Breathing is one of the vital functions and is essential to human life. In an emergency, ensuring the airways is a top priority. In this article, you will learn how breathing works, what we need it for, and how it is controlled by the body.

Airways

Air flows into our lungs by inhalation. But until it arrives there, it travels through various passageways. Depending on whether we breathe through the nose or the mouth, the air enters through the naso- or the oropharynx. Next, it passes through the laryngopharynx and reaches the **trachea**. The trachea is divided into two main bronchi, one leading to the right lung and one to the left. The main bronchi branch out further into lobar and segmental bronchi and finally become bronchioles. Only when they divide into **respiratory bronchioli**, the first air sacs, so-called **alveoli**, can be found. From here on forward, gas exchange takes place.
Dead space

Up to the respiratory bronchioli, there are 16 divisions. This results in a space of 0.15 l, which is ventilated but not used for gas exchange. It is called the **anatomic dead space**. With an average breath of 0.5 l and a normal respiratory rate of 15 breaths per minute, the dead space ventilation comes to 2.25 l/min. This amounts to one-third of the total respiratory minute volume of 7.5 l/min.

The purpose of the dead space is to warm up and moisturize the breathing air. Furthermore, the **ciliated epithelium**, which the dead space is equipped with, is supposed to keep foreign bodies away from the gas exchange surfaces.

The **functional or physiological dead space** includes, next to the anatomic dead space, the alveoli, which are ventilated but not perfused, and therefore not contributing to the gas exchange. However, in a healthy person, these are so few that the functional dead space is more or less equivalent to the anatomic dead.

Alveolar space

The alveolar space has a volume of about four liters. The gas exchange by diffusion takes
Fick’s law of diffusion states that the number of diffused particles per unit of time depends on the area available for diffusion. The area of the alveolar space that can be used for diffusion amounts, with its many ramifications, to approximately 80 m² and is sufficient to meet our need of oxygen even during physical labor.

The alveoli are all connected with each other via the alveolar ducts. When considering two differently sized alveoli that are connected to each other, we can see that the pressure in the alveoli can be described with Laplace’s law:

$$P = \frac{2 \times T}{r}$$

where $T = \text{wall tension}$, and $r = \text{radius}$.

The wall thickness can be neglected in this case, since it is the same with all the alveoli. Also, the surface tension ensures that the wall tension of all alveoli is equal. This brings us to the conclusion that the pressure in the smaller alveolus is greater than the one in the larger alveolus. Consequently, the gas from the smaller alveolus will be emptied into the larger alveolus in order to compensate pressure. The smaller alveolus collapses. If this happens in the entire lung, it is called atelectasis.

Atelectasis usually occurs in premature babies. They do not yet produce the surface active agent (surfactant) or anti-atelectasis factor. Pulmonary surfactant is formed starting in pregnancy week 24 by the type-II-pneumocytes of the respiratory epithelium. It consists of 90 % phospholipids and 10 % surfactant proteins.

The surfactant molecules reduce the wall tension $T$ in the alveoli. The smaller the radius of the alveolus, the narrower the surfactant molecules are placed together, reducing the wall tension even more. This way, the pressure is compensated and the smaller alveoli do not collapse.

Surfactant does not only prevent atelectasis, it also has immunoregulatory functions. Furthermore, surfactant prevents excessive water inflow from the capillaries into the alveoli.

Lung Volume and Lung Capacities

Depending on the depth of breathing and the anatomical conditions, different lung volumes can be defined. Lung capacities describe an additive combination of individual volumes. The volumes and capacities are shown in the image below.
This process starts in the respiratory rest position with normal inspiration. After one and a half cycles, the minimum is reached by maximal exhalation of the patient. Now, the lungs only contain the residual volume, which is divided into collapse volume and minimum volume. Next, a maximal inhale follows and again a maximal exhalation. Then the patient returns to quiet respiration.

The metrological examination of the lung parameters has to separate static variables from dynamic variables, which are time dependent. Using spirometry, which allows for a time-dependent determination of changes in volume, it is possible to determine these parameters.

The FEV1/FVC ratio, which allows determining the relative forced expiratory volume in one second (rFEV1), is an important tool in the differential diagnosis of pulmonary diseases. The rFEV1 is calculated as follows:

\[ rFEV_1 = \text{forced expiratory volume in one second (FEV1)} / \text{vital capacity (FVC)} \]

The forced expiratory volume in one second describes the volume that a patient can exhale after maximum inhalation in one second at the maximum possible effort (i.e., forced expiration). It is important to note that this test is highly dependent on the motivation and cooperation of the patient.

**Respiratory Mechanics**

For the air and respiratory gases to have a directed flow, there has to be a certain pressure difference. This is achieved during inhalation by increasing the lung volumes using the respiratory muscles. In chest breathing, this is done by the external intercostal muscles.

In the so-called abdominal breathing, this task is fulfilled by the diaphragm.
Accessory respiratory muscles facilitate inspiration. These are the mm. scaleni, the m. sternocleidomastoideus and the m. pectoralis major, when the shoulder girdle is fixed. When we support our arms on our knees after jogging, we instinctively support our breathing.

Exhalation occurs mainly passively. Due to the tension of elastic elements and the surface tension of the alveoli, the lung seeks to contract. Because of the adhesion forces between lamina visceralis and parietalis of the pleura, the lungs do not collapse in situ, but follow the movements of the chest wall. With the relaxation of the previously contracted muscles, air flows out of the lung.

The thorax, in turn, seeks to expand, which counteracts the tendency of the lung to retract. The resting position is achieved when the resulting force \( F_{\text{result}} \) of these two opposing forces on the overall lung-thorax system is zero, which means that the volume of the lung is equivalent to the functional residual capacity (FRC = ERV + RV).

**Respiratory cycle**

The respiratory cycle can be divided into four steps:

1. The thorax rises; the diaphragm contracts.
2. The lungs follow this movement, led by the adhesive forces in the pleural space; air flows into the lungs.
3. The respiratory muscles relax.
4. The lung follows its disposition to collapse as far as the thorax allows; air flows out of it.

Step one and two describe the **active inspiration** by increasing the thorax, while step three and four address **passive expiration**.
However, expiration can also be forced. For this, the abdominal press of the abdominal muscles is used. If the pressure in the pleural space becomes too large, the airways can collapse because of the decreasing pressure difference. A resistor outside of the chest, like pursed lip breathing, can remedy this.

Compliance and lung hysteresis

Compliance (C) generally describes the elasticity of a system and is defined as:

\[ C = \frac{\Delta V}{\Delta p} = \text{change in volume / change in pressure} \]

Compliance of the lungs is determined by the elastic characteristics of the connective tissue and by the surface tension of the alveoli. The compliance of the thorax is influenced by parts of the passive and active locomotor system of the torso, i.e., by the ligaments and muscles.

Plotting volume against transmural pressure yields the lung hysteresis curve, whose slope represents compliance. The lung hysteresis of the total respiratory system, i.e., both lung and thorax, is influenced by the intrapulmonary pressure, which is the pressure difference between the alveolar and the atmospheric pressure. It has an S-shaped course. In the region of normal breathing, it behaves approximately linear. Here, the inspiration movement is set against a relatively constant resistant.

Stretching of the chest is dependent on the intrapleural pressure, i.e., the pressure between the intrapleural space and the outer space. Its compliance increases for larger volumes. The hysteresis curve of the thorax thus resembles the course of an exponential function.

The difference of intrapulmonary and intrapleural pressure is relevant for the stretching of the lung. Here, compliance and the steepness of the curve decrease with increasing the filling amount. Thus, the lung hysteresis behaves contrary to the hysteresis of the thorax. This makes for the S-shaped profile of the curve of the total system.

Pressure change in dynamic respiration
When resting, the pleural space is affected by the elastic pull of the lung, which results in a “negative” pressure, i.e., suction. This is called **intrapleural pressure**. During inspiration, this pressure becomes more negative; during expiration, it becomes more positive.

The **intrapulmonary pressure**, i.e., the pressure difference between alveoli and outside air, remains constant at zero during the entire respiratory cycle, provided the glottis is opened and constant pressure equalization can take place.

In dynamic breathing, which corresponds to our regular breathing, the pressure compensation is restricted and thus delayed. The air cannot flow into the alveoli fast enough because of the viscous resistance, which is produced by the airways. This results in a pressure in the alveolar space that is lower than that of the outside air. The intrapulmonary pressure amounts to -1 cm H$_2$O. During expiration, the reverse is the case, with an intrapulmonary pressure of 1 cm H$_2$O.

This change of the intrapulmonary pressure also has an effect on the intrapleural pressure: during dynamic breathing, it reaches its minimum shortly before the end of inspiration. Analogously, the maximal intrapleural pressure can be measured shortly before the end of expiration.

**Pulmonary Gas Exchange**

The purpose of pulmonary respiration is to supply the body’s cells with oxygen and to release carbon dioxide into the surrounding air. The transport of oxygen from the surrounding air to the oxygen-consuming cells follows four steps:

1. Convective transport through ventilation.
2. Diffusion from the alveoli into the pulmonary capillaries.
3. Convective transport through the blood to the capillaries in the peripheral tissue.
4. Diffusion from the capillary blood into the tissue.

Partial pressures of the respiratory gases

Dalton’s law states that each gas in a mixture exerts a partial pressure, which corresponds to its share of the total volume. Consider the partial pressures of the respiratory gases in the alveolar space at standard conditions:

\[ p_{O_2} = 100 \text{ mm Hg} \text{ and } p_{CO_2} = 40 \text{ mm Hg} \]

These partial pressures are influenced by the composition of the outside air but also by the alveolar ventilation. When the ventilation increases, the alveolar partial pressure of oxygen increases, while the partial pressure of carbon dioxide decreases. This is due to the fact that new oxygen is supplied by the breathing air, while carbon dioxide is exhaled completely and (almost) does not exist in the atmospheric air.

The venous blood in the pulmonary capillaries flows past the alveoli with an oxygen partial pressure of approximately 40 mm Hg and a carbon dioxide partial pressure of 46 mm Hg. These pressure differences ensure that the respiratory gases can diffuse through the barrier of the alveolar epithelium, which is a thin layer of interstitial and capillary endothelium. Thus, they are the driving force for the pulmonary gas exchange.

The blood leaves the capillaries with an oxygen partial pressure of 100 mm Hg and a carbon dioxide partial pressure of 40 mm Hg. Thus, the partial pressures in the blood have been adjusted to those of the alveolar gas mixture. Of the contact time of 0.75 seconds, only 0.25 seconds are needed to completely saturate the blood with oxygen. In a healthy person, the resting oxygen uptake is, therefore, limited not by diffusion but by perfusion. If less blood flows through the capillaries, less blood will be oxygenated.

In sum, gas exchange is influenced by the driving pressure difference, by the area available for diffusion, by perfusion and by the barrier to be overcome.

Ventilation-perfusion ratio

In standard conditions, the ventilation-perfusion ratio equals one. If an area of the lung is less ventilated though, e.g., due to a blocked bronchus, the alveolar oxygen partial pressure of the affected alveoli aligns itself with the venous blood. This causes vasoconstriction of the vessels in this region (hypoxic pulmonary vasoconstriction), also called Euler-Liljestrand mechanism. A portion of the blood is diverted to increase the perfusion of the better ventilated areas. The ventilation-perfusion ratio of the less ventilated area is less than one.

In contrast, if an area of the lung is less perfused, e.g., due to stenosis, the alveolar oxygen partial pressure in the affected alveoli rises and is similar to the outside air. The ventilation-perfusion ratio of the less ventilated area is greater than one.

With an upright upper body, a physiological ventilation-perfusion imbalance sets in. Due to gravity, perfusion and alveolar ventilation increase from the top down. Thereby, perfusion correlates more strongly with height than ventilation does, as the apex of the lung is supplied with blood only in the systole because of its position above the heart. This means that the ventilation-perfusion ratio at the apex of the lung is higher than average. At the base of the lung, it is less than one.
Respiratory Gas Transport

The transport of oxygen in the blood is the responsibility of hemoglobin, which is contained in the erythrocytes. It binds the oxygen to its central divalent iron. The maximal oxygen binding capacity of one gram of hemoglobin is described by Huefner's number. It is 1.34 ml. Thus, a healthy adult with 150 gram hemoglobin per liter of blood can transport 0.2 liter of oxygen in one liter of blood.

Oxygen binding curve

![Oxygen-Hemoglobin Dissociation and Effects of pH and Temperature](Image: "Oxygen-Hemoglobin Dissociation and Effects of pH and Temperature" by Phil Schatz. License: CC BY 4.0)

The oxygen binding curve shows the relationship between oxygen saturation and oxygen partial pressure in the blood. The tetrameric structure of hemoglobin and the cooperative interactions of its individual units result in a sigmoidal plot for the oxygen binding curve. If oxygen binds to one of the four sub-units, a conformational change of the molecule occurs. This facilitates further oxygen uptake of the remaining units.

The higher the oxygen partial pressure, the greater the affinity of hemoglobin to oxygen and, therefore, the oxygen uptake in the erythrocytes. The sigmoidal path of the oxygen binding curve is necessary for the oxygen to be taken up in the lung and released in the tissue.

The course of the bond curve is influenced by various factors: With increasing temperature, the affinity of hemoglobin for oxygen decreases. The same is true for decreasing pH-value (Bohr effect). This facilitates the release of oxygen in the tissue because venous blood is more acidic than arterial blood. The same effect is produced by rising carbon dioxide partial pressure in the periphery. Moreover, 2.3-
bisphosphoglycerate, which is produced by the erythrocytes themselves, can also reduce the oxygen affinity of hemoglobin.

Carbon dioxide transport

Carbon dioxide is mainly transported in the plasma in the form of bicarbonate. For this to happen, CO₂ is first converted to carbonic acid H₂CO₃ by the carbonic anhydrase in the erythrocytes. This breaks down immediately to bicarbonate and protons. Then, the bicarbonate leaves the erythrocytes in exchange for chloride ions (chloride/Hamburger shift). A small amount of the carbon dioxide is bound to the hemoglobin and transported. The result is carboxyhemoglobin.

The carbon dioxide binding curve is approximately linear and dependent on the blood’s oxygenation level. Deoxygenated blood has a higher affinity for carbon dioxide (Haldane effect).

Regulation of Breathing

The respiratory control center is located in the medulla oblongata and the pons. Three different types of neurons form the ventral respiratory group:

- Inspiratory neurons
- Post-inspiratory neurons
- Expiratory neurons

Each of them is active in its respective phase.
The medulla oblongata contains the dorsal respiratory group (DRG) and the ventral respiratory group (VRG). This group is influenced by two other modifying groups of neurons: The **pontine respiratory group** has an inhibitory effect, while the **dorsal respiratory group** processes signals from the airways and the cardiovascular system.

Chemosensors serve as afferents; they are located peripherally at the carotid bifurcation, at the aortic arch, and centrally in the brainstem. The peripheral sensors are located in the aortic bodies (glomera). They respond to decreasing oxygen concentrations, decreasing pH-value or increasing CO$_2$ levels. The CO$_2$ partial pressure exerts the strongest stimulus, increasing the respiratory minute volume by up to 80 l/min.

Other influences on the respiratory control center include free nerve endings in the airways, stretch receptors of the bronchial wall and muscle spindles of the intercostal.
muscles. These allow, for example, the sneeze reflex, the **Hering-Breuer reflex** and the deflation reflex.

Furthermore, breathing is influenced by the autonomic nervous system and the endocrine system. Breathing increases, for example, because of the influence of the sympathetic nervous system.

**Review Questions**

Solutions can be found below the references.

1. **Which of the following statements is true?**
   
   A. Total capacity is the sum of functional residual capacity and inspiratory reserve volume.
   
   B. Vital capacity is the sum of inspiration capacity and expiratory reserve volume.
   
   C. Inspiratory reserve volume is the volume that can be inhaled in the resting position.
   
   D. In a pneumothorax, the lungs collapse to their residual volume.
   
   E. After maximal exhalation, only the functional residual capacity remains in the lungs.

2. **Which of the following statements is true?**
   
   A. The alveolar pressure during inspiration is higher than the environmental pressure.
   
   B. The alveolar pressure during expiration is lower than the alveolar pressure during inspiration.
   
   C. The alveolar pressure never exceeds the interpleural pressure.
   
   D. The alveolar pressure is always less than the interpleural pressure.
   
   E. The interpleural pressure may exceed the intrapulmonary pressure during forced expiration.

3. A patient has a tidal volume of 0.5 l and a respiratory rate of 15 breathings per minute. The alveolar pressures are: \(O_2 = 95\) mm Hg, \(CO_2 = 40\) mm Hg. The blood pH value is 7.4. The patient spontaneously doubles his tidal volume and halves his respiratory rate. Which of the following statements are true?

   A. The respiratory minute volume has increased.
   
   B. The dead space ventilation is unchanged.
   
   C. The alveolar ventilation has increased.
   
   D. The alveolar \(Co_2\) pressure is decreased to about half.
   
   E. The pH value in a blood gas analysis is shifted towards acidosis.

**References**


**Correct Answers:** 1B, 2D, 3C