RESPIRATION

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**INSPIRATION:**

- **INSPIRATION:** Inspiration is the active part of the breathing process, which is initiated by the respiratory control centre in medulla oblongata (Brain stem).

- Activation of medulla causes a contraction of the diaphragm and intercostal muscles leading to an expansion of thoracic cavity and a decrease in the pleural space pressure. The diaphragm is a dome-shaped structure that separates

- The thoracic and abdominal cavities and is the most important muscle of inspiration. When it contracts, it moves downward and because it is attached to the lower ribs it also rotates the ribs toward the horizontal plane, and thereby further expands the chest cavity
• In normal quiet breathing the diaphragm moves downward about 1 cm but on forced inspiration/expiration total movement could be up to 10 cm. When it is paralysed it moves to the opposite direction (upwards) with inspiration, paradoxical movement.
**EXPIRATION:**

Expiration is a passive event due to elastic recoil of the lungs. However, when a great deal of air has to be removed quickly, as in exercise, or when the airways narrow excessively during expiration, as in asthma, the internal intercostal muscles and the anterior abdominal muscles contract and accelerate expiration by raising pleural pressure.
THORACIC CAVITY
THORACIC CAVITY

- Lung
- Pleural sac
- Parietal pleura
- Visceral pleura
- Diaphragm
- Intercostal muscle
- Pleural cavity
PRESSURE-VOLUME RELATIONSHIPS:

• In the pulmonary physiology absolute pressure means atmospheric pressure (760 mm Hg at sea levels). The pressures and the pressure differences of the respiratory system are expressed as relative pressures to the atmospheric pressure. When it is said that alveolar pressure is zero, it means that alveolar pressure = atmospheric pressure.

• Important point is the volume at a given pressure during deflation is always larger than during inflation. Even when the pressure outside the lung is increased above the atmospheric pressure, very little further air is lost and the air is trapped in the alveoli. The volume of the air trapped in the lung is increased with age and in some respiratory diseases.
The volume change per unit pressure is known as compliance. In normal expanding range (2-10 mm water) the lung is very dispensable, in other words it is very compliant. The compliance of the human lung is 0.15 L/cm H2O. However, it gets stiffer (compliance smaller) as it is expanded above the normal range.
Compliance is reduced when:

1. The pulmonary venous pressure is increased and the lung becomes engorged with blood.
2. There is alveolar oedema due to insufficiency of alveolar inflation.
3. The lung remains unventilated for a while e.g. atelectasis and because of diseases causing fibrosis of the lung e.g. chronic restrictive lung disease.
• On the contrary in chronic obstructive pulmonary disease (COPD, e.g. emphysema) the alveolar walls progressively degenerate, which increases the compliance. The lung compliance is changed according to the lung size.

• At the birth the lung compliance is the smallest and increased with age (until adulthood) due to increase in the size of the lungs. Specific compliance (compliance per unit of lung volume) could be calculated in order to correct this value for lung size. In asthma (hyperactive airway smooth muscle) the lung compliance is usually normal.
CHEST WALL COMPLIANCE:

- Changes in chest wall compliance are less common than changes in the lung compliance.
- Pathologic situations preventing the normal movement of the rib cage, such as:
  1. Distortion of the spinal column,
  2. Pathologic (cancer) or physiologic (pregnancy) reasons increasing the intra abdominal pressure,
  3. Stiff chest, such as broken ribs.
SURFACE TENSION

• A thin film of liquid lines the alveoli and the surface tension of this film is another important factor in the pressure-volume relationship of the lung. The surface tension arises because the attractive forces between adjacent molecules of the liquid are much stronger than those of between the liquid and the gas.

• The most important component of this liquid film is surfactant. It is produced by type 2 alveolar epithelial cells and its major constituent is dipalmitoyl phosphatidylcholine (DPPC), a phospholipid with detergent properties.
• Surfactant synthesis starts relatively late in foetal life and premature babies without adequate amount of surfactant develop respiratory distress which could be life threatening.
What are the advantages of having surfactant and the low surface tension?

• 1. It increases the compliance of the lung
• 2. It reduces the work of expanding of the lung with each breath
• 3. It stabilises the alveoli (thus the smaller alveoli do not collapse at the end-expiration)
• 4. It keeps the alveoli dry (as the surface tension tends to collapse alveoli, it also tends to suck fluid into the alveolar space from capillaries).
Basic elements of the respiratory control system are:

(1) strategically placed sensors
(2) central controller
(3) respiratory muscles
Breathing is mainly controlled at the level of brainstem. The normal automatic and periodic nature of breathing is triggered and controlled by the respiratory centres located in the pons and medulla. These centres are not located in a special nucleus or a group of nuclei but they are rather poor defined collection of neurones.
Medullary respiratory centre

- Dorsal medullary respiratory neurones are associated with inspiration: It has been proposed that spontaneous intrinsic periodic firing of these neurones responsible for the basic rhythm of breathing.

- As a result, these neurones exhibit a cycle of activity that arises spontaneously every few seconds and establish the basic rhythm of the respiration.
Ventral medullary respiratory neurones

- Ventral medullary respiratory neurones are associated with expiration. These neurones are silent during quite breathing because expiration is a passive event following an active inspiration. However, they are activated during forced expiration when the rate and the depth of the respiration is increased e.g. exercise.
During heavy breathing increased activity of the inspiratory centre neurones activates the expiratory system. In turn, the increased activity of the expiratory system inhibits the inspiratory centre and stimulates muscles of expiration. The dorsal and ventral groups are bilaterally paired and there is cross communication between them. As a consequence they behave in synchrony and the respiratory movements are symmetric.
Pneumotaxic centre

Respiratory center

Pneumotaxic Area
Apneustic Area

Medullary Rhythmicity Area

Inspiratory Area
Expiratory Area

Pons
Medulla Oblongata
Spinal Cord
Pneumotaxic centre:

- It is located in the upper pons. This centre is a group of neurones that have an inhibitory effect on the both inspiratory and apneustic centres. It is probably responsible for the termination of inspiration by inhibiting the activity of the dorsal medullar neurones.

- It primarily regulates the volume and secondarily the rate of the respiration. Because in the lesions of this area normal respiration is protected it is generally believed that upper pons is responsible for the fine-tuning of the respiratory rhythm.
• Breathing in some extent is also controlled consciously from higher brain centres (e.g. cerebral cortex).

• This control is required when we talk, cough and vomit. It is also possible voluntarily change the rate of the breathing.

**Voluntary Breathing**

• Hyperventilation can decrease blood partial carbon dioxide pressure (PCO₂) due to loss of CO₂ resulting in peripheral vasodilatation and decrease in blood pressure. One can also stop breathing voluntarily. That results in an increase in arterial partial oxygen pressure (PO₂), which produces an urge to breathe. When eventually PCO₂ reaches the high enough level it overrides the conscious influences from the cortex and stimulates the inspiratory system.
• If one holds his breath long enough to decrease PO2 to a very low level one may lose his consciousness. In an unconscious person automatic control of the respiration takes over and the normal breathing resumes.

• Other parts of the brain (limbic system, hypothalamus) can also alter the breathing pattern e.g. affective states, strong emotions such as rage and fear. In addition, stimulation of touch, thermal and pain receptors can also stimulate the respiratory system.
RESPIRATORY MUSCLES:

Diaphragm, intercostal muscles and the other accessory respiratory muscles work in co-ordination for normal breathing under central controller. There is evidence suggesting that in premature new-born babies this co-ordination is not mature enough and this could be responsible for the sudden infant death syndrome.
1. MECHANORECEPTORS:

- These receptors are placed in the walls of bronchi and bronchioles of the lung and the main function of these receptors is to prevent the over inflation of the lungs.

- Inflation of the lungs activates these receptors and activation of the stretch receptors in turn inhibits the neurones in inspiratory centre via vagus nerve.

- When the expiration starts activation of the stretch receptors gradually ceases allowing neurones in the inspiratory neurones become active again. This phenomenon is called Hering-Breuer Reflex. It is particularly important for infants. In adults it is functional only during exercise when the tidal volume is larger than normal.
2. CHEMORECEPTORS:

- The respiratory system maintains concentrations of O₂, CO₂ and the pH of the body fluids within the normal range of values. Any deviation from these values has a marked influence on the respiration. Chemoreceptors are specialised neurones activated by changes in O₂ or CO₂ levels in the blood and the brain tissue, respectively.
Chemoreceptor

Other receptors (e.g., pain) and emotional stimuli acting through the hypothalamus

Higher brain centers (cerebral cortex—voluntary control over breathing)

Peripheral chemoreceptors:
- $O_2$, $CO_2$, $H^+$

Central chemoreceptors:
- $CO_2$, $H^+$

Stretch receptors in lungs

Irritant receptors

Receptors in muscles and joints

Respiratory centers (medulla and pons)
• They are involved in the regulation of respiration according to the changes in PO2 and pH. O2-sensitive chemoreceptors (Peripheral chemoreceptors) are located at the bifurcation of the carotid artery in the neck and the aortic arch.

• They are small vascular sensory organs encapsulated with the connective tissue. They are connected to the respiratory centre in the medulla by glossopharingeal nerve (carotid body chemoreceptors) and the vagus nerve (aortic body).

• They actually respond to changes in H+ concentration in these compartments. When the blood partial PCO2 is increased CO2 diffuses into the CSF from cerebral vessels and liberates H+.

• (When CO2 combines with water forms carbonic acid and liberates H+ and HCO3-)
• An increase in H+ stimulates chemoreceptors resulting in hyperventilation which in turn reduces PCO2 in the blood and therefore in the CSF. Cerebral vasodilatation always accompanies an increased PCO2 and enhances the diffusion of CO2 into the CSF.

• \( \text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \)

• \( \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+ \)
• An increase in H+ stimulates chemoreceptors resulting in hyperventilation which in turn reduces PCO2 in the blood and therefore in the CSF. Cerebral vasodilatation always accompanies an increased PCO2 and enhances the diffusion of CO2 into the CSF. Because CSF has less protein than blood it has a much lower buffering capacity. As a result changes in pH for a given change in PCO2 is always bigger than the change in blood.

• CO2 level is a major regulator of respiration. It is much more important than oxygen to maintain normal respiration. Even very small changes in carbon dioxide levels (5 mm Hg increase in PCO2, hypercapnia) in the blood cause large increases in the rate and depth of respiration (100 % increase in ventilation).
Hypocapnia, lower than normal PCO2 level in the blood causes in periods in which respiratory movements do not occur. Effects of PO2 (if the changes occur within the normal range) on respiration is very minor. A decrease in PO2 is called hypoxia and only after 50% decrease in PO2 can produce significant changes in respiration. This is due to the nature of O2-Hb saturation that at any PO2 level above 80 mm Hg Hb is saturated with O2.
• Consequently only big changes in PO2 produce symptoms otherwise it is compensated by O2, which is bound with Hb.

• In stroke patients or physiologically at high altitude blood PO2 level may drop considerably and activate peripheral chemoreceptors and activate stimulation. At high altitude because the ability of the lung to eliminate CO2 is not affected, in response to increased respiration, blood PCO2 is decreased. If PO2 drops under certain level respiratory system does not respond and death will occur.
Where do our cells get energy?

- 6-C sugars are the MAJOR source of energy for cell
- What type of macromolecule are 6-C sugars?
- Carbohydrates
- Cells break down glucose a 6-C sugar to make ATP “energy”

\[ C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + \text{usable energy} \]  
\( \text{(ATP)} \)
Cellular Respiration (3-stages)

- Glycolysis
- Krebs Cycle (Citric Acid Cycle)
- Electron Transport Chain (ETC)

![Cellular Respiration Diagram]
Glucose ($C_6H_{12}O_6$) + Oxygen ($O_2$) → Glycolysis → Krebs Cycle → Electron Transport Chain → Carbon Dioxide ($CO_2$) + Water ($H_2O$) + ATP
Glycolysis

Glucose to the electron transport chain

Glycolysis

2 Pyruvic acid

To the electron transport chain
Breakdown of Pyruvic Acid

- Glucose $\rightarrow$ mitochondria
- Pyruvate (3-C) $\rightarrow$ Acetic acid (2-C)
- 3rd C forms CO$_2$
- Acetic acid combines with Coenzyme A to form ACETYL-CoA
The Krebs Cycle

A.

Pyruvic acid

\[ \text{CO}_2 \]

Acetyl-CoA

\[ \text{CO}_2 \]

CoA

Coenzyme A

NADH

NAD^+

FADH_2

FAD

Citric acid

4-carbon compound

5-carbon compound

NADH

NAD^+

ATP

ADP

Mitochondrion

B.

Energy Extraction
TOTAL ENERGY YIELD

- Glycolysis → 2 ATP
- Krebs Cycle → 2 ATP
- ETC → 32 ATP
- Total → 36 ATP
AIRWAYS AND AIRFLOW:

- Inhaled air passes through the conducting airways and eventually reaches the respiratory epithelium of the lungs. The conducting airways consist of a series of branching tubes which become narrower, shorter and more numerous as they penetrate deeper into the lung.
- The trachea divides into right and left main bronchi, which in turn divide into lobar, then segmental bronchi.
- This process continues down to the terminal bronchioles, which are the smallest airways without alveoli. Since the conducting airways have no alveoli they do not take part in gas exchange but constitute the anatomical dead space. Its volume is about 150 ml but it varies because airways are not rigid; during inspiration, respiratory tubes are lengthened and dilated, especially in deep breathing.
Trachea

Bronchus

Bronchiole

Conducting Zone

Respiratory Zone

Respiratory Bronchiole

Alveolar duct

Alveolar sac
Gas exchange

- Blood is brought to the other side of the blood-gas barrier from the right heart by pulmonary arteries, which also form a series of branching tubes leading to the pulmonary capillaries and back to the pulmonary veins. The capillaries lie in the walls of the alveoli and form a dense network that the blood continuously runs in the alveolar wall.

- At resting not all the capillaries are open but when the pressure rises (e.g. exercise) recruitment of the close capillaries occurs.
Respiratory Volumes

- **Tidal volume (TV):** Volume of air inhaled or exhaled with each breath during normal breathing (0.5 L).
- **Inspiratory reserve volume (IRV):** Maximal volume of air inhaled at the end of a normal inspiration (3 L).
- **Expiratory reserve volume (ERV):** Maximal volume of air exhaled at the end of a tidal volume (1.2 L).
- **Inspiratory capacity (IC):** Maximal volume of air inhaled after a normal expiration (3.6 L) (TV+IRV).
- **Functional Residual Capacity (FRC):** The volume of gas that remains in the lung at the end of a passive expiration. (2 - 2.5 L or 40% of the maximal lung volume) (ERV+RV).
- **Residual Volume (RV):** The volume of gas remains in the lung after maximal expiration. (1 - 1.2 L)
Respiratory volumes

- Total lung capacity
- Residual volume
- Functional residual capacity
- Inspiratory capacity
- Vital capacity
- Expiratory reserve volume
- Inspiratory reserve volume
- Varying tidal volume
• **Total Lung Capacity (TLC):** The maximal lung volume that can be achieved voluntarily. (5 - 6 L) (IRV+ERV+TV+RV)

• **Vital capacity (VC):** The volume of air moved between TLC and RV. (4 - 5 L) (IRV+ERV+TV).

• Multiplying the tidal volume at rest by the number of breaths per minute gives the total minute volume (6 L/min). During exercise the tidal volume and the number of breaths per minute increase to produce a total minute volume as high as 100 to 200 L/min.
TOTAL VENTILATION

- The total volume of the gas leaving the lung per unit time. If TV is 500 ml and there are approximately 15 breaths/min the total volume of the gas leaving the lung, total ventilation will be $500 \times 15 = 7500$ ml/min. It can be measured by having the subject breath through a valve that separates the inspired air from expired air and collecting the expired air.
ALVEOLAR VENTILATION:

• The volume of the gas reaching the respiratory zone of the airways.
• However, not all of the total ventilation volume reaches the alveoli. 150 ml of the TV (500 ml) is left behind in the airways, which does not contain alveoli, therefore does not contribute to the diffusion (Anatomic death space).

• Thus, the volume of gas entering the respiratory zone, alveolar ventilation, is \((500-150) \times 15 = 5250\) ml/min. The measurement of alveolar ventilation is more difficult. One way is to measure the volume of anatomic dead space and calculate the dead space ventilation. This then subtracted from the total ventilation.
• **Alveolar ventilation** = Total ventilation – Anatomic death space ventilation

• **Anatomic dead space ventilation** = Anatomic dead space volume x respiration frequency

• **VE**: total expiration volume
• **VT**: Tidal volume
• **VD**: Dead Space volume
• **VA**: volume of alveolar gas during tidal breathing
• **V**: volume per unit time
• **VT** = **VD** + **VA**
• \((VT \times n) = (VD \times n) + (VA \times n)\)
• \(V\): volume per unit time
• \(VE\): Expired total ventilation
• \(VD\): dead space ventilation
• \(VA\): alveolar ventilation
• \(VE = VD + VA\)
• \(VA = VE - VD\)
PULMONARY FUNCTION TESTS

Pulmonary function tests are very useful tests to diagnose several lung diseases. The simplest but one of the most informative tests of lung function is a forced expiration.

TESTS OF VENTILATORY CAPACITY

Forced Expiratory Volume (FEV): It is the volume of gas exhaled in one second by a forced expiration following a full inspiration (FEV1). The total volume of the gas exhaled after a full inspiration represents the vital capacity. However, this value could be slightly smaller than the vital capacity measured with a slow (normal speed) expiration. Therefore, this value is called forced vital capacity (FVC). The normal ratio of the FEV1 is 80% of FVC.
- Forced Expiratory Flow (FEF25-75): This measurement represents the expiratory flow rate over the middle half of the FVC (between 25 – 75 %). It is obtained by identifying the 25 % and 75 % volume points of FVC, measuring the time between these points and calculating the flow rate.
Interpretation of tests of forced expiration:

On the basis of the knowledge obtained from these functional tests, lung diseases can be classified as restrictive or obstructive. In restrictive lung diseases (such as pulmonary fibrosis), the vital capacity is reduced to below normal levels. However, the rate at which the vital capacity is forcefully exhaled is normal. In obstructive lung disease (such as asthma, emphysema, bronchitis) the vital capacity is normal because lung tissue is not damaged and its compliance is unchanged. In asthma the small airways (bronchioles) constrict, bronchoconstriction increases the resistance to airflow.
Although the vital capacity is normal, the increased airway resistance makes expiration more difficult and takes longer time. Obstructive disorders are therefore diagnosed by tests that measure the rate of forced expiration, such as the FEV1 and FEF25-75. A significant decrease in these values suggests an obstructive lung disease.
DIFFUSION

How do gasses get across the blood-gas barrier?

• **BLOOD-GAS EXCHANGE**: Oxygen and carbon dioxide move between air and blood by simple diffusion: from an area of high to low partial pressure, as simple as water runs downhill. It is a passive process which means requires no energy. Fick’s law of diffusion determines the amount of gas moves across the tissue is proportional to the area of the tissue but inversely proportional to its thickness.

• Because the blood-gas barrier in the lung is extremely thin and has a very large area (50-100 m²), it is well suited to its function.
DIFFUSION
(Gas Exchange)
Calculations of Oxygen and Carbon Dioxide Partial Pressures:

**Dalton’s Law:** Total pressure of a gas mixture (in our case air) is equal to the sum of the pressures that each gas in the mixture would have independently (Partial Pressure of each gas).

- Dry atmosphere = PN₂ + PO₂ + PCO₂ = 760 mmHg
- Since oxygen constitutes 21% of the atmosphere, PO₂ = 159 mm Hg.
- Nitrogen 78 PN₂ = 593 mmHg

Inspired air also contains moisture and its amount may vary with temperature etc. However when the inspired air arrived the alveoli it is normally saturated with water vapour. Because the temperature in the lungs does not change significantly water vapour of the alveolar air could be considered constant (47 mm Hg)

- Wet atmosphere = PN₂ + PO₂ + PCO₂ + PH₂O = 760 mmHg
- PO₂ = 0.21 (760-47) = 150 mm Hg (oxygen partial pressure of the inspired air when it arrives alveoli, before the gas exchange).
Why are the measurements of PO2 and PCO2 important?

• The measurement of PO2 of arterial blood is particularly important because it provides a good index of lung function. The actual amount of dissolved O2 is a linear function of the PO2: The higher PO2 indicates that more O2 is dissolved.

• Blood PO2 measurements are not affected by the O2 in red cells (bound with Hb, see below for details). A normal PO2 in the inspired air together with low arterial PO2 means that the gas exchange in the lungs is impaired. In summary, the measurement of PO2 is important for
  • (1) treating patients with pulmonary diseases
  • (2) performing safe surgery (when anaesthesia is used)
  • (3) the care of premature babies with respiratory distress syndrome
PERFUSION

• The main function of the pulmonary circulation is to bring systemic venous blood into contact with alveoli for gas exchange. It begins at the main pulmonary artery, which receives the mixed venous blood pumped by the right ventricle. This artery then branches successively like the system of airways.

• Each time the airway branches, the arterial tree branches that the two parallel each other.

• The oxygenated blood is collected from the capillary bed by the pulmonary vein, which drains into the left atrium. In addition, pulmonary vessels protect the body from obstruction of important vessels in other organs such as renal or cerebral vessels.
• When air, fat or blood cloths enter the blood stream (e.g. during surgery or trauma) pulmonary vessels trap this emboli and endothelial cells release fibrinolytic substances that help dissolve thrombi. The pulmonary circulation serves as a blood reservoir and the volume in the lung capillaries is approximately equal to the stroke volume of the right heart.
The differences between the pulmonary and the systemic circulation:

• 1. The pressures in the pulmonary circulation are remarkably low: The pressure in the main pulmonary artery is 25 mm Hg (systolic) and 8 mm Hg (diastolic), in average 15 mm Hg. This is a very low pressure compare to the pressure in aorta, 100 mm Hg.

• 2. Another striking property of the pulmonary arteries is their exceedingly thin walls. This anatomical adaptation of the lung is critically important for its function: The lung is required to receive the whole of the cardiac output at all times. Keeping the pulmonary pressure as low as possible allows the right heart answer this demand with a minimum work.

• 3. Unlike the systemic capillaries, which are organised as tubular network with some interconnections, the pulmonary capillaries mesh together in the alveolar wall so the blood flows as a thin sheet (capillary bed).
4. Another unique property of the pulmonary circulation is its ability to decrease resistance as cardiac output increases. Two mechanisms are responsible for this function.

1. **Capillary recruitment**: opening of initially closed capillaries when cardiac output increases.

2. **Capillary distension**: The decrease in pulmonary pressure with increased cardiac output has several beneficial effects: It
   - (1) minimise the load on the right heart,
   - (2) prevents pulmonary oedema,
   - (3) maintains the adequate flow rate of the blood in the capillary and
   - (4) increases the capillary surface area.
GAS TRANSPORT TO THE PERIPHERY

(How do gases move to the peripheral tissues?)

• **OXYGEN:**

  Oxygen is carried in the blood in two forms, dissolved and combined with haemoglobin (Hb).

  • Dissolved Oxygen: The amount of oxygen dissolved in the blood is proportional to its partial pressure (Henry’s Law). 100 ml of arterial blood with normal oxygen partial pressure (100 mm Hg) contains 0.3 ml oxygen. By this way amount of oxygen delivered to the tissues is only about 90 ml/min. Taking 25 in to account that the tissue requirements are about 3000 ml Oxygen/min, it is obvious that this way of transporting oxygen is not adequate for human.
HAEMOGLOBIN:

- Haemoglobin (Hb) = Heme (iron-porphyrin) + globin (protein)

- Globin has 4 protein polypeptide chains: 2 alpha (each has 141 aa) and 2 beta (each has 146 aa).

- Differences in the amino acid sequence of these chains give rise to various types of Hb.
  - Hb-A: Normal adult Hb
  - Hb-F: Foetal Hb, which makes part of the total Hb at birth and is gradually replaced by Hb-A.
  - Hb-S: S stands for sickle. This Hb has valine in the beta chain instead of glutamic acid.
• The oxygen saturation of Hb, O2 combined with Hb / O2 capacity

• One gram of Hb can combine with 1.39 ml oxygen and because normal blood has 15 mg of Hb/100 ml and the oxygen capacity of the 100 ml blood is 20.8 ml.

• Oxygen saturation of the arterial blood (PO2=100 mm Hg) is 97.5 % while oxygen saturation of the venous blood (PO2= 40 mm Hg) is 75 %.
Why is the relationship between PO$_2$, O$_2$ saturation and O$_2$ concentration important?

- In anaemic patients Hb concentration can be as low as 10 mg/100ml blood. In such patient with normal respiratory functions (PO$_2$=100 mm Hg), O$_2$ capacity will be lower (20.8 x 10/15 = 13.9 ml/100 ml blood) and though the O$_2$ saturation still be 97.5 %, the amount of oxygen combined with Hb will be lower. Because the reduced Hb is purple a low arterial oxygen saturation causes cyanosis.
The oxygen dissociation curve is shifted to the right by

1. an increase in H+ concentration,
2. an increase in PCO2 (Bohr effect),
3. an increase in temperature
4. an increase in 2, 3-diphosphoglycerate (DPG). A rightward shift means more unloading of oxygen at a given PO2 in a tissue capillary. DPG is an end product of red cell metabolism and an increase in its concentration occurs in chronic hypoxia (e.g. at high attitude or in patients with chronic lung disease).

• Because CO has a much higher affinity to Hb (forms carboxyhemoglobin, COHb), even small amounts of CO bind the large proportion of Hb making it unavailable for oxygen: The Hb concentration and PO2 of blood may be normal but its oxygen content is grossly reduced.
CARBONDIOXIDE:

• CO2 is carried in the blood in three forms: Dissolved CO2, as bicarbonate and as carbamino compounds (combined with proteins).
• Dissolved CO2: Because CO2 is more soluble than oxygen this fraction of CO2 in the blood plays an important role in its transport (about 10%).
• Bicarbonate:

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^{-}
\]
• The first reaction is very fast and involves carbonic anhydrase enzyme, which is present in red cells, while the second reaction does not involve an enzyme. When the concentrations of the products of the carbonic acid dissociation reaction bicarbonate diffuses into the blood but not hydrogen ion because the red cell membrane is relatively impermeable to the positively charged ions.

• In order to maintain electrical neutrality Cl- ions diffuse into the red cells according to the Gibbs-Donnan equilibrium (chloride shift).

Some of the H+ are bound to Hb:

• H+ + HbO2 $\leftrightarrow$ H+Hb + O2

• The reduced Hb is a better proton acceptor than oxygenated Hb meaning deoxygenation of the blood increases its ability to carry CO2 = Haldane effect.
The diagram illustrates the process by which carbon dioxide (CO₂) is transported from tissue to the blood and eventually to the red blood cells. The process begins with dissolved CO₂ in tissue, which diffuses into the blood capillary. In the presence of carbonic anhydrase, CO₂ reacts with water (H₂O) to form carbonic acid (H₂CO₃), which then breaks down into bicarbonate (HCO₃⁻) and hydrogen ions (H⁺) via the chloride shift. The bicarbonate is transported into the red blood cells, where it plays a role in maintaining pH homeostasis.
• In arterial blood CO2 is carried 90% as bicarbonate, 5% combined with carbamino proteins and 5% as dissolved CO2. In venous blood these values are 60, 30 and 10, respectively.
ACID-BASE REGULATION

• By altering the CO2 elimination the lungs can control the acid-base balance of the body.

\[
\begin{align*}
H_2CO_3 & \leftrightarrow H^+ + HCO_3^- \\
K_A (H_2CO_3) & = (H^+ + HCO_3^-)/ H_2CO_3 \\
K_A & = (H^+ + HCO_3^-)/ CO_2 \\
\log K_A & = \log H^+ + \log (HCO_3^-/ CO_2) \\
-\log H^+ & = -\log K_A + \log (HCO_3^-/ CO_2) \\
pH & = pK_A + \log (HCO_3^-/ CO_2) \\
pH & = pK_A + \log (HCO_3^-/ 0.03 PCO_2) \\
pH & = 6.1 + \log 24/0.03 \times 40 \\
pH & = 6.1 + \log 20 \\
pH & = 6.1 + 1.3 = 7.4
\end{align*}
\]
RESPIRATORY ACIDOSIS:

- It is due to an increase in PCO₂ (e.g. hypoventilation, ventilation perfusion inequality). Whenever PCO₂ is increased the bicarbonate concentration is also rises due to dissociation of carbonic acid but nevertheless HCO₃⁻/PCO₂ falls. In response to these changes the kidneys start conserving HCO₃.

RESPIRATORY ALKALOSIS:

- It is caused by a decrease in PCO₂ (which in turn increases the HCO₃⁻/PCO₂) due to hyperventilation (e.g. at high attitude, voluntary). The kidneys compensate it by increasing the HCO₃ excretion.
METABOLIC ACIDOSIS:

• Metabolic refers changes in HCO₃⁻. In this case HCO₃⁻/PCO₂ decreases by lowering HCO₃⁻ in the blood. It occurs in conditions accompanied by an accumulation of acids in the blood (e.g. diabetes mellitus, lactic acid accumulation after tissue hypoxia)

• Respiratory compensation occurs by an increase in ventilation that lowers PCO₂. This stimulation is mainly due to stimulation of peripheral chemoreceptors by H⁺.
METABOLIC ALKALOSIS:

- An increase in HCO₃⁻ raises the HCO₃⁻/PCO₂. Common reasons are excessive ingestion of alkalis and loss of gastric acid due to vomiting. In response the metabolic acidosis a reduction in alveolar ventilation occurs and PCO₂ is increased.
RESPIRATORY SYSTEM UNDER STRESS

- **EXERCISE:** During exercise the rate and the depth of breathing are increased. This increase in ventilation (hyperpnea) matches the simultaneous increase in oxygen consumption and carbon dioxide production that the arterial blood carbon dioxide and oxygen partial pressures and pH do not change dramatically (hyperpnea is different from hyperventilation. In hyperventilation PCO2 is decreased). The mechanism underlying the exercise-induced changes in ventilation is not clear.
ACCLIMATIZATION TO HIGH ALTITUDE:

- In the high altitude the human body compensates the low partial oxygen pressure by changing ventilation or affinity of Hb to oxygen or total Hb concentration.

- **Hypoxic ventilatory response:** Hyperventilation induced by the decreased partial oxygen pressure.

- This lowers the arterial partial carbon dioxide pressure and causes respiratory alkalosis. The rise in blood pH in turn set the ventilation to a more stable but still slightly higher levels.
Changes of lung volumes in Hyperventilation

- Hyperventilation increases the tidal volume and reduces the proportion of the anatomical death space in the inspired air.
- This also improves the oxygenation of the blood. However, in spite of all these adaptation mechanisms, the partial oxygen pressure in the arterial blood can not be increased more than the partial oxygen pressure in the inspired air. As a result partial pressure of oxygen in the arterial blood decreases with increasing altitude.
**Altitude and oxygen saturation**

- At sea levels arterial blood loses 22% of its oxygen load in tissues.
- The oxygen saturation of the arterial and venous blood is 97% and 75%, respectively. At high altitude the low oxygen content of red blood cells stimulates 2-DPG production and decreases the affinity of Hb to oxygen, which in turn facilitates the oxygen transport to the tissues. However, at very high altitudes increase in blood pH causes a shift to the left in the oxygen saturation curve and increases the affinity of Hb to oxygen.
This second step is indeed beneficial at very high altitude by increasing the oxygenation of the blood in the lungs. Due to low oxygen partial pressure in the arterial blood at high altitude the tissue hypoxia occurs and in response the kidneys secrete erythropoietin hormone. Erythropoietin stimulates the production of red blood cells resulting in polycythemia, which can cause oedema, ventricular hypertrophy and heart failure.
Thank you