center located in the dorsal respiratory group
b) The center that inhibits the apneustic center
c) The center that is inactive during normal quiet breathing
d) The center that maintains the rate of inspiration

4) Which of the following causes inhibition of the apneustic center?

a) Apneusis
b) Passive expiration
c) Activation of inspiratory center
d) Increased action potential via the phrenic nerve

5) True or False.

Aortic bodies are stimulated when the PaO_2 is 70 mmHg	**T / F**
Central chemoreceptors are directly stimulated by CO_2	**T / F**
Irritant receptors are also called rapidly adapting receptors	**T / F**
Hypoventilation leads to ↓ Pa_{CO2}	**T / F**

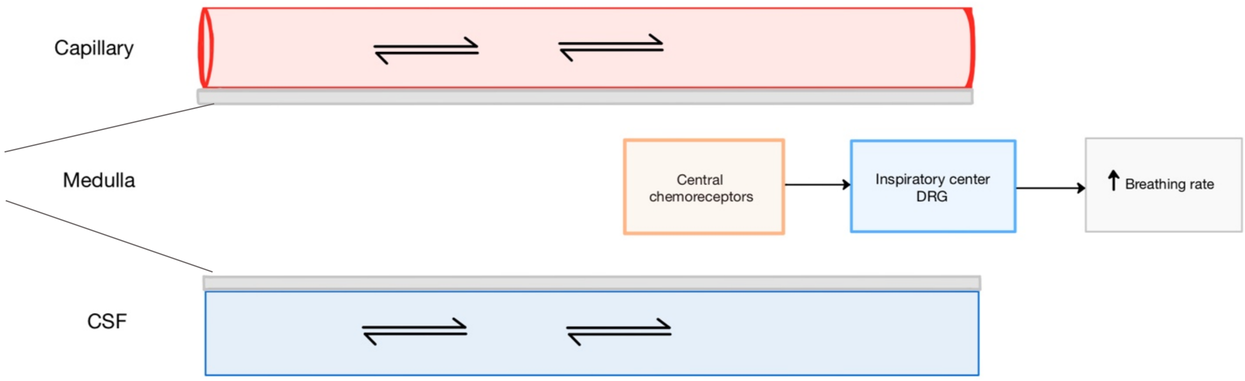
6) Choose the correct statement.

a) C-fibers are also known as juxtaglomerular receptors
b) The Hering-Breuer reflex is activated when V_T > 1,5 liters
c) Lung stretch receptors increase respiratory rate
d) Rapidly adapting receptors are found in airway smooth muscle

7) Fill in the blanks.

a) Symptoms of ______________ are prolonged deep inspiration followed by a brief, insufficient expiration. This is caused by damage to the ____________ center.
b) Hyperventilation leads to ___ Pa_{CO2}
c) Hypoventilation leads to ___ Pa_{CO2} and ___ Pa_{O2}
d) The posterior neurons of the DRG receive information from the ____________

8) Finish the central chemoreceptor activation pathway.



9) Fill in the blanks.

The central chemoreceptors are _________ stimulated by CO_2 and _________ stimulated by H^+ (decreased pH).

10) Fill in the table.

		Joint and muscle receptors		Juxtacapillary[2] receptors
Type	Mechanoreceptor		Rapidly adapting receptors	
Location		Joints and muscles		Alveolar walls
Stimulation	Distension of the lungs		Noxious chemicals and particles	- __ Blood volume - __ Interstitial fluid volume
Effect on respiratory rate				
Comments/ reflexes	Hering-Breuer reflex		Coughing reflex	

Section 4 – Integrative Functions

4.0 – Exercise

I. **Hyperpnea**

- **Definition:** Increase in depth and/or respiratory rate without changing the *arterial* blood chemistry
- In physiological conditions; increased oxygen demand during exercise or lack of oxygen in high altitudes

II. **Increased oxygen demand**

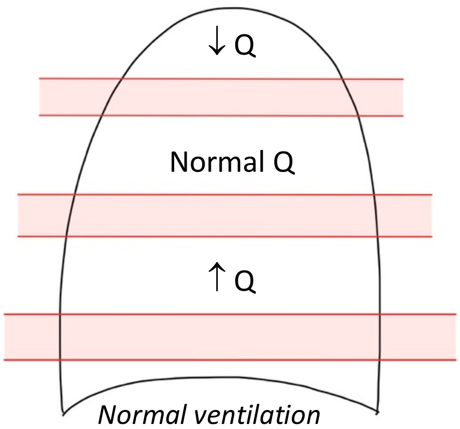
- During exercise, there is increased muscle work which requires ATP
- Increased muscle work → increased ATP utilization → increased oxygen demand
- During **anaerobic exercise** oxygen demand overrides oxygen supply to tissue → production of lactic acid and decreased pH
- Decreased pH activates carotid chemoreceptors → increased ventilation and increased oxygen

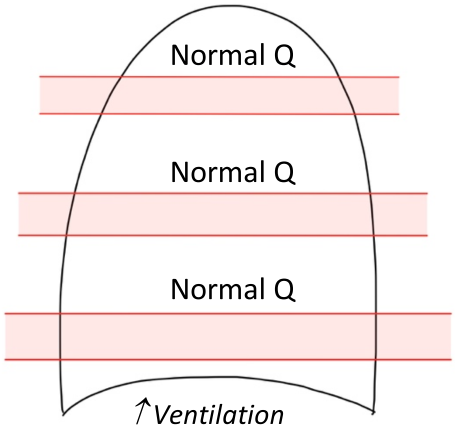
III. **Increased ventilation**

- Contraction of muscles stimulate muscle-joint receptors which send signals to the DRG → increased respiratory rate
- During exercise VRG is also activated leading to stimulation of expiratory muscles
- Increased ventilation and expiratory force → increased oxygenation of *all* parts of the lung → increased gas exchange and decreased physiological dead space

IV. **Increased cardiac output**

- **Normal:** 5 L/min
- **Exercise:** Up to 6x normal CO (≈ 30 L/min)
- **Effects:** Increased perfusion (Q) of lungs from right ventricle → increased gas exchange

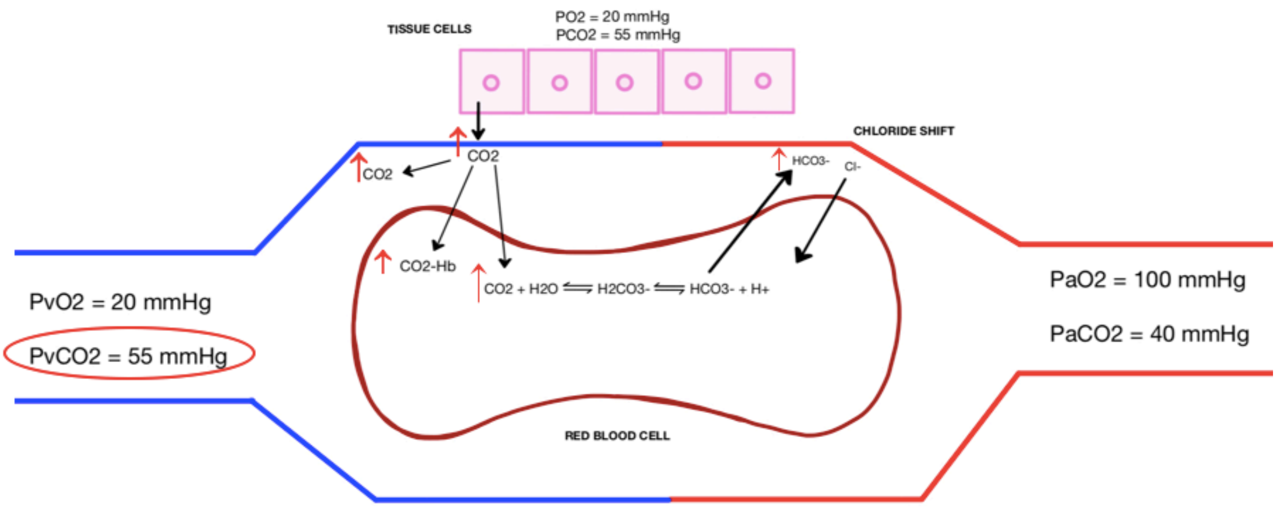




V. Gas exchange at tissue site

- **No change** in *arterial* P_{O2} and P_{CO2}
- **Change** in *venous* P_{CO2}
- Tissue P_{O2} is decreased and tissue P_{CO2} is increased
- Venous P_{CO2} is increased due to excess production of CO_2 by exercising muscle cells

	Normal conditions	Exercise
Pa_{O2}	100 mmHg	No change
Pa_{CO2}	40 mmHg	No change
Tissue P_{O2}	40 mmHg	↓
Tissue P_{CO2}	47 mmHg	↑
Venous P_{O2}	40 mmHg	↓
Venous P_{CO2}	47 mmHg	↑



VI. **Bohr effect**

- **<u>Definition:</u>** Increased CO_2 and decreased pH
- **<u>Exercise on CO_2 levels:</u>** Increased metabolism will increase in venous, hemoglobin and red blood cell CO_2 concentration
- **<u>Effects of increased venous CO_2</u>**: Decreased pH
- **<u>Effects on hemoglobin</u>**: Decreased affinity of hemoglobin to oxygen and increased oxygen-delivery to tissues

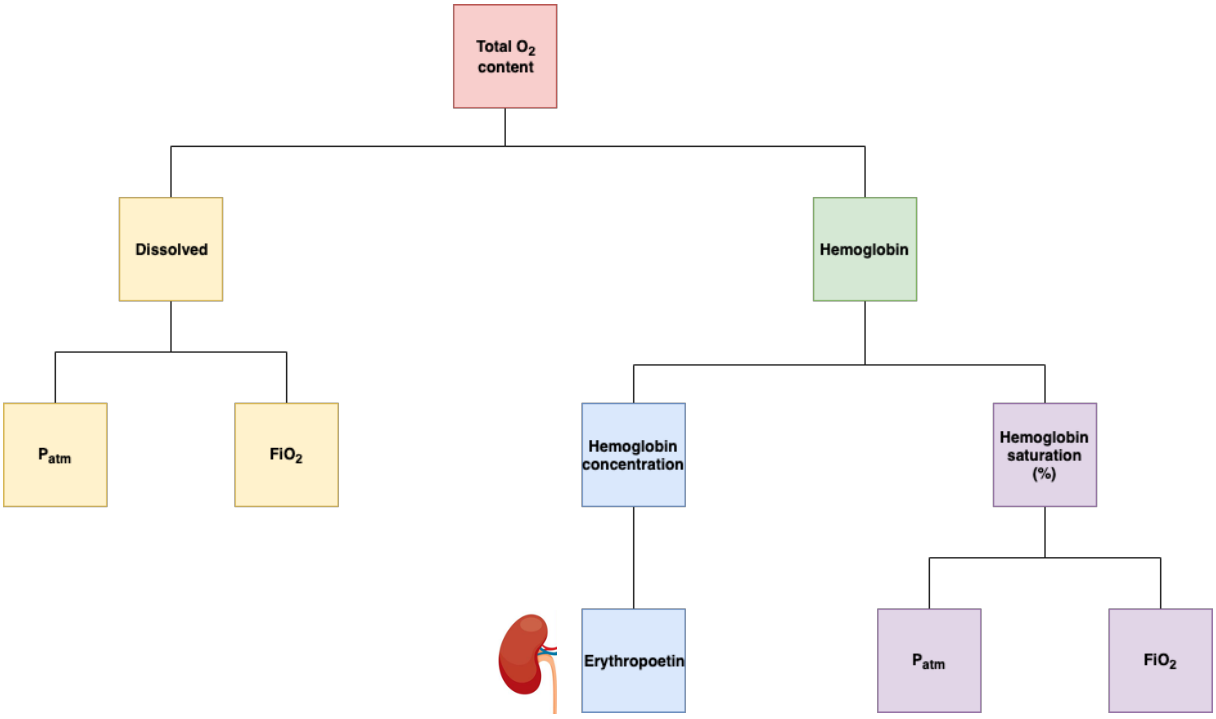
VII. **2,3 BPG**

- Increased production by red blood cells during hypoxia
- **<u>Effects on hemoglobin:</u>** Decreased affinity of hemoglobin to oxygen and increased oxygen-delivery to the tissues

4.1 – High Altitude

4.1.1 – O_2 content dependent factors

- Total oxygen content = Pa_{O2} + [Hb] + Sa_{O2}



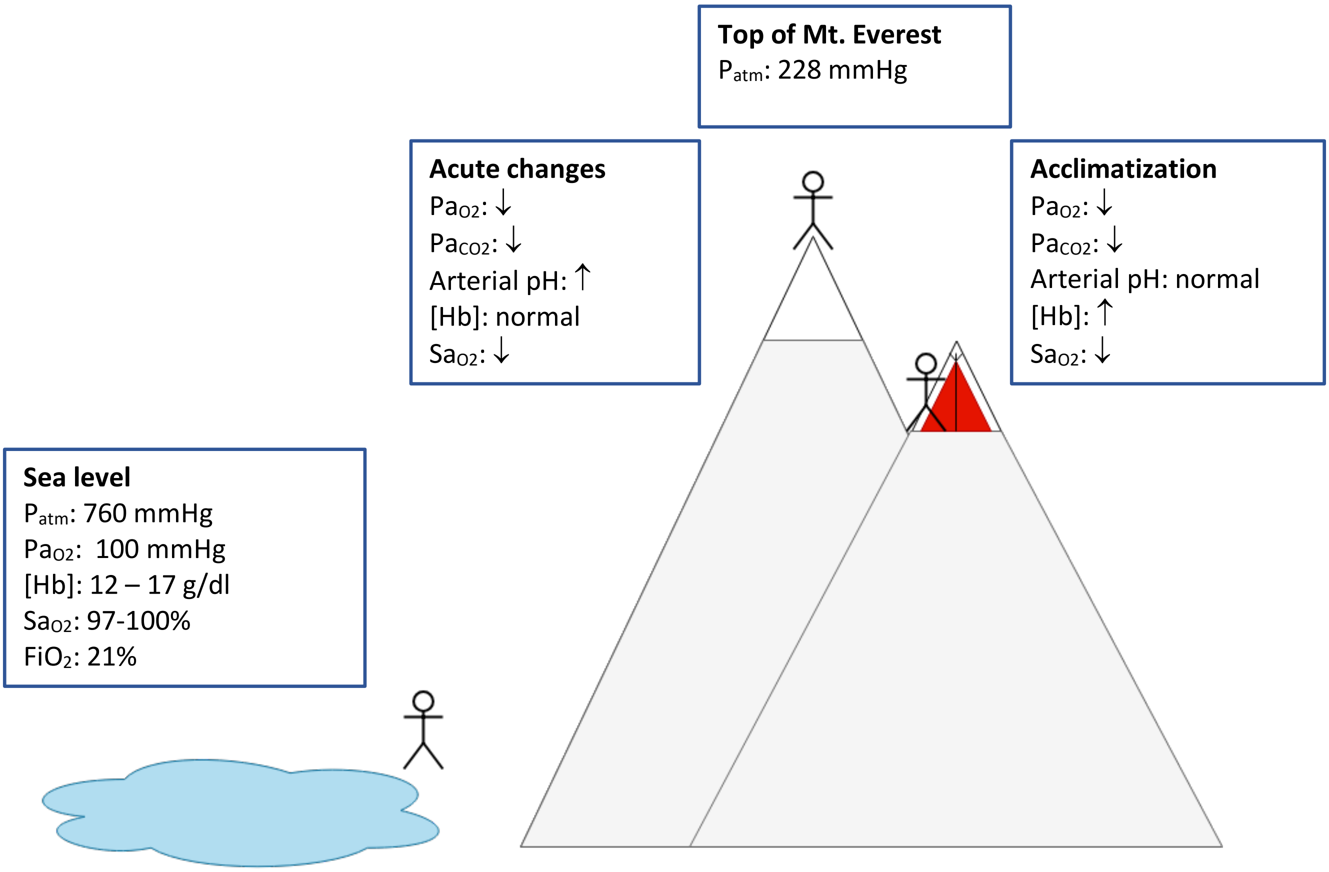
I. Acute changes

- Decreased Pa_{O2} is due to low P_{atm} → activation of peripheral chemoreceptors → ↑ RR and **hyperventilation**
- Decreased Pa_{CO2} due to hyperventilation
- Increased arterial pH, respiratory alkalosis, due to decreased CO_2
- Hemoglobin concentration is unaffected
- Decreased Hb saturation due to low P_{atm}

II. Acclimatization

- Decreased Pa_{O2} due to low P_{atm}
- Decreased Pa_{CO2} due to persistent hyperventilation
- **Arterial pH stabilizes** due to compensatory increase in HCO_3^- excretion from the kidney (compensatory metabolic acidosis)
- Increased hemoglobin concentration, **polycytemia**, is due to activation of erythropoietin in kidney due to decreased O_2 content. Erythropoietin promotes production of RBC in bone marrow
- Decreased Hb saturation due to low P_{atm}

III. Summary



	Acute changes	Acclimatization
PaO_2	↓	↓
$PaCO_2$	↓	↓
Arterial pH	↑	normal
[Hb]	normal	↑
Hb saturation (%)	↓	normal

4.2 – Test Yourself

1) Fill in the correct answer.

During exercise, there is ________ (increased/decreased) muscle exertion. The working muscle requires O_2 to produce ____ (lactic acid/ATP), resulting in __ (increased/decreased) O_2 demand.

2) What receptor is activated during exercise (that is inactive during normal, quiet breathing)?

a) Dorsal Respiratory Group

b) Pneumotaxic center

c) Central chemoreceptors

d) Ventral Respiratory Group

3) Explain why perfusion (Q) in the lungs increases with increased ventilation.

4) Select the correct response to exercise.

a) PaO_2 increases

b) Venous PCO_2 has no change

c) $PaCO_2$ decreases

d) Tissue PO_2 decreases

5) True or false.

a) 2,3-BPG increases oxygen affinity to hemoglobin	**T/F**
b) In response to increased oxygen demand more 2,3-BPG is produced	**T/F**
c) The Bohr effect refers to a change in oxygen-hemoglobin dissociation curve due to changes in CO_2, pH, and 2,3-BPG	**T/F**
e) O_2-Hemoglobin dissociation curve shifts to the right during exercise	**T/F**

6) Place the correct responses to acute changes and acclimatization to high altitude. The responses may be used once, twice or not at all.

Acute changes	Acclimatization

↓ PaO_2, ↑ $PaCO_2$, hyperventilation, hypoventilation, respiratory alkalosis, respiratory acidosis, normal pH, ↓ Hb saturation, ↑ Hb saturation, normal Hb concentration, ↑ Hb concentration, ↓ Hb concentration

7) Choose the correct statement.

a) Exposure to high altitude leads to hypoventilation

b) Decrease in atmospheric pressure leads to increased hemoglobin saturation

c) pH stabilized back to normal during acclimatization due to increased HCO_3 excretion from the kidneys

d) Exposure to high altitude leads to left shift of the oxygen-hemoglobin dissociation curve

8) Choose the correct statement describing hypoxemia.

a) Respiratory rate above 20 breaths/minute

b) Insufficient levels of Pa_{O2}

c) Respiratory rate below 12 breaths/minute

d) Insufficient oxygen at the cellular level

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