Chapter 2

An Overview of Lung Anatomy and Physiology

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Lung Anatomy

At the most basic level, normal human anatomy consists of two lungs. Each lung is divided into different lobes by separations known as fissures. The left lung consists of a superior and inferior lobe, separated by the oblique fissure located at the T4–5 vertebral level. The right lung is divided into superior, middle, and inferior lobes by the oblique and horizontal fissures. The right lung is larger and heavier, but also shorter and wider than the left lung. This is due to the diaphragm extending higher on the right and the heart bulging more to the left. The left and right lungs have different anatomical features. One of the most prominent features of the left lung is the cardiac notch which is an indentation on the anterior margin that allows for the leftward bulging of the heart. The right lung has vasculature grooves which allow for the passage of the superior and inferior vena cava.

Each lung has an apex, three surfaces, and three borders. The apex of the lung is the most superior aspect, ascending above the first rib into the root of the neck. The lung also has three surfaces: the costal surface, which is adjacent to the sternum and ribs; the mediastinal surface, which is found medially to the mediastinum and posteriorly to the vertebrae; and the diaphragmatic surface, which rests on the convex dome of the diaphragm. Each lung has an anterior, posterior, and inferior border.

The mediastinal surface includes the hilum of the lung, the medial aspect where structures enter and exit the lung. These structures form the root of the lung which has different orientations of structures for the left and right lungs. The most notable

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difference is the location of the main bronchus. In the left lung, the main bronchus is located inferior to the pulmonary arteries. In the right lung, the main bronchus is located posterior to the pulmonary arteries.

Both lungs are enclosed by a serous pleural sac that consists of two continuous layers of membranes, the visceral and parietal layers. Together, these layers are known as the pleurae. The visceral pleura fully covers the lungs and adheres to all its surfaces. The parietal pleura lines the pulmonary cavities, providing support for the lungs by adhering to the thoracic wall, mediastinum, and diaphragm. At rest, the inferior boundary of the lungs is at vertebral level T10, whereas during inhalation, the inferior boundary is at T12, the boundary of the pulmonary cavity. The pleural cavity contains two recesses: the costodiaphragmatic recess and the costomediastinal recess. The costodiaphragmatic recess is a bilateral recess that is bound by the lung superiorly and by the diaphragm inferiorly. The costomediastinal recess is a lateral recess that is located posterior to the sternum [1].

Trachea and Bronchi

The trachea, commonly referred to as the windpipe, is the airway that leads from the larynx to the large airways of the lungs known as the bronchi. Beginning at vertebral level C6, the trachea extends inferiorly to the carina, where it then bifurcates into the left and right main bronchi. The trachea is a tough airway surrounded by C-shaped cartilage rings.

The main bronchi extend inferolaterally and enter the lung at the hilum. It is one of the structures that form the root of the lung. The opposing sides of the bronchi have differing features. The right bronchus is wider, shorter, and more vertical than the left main bronchus. These bronchi branch into secondary bronchi: two secondary bronchi on the left and three on the right. Each secondary bronchus then divides into several tertiary bronchi that supply the bronchopulmonary segments. The right lung contains ten bronchopulmonary segments to supply three lobes. The left lung contains nine bronchopulmonary segments to supply two lobes.

Tertiary bronchi continue within the lung, dividing into smaller and smaller airways, termed as bronchioles. The tertiary bronchi continue as 20–25 generations of conducting bronchioles and terminal bronchioles. This represents the end of the conducting component of the airway. Terminal bronchioles extend as respiratory bronchioles, followed by alveolar ducts, sacs, and finally the alveoli, the main respiratory component of the lung.

Pulmonary Neurovasculature

Pulmonary arteries carry poorly oxygenated blood from the heart to the lung for oxygenation. They enter the lung at the hilum, descend to the main bronchi, and divide into several lobar and segmental arteries in a pattern similar to the main bronchi. This ultimately allows for a branch to go into each lobe and segment of the lung. There are two pulmonary veins in each lung that carry oxygenated blood back to the heart to then be circulated to the rest of the body.

The innervation of the lungs and pleura is rather simple. Both are innervated by autonomic fibers derived from the pulmonary plexus. The pulmonary plexus consists of the vagus nerve (cranial nerve X) and fibers from the sympathetic trunk. The vagus nerve supplies parasympathetic fibers whereas the sympathetic trunk supplies sympathetic fibers. Parasympathetic innervation will dilate the pulmonary vessels, constrict the bronchioles, and excite glandular secretions. Sympathetic innervation will constrict the pulmonary vessels, dilate the bronchioles, and inhibit glandular secretions [2].

Lung Mechanics

Before discussing lung mechanics, we must first discuss pressure and how it is measured. It is commonplace in lung mechanics for units of pressure to be measured in cmH_2O. Historically, physiologists conducted experiments by applying air pressure to the lungs using columns of water. A column of water 50 cm high produces a pressure of 50 cmH_2O. 1033 cmH_2O is equal to one standard atmosphere, or to 760 mmHg. It is standard practice in lung mechanics and clinical settings to report pressures relative to atmospheric pressure. Thus, atmospheric pressure is equal to 0 cmH_2O.

There are four locations where air pressure is determined. First is alveolar pressure (P_{alv}) which is the pressure inside the alveolar regions. Second is the pressure at the airway opening (P_{ao}). Third is the pressure inside the chamber but outside the lung, the pleural pressure (P_{pl}). Fourth is the pressure outside of the system, or barometric pressure (P_{B}).

Much of what we know now about static lung mechanics is a result of physiology experiments conducted in the last century. Lungs removed from autopsies were studied by suspending them in a humidified chamber. The airways were connected to a pressure gauge and a syringe was used to inflate and deflate the lungs. An open pipe was placed in the chamber so that the chamber was always equal to atmospheric pressure. In one particular experiment, researchers discovered that the resting lung volume is roughly 1/5th of the total lung capacity. This experiment demonstrated that this volume, termed the residual volume (RV), is typically observed in normal human lungs. The pressure of lungs at rest is roughly measured at 2 cmH_2O [3].

Another important experiment was conducted in a similar manner. In this case, a syringe was placed on the pipe so that it is no longer completely open to the atmosphere. When the pressure is advanced to +5 cmH_2O, the lungs are at roughly 50% of the total lung capacity. This volume is referred to as the functional residual capacity (FRC). Since we are discussing static lung mechanics, there is no flow of air. As a result, the pressure in the airway and the alveolar pressure are the same value. In a human body, this is referred to as the mouth pressure.

If we were to continue to inflate the lungs to its maximum capacity, or the total lung capacity (TLC), the pressure would reach +25 cmH_2O. Further pressure on the system would not result in additional air inflation to the lungs but may result in rupturing of the lungs. In this scenario, a constant pressure must be applied to the syringe to keep it at +25 cmH_2O. If the syringe was let go, or disconnected, air will be expelled rapidly until the lung is approximately 1/10th of the total lung capacity. So, to maintain a given lung volume, there must be pressure continuously applied. As a result, researchers concluded that the lung generates an opposing pressure, termed the elastic recoil of the lung, which is working to expel air [3]. The elastic recoil is always acting to expel air from the lung at any lung volume.

In the previous experiments, the syringe and pressure gauge were connected to the airways. Although useful, these experiments failed to provide an accurate representation of lung mechanics in humans, as the pressure differential is not derived in such a manner. To account for this, researchers removed the gauge and syringe from the airways and instead attached them to the pipe that invaded the chamber, representing our pleural cavity. In this case, as in the case of a normal respiratory system, the airways and alveoli are open to the atmosphere. By pulling on the syringe, we create a negative pressure inside the chamber, and the lungs inflate. A chamber or pleural pressure of −2 cmH_2O would cause the lung volume to be approximately 1/5th of the total lung capacity [3].

Notice the similarities between this and the previous experiment. At total lung capacity in the first example, the pressure gauge read +25 cmH_2O, as that was the pressure being applied directly to the airway. In this example, the gauge would read −25 cmH_2O, as this subatmospheric pressure in the chamber still causes the lungs to fully inflate. An important note is that the elastic recoil of the lungs is the same in both experiments, and is +25 cmH_2O, as the elastic recoil is always positive.

These experiments set the basis for discussion of lung mechanics in the thoracic cavity. We previously discussed the FRC including that it corresponds to roughly ½ of the total lung inflation and is approximately +5 cmH_2O if one were to measure the pressure inside the lung, or −5 cmH_2O if one were to measure the pressure inside the pleural cavity. For our purposes, we will refer to pressure as pleural or chamber pressures, as is commonplace in literature. In a clinical setting, FRC is defined as the volume of air in the lungs at the resting expiratory level. In simple terms, it is the volume of the lungs when the glottis (vocal cords), or the airway to the atmosphere, is open and there is no airflow or effort to breathe. It is also the lung volume at the end of a quiet breath. Although muscular effort is required to inhale, no effort is required to exhale back to FRC, because the elastic recoil of the lungs does all the work. Thus, the pressure in the pleural cavity, at rest, is at −5 cmH_2O [3].

If the pleural region is sealed and intact, the respiratory system is stable at FRC. If air is introduced into the pleural space, the integrity of the system is compromised, and the pleural space is no longer at −5 cmH_2O, but now equal to atmospheric pressure. This causes the lung to deflate and collapse. Clinically, this is known as a pneumothorax.

Compliance and Elastance

To understand the basic physiology of the lungs, key biophysical concepts intertwining lung anatomy and mechanics must be outlined. Two of these concepts, which are inversely related, include compliance and elastance. Compliance refers to the propensity of the anatomic structure, in this case both the lung and the chest wall, to allow expansion of volume to accommodate pressure changes. Elastance, on the other hand, refers to the propensity of the lungs or chest wall to return to resting volume after being expanded. Mathematically, compliance can be represented by change in lung volume (DV) divided by the change in pressure (DP), while elastance can be represented by the reciprocal, DP divided by DV. Both of them must work in tandem for both the chest wall and the lungs themselves to maintain optimal inflation and deflation for adequate gas exchange [4]. Deviations to this lead to common lung pathologies, including restrictive interstitial lung diseases with reduced lung compliance and chronic obstructive pulmonary disease with diminished lung elastance [5].

Airway Resistance and Drive Pressure

The next key factor affecting the amount of air that enters the lung during inspiration and exits the lung during exhalation is airway resistance. As discussed earlier in the chapter, the airway progresses from the trachea down to the individual alveolar air sacs where gas exchange ultimately occurs. As air travels through this pathway, it experiences resistance to flow. For simplicity, this resistance can be represented through modeling of airflow as laminar flow. With that assumption, resistance to flow at a specific point along the airway can be modeled with the following parameters: air viscosity (m), length of the airway (L), and radius of the airway (r), with the overall resistance equation, $R = \frac{8\,\mathrm{mL}}{\neq r^4}$.

Using this model at specific points in the airway, it is clear that smaller diameter bronchioles have a much larger resistance to airflow than the larger diameter bronchi or trachea. However, as air travels down the airway, the trachea splits into two bronchi which continually branch further eventually leading to terminal bronchioles and ultimately alveoli. As the airway splits, it becomes a parallel resistance circuit leading to an overall decrease in resistance at the terminal small airways compared to the large airways (trachea, bronchi). Furthermore, when looking at inspiration versus expiration, the overall diameter of the airways is increased during inspiration compared to expiration, so the overall airway resistance is greater during exhalation [6].

Lastly, a key aspect of ventilation includes the drive pressure, which is the pressure gradient that provides the force behind the airflow during inspiration and expiration. Using the concepts discussed earlier, the drive pressure can be described by the ratio between the tidal volume, which is the volume of air that goes into and out of the lung during a normal breathing cycle, and the overall compliance of the respiratory system, assuming a static overall compliance. This concept is key, because it attempts to quantify the pressure gradient needed to produce adequate volume expansion of the lungs. The ability to model and calculate this value can be used to guide therapy for patients. This will be useful later when mechanical ventilation strategies are discussed [7].

Work of Breathing

In normal physiology, to create the drive pressure needed to achieve the tidal volume, energy is required via adenosine triphosphate (ATP) to create mechanical changes through respiratory muscles moving the chest wall and the diaphragm. The amount of energy required for both inspiration and expiration can be quantified as work of breathing, expressed in units of energy (joules). To understand this in terms of respiratory physiology, the units can be manipulated to describe the energy expended in terms of a product of pressure and volume. Looking at the inspiratory work of breathing, several components discussed earlier are involved. First, work must be done to overcome the elastance or elastic recoil of both the chest wall and the lung. Second, work must be done to overcome the overall resistance from both the lung and chest wall tissue, as well as the airway resistance described above. The overall work for inspiration is the sum of these different components. As properties including elastance and resistance change, the work necessary to produce a specific tidal volume changes as well. This remains true when looking at the expiratory work of breathing. Overall, the drive pressure is generated through the contraction of respiratory muscles, which occurs using ATP created mainly from the metabolic pathway oxidative phosphorylation. Understanding the concept of the work of breathing will be necessary in subsequent chapters [8].

Gas Exchange

At the most fundamental level, the main function of the respiratory system is the exchange of oxygen (O_2) and carbon dioxide (CO_2) in a process known as gas exchange. As these gases are constantly produced and consumed during bodily reactions, there must be an efficient system for this exchange to occur. In the human body, gas exchange occurs in two predominant areas—the lungs and the peripheral tissues. The lungs provide the first location for gas exchange in a process known as ventilation while the peripheral tissues provide the second location for gas exchange in a process called oxygenation. The goal for the respiratory system is to bring atmospheric O_2 into the lungs for eventual distribution to the cells for cellular respiration. At the same time, these cells must rid themselves of their gaseous waste product, CO_2, for removal via the lungs. Thus, the respiratory system functions as a circuit, bringing O_2 into the body while removing CO_2. We will begin our discussion of gas exchange by exploring the concepts of ventilation and oxygenation. Ventilation is the process of bringing O_2 from the atmosphere into the lungs whereas oxygenation is the uptake of O_2 in the lungs followed by O_2 delivery to the body. Oxygenation is the process that delivers oxygenated blood from our pulmonary and systemic circulation to the peripheral tissues.

Ventilation

Ventilation is a topic central to lung physiology that brings together foundational concepts of chemistry and physics. Simplistically, ventilation is the movement of gases in and out of the lungs. The impact of this seemingly simple process influences a number of systems, best understood beginning with blood flow to the lungs, following it as it interfaces with alveoli, and finally finishes at the tissue level in the body. Air enters the body via the upper respiratory tract which includes the nasal cavities, pharynx, and larynx. Along the upper respiratory tract, the air is humidified by mucus in the airway and heated from the blood traveling in adjacent blood vessels. Beyond the upper airway, the air continues into the lower respiratory tract which contains the trachea, bronchi, bronchioles, and alveoli. The upper airway, trachea, and bronchi predominantly function in the conduction of air and do not play a major role in gas exchange. Alternatively, the respiratory bronchioles and alveoli of the lower respiratory tract play a major role in gas exchange.

Once the now humidified and heated air reaches the terminal portions of the lower respiratory tract, it diffuses across the lung's air-filled sacs called alveoli. Each human lung contains roughly 150 million alveoli whose compact shape and distribution allow for roughly 50–75 m^2 of surface area for gas exchange. The alveolar epithelium is composed of simple squamous epithelium that enables efficient diffusion of gases. On the basal lamina of the alveoli, there is a very thin membrane (varying from 0.2 mm to 2.2 mm in thickness) known as the respiratory membrane. It is across this membrane that the O_2 diffuses from alveoli to the pulmonary capillaries. The alveolar respiratory membrane is separated from the pulmonary capillaries by only a tiny interstitial space, providing an advantageously small distance for gaseous diffusion into the capillary blood. CO_2 diffuses out of the pulmonary capillaries into the airway and is removed from the body via the respiratory tract [3].

Perfusion

Cardiac output from the heart is a mostly parallel circuit with equal quantities of blood delivered to both the systemic and pulmonary circulations. The delivery of blood and its "perfusion" to the lungs differ from that of systemic circulation in a number of ways.

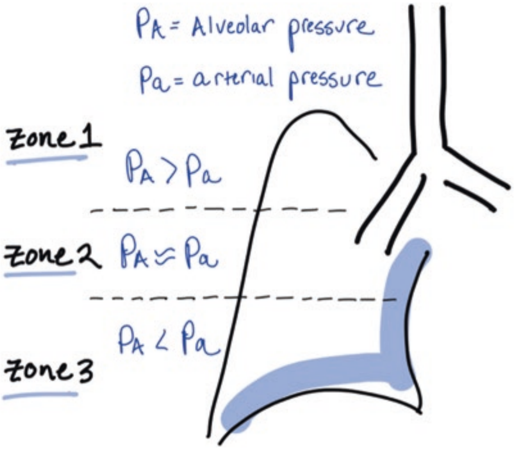
First, the pressures within the pulmonary vasculature are low, with average systolic of 25 mmHg, diastolic of 8 mmHg, and mean of 15 mmHg, denoted with the syntax 25/8 (15). These numbers are approximately 1/4 to 1/5 that of systemic circulation [9]. Additionally, unlike systemic circulation where the majority of pressure loss in the system occurs at an arteriole level, instead in pulmonary vessels, this loss occurs directly at the capillary bed [10].

Also unique to pulmonary perfusion is its "capacitance" or ability to handle increases in cardiac output without a proportional increase in pressure. For example, during exercise, flow to lungs can increase 4–5 times that of baseline with relatively unchanged pressures. Systemic circulation significantly contrasts this, with increases in systolic pressure in excess of 50% during exercise. Consequently, when comparing both circulations, pulmonary resistance can be as much as ten times lower than that of systemic [9].

The capacitance of the pulmonary circuit can partly be described by a phenomenon where areas of the lungs, at rest, are unequally perfused. During times of increased cardiac output, recruitment of additional alveoli to participate in gas exchange as well as dilation of blood vessels occurs which is reflected in a large drop in resistance. "West zones" dividing the lung into base or 1, midportion or 2, and apex or 3 help describe the relationship between alveolar and arterial pressure with the result of lung bases being preferentially perfused (Fig. 2.1) [11].

Finally, a remnant of fetal physiology also has large impacts on lung perfusion. In utero, O_2 levels are much lower than those seen after birth and this results in vasoconstriction of pulmonary vasculature [11]. Aptly named "hypoxic

Fig. 2.1 Alveolar pressure (P_A) and arterial pressure (P_a) differences between the West zones of the lung



vasoconstriction," this mechanism persists beyond the womb. Alveoli not participating in gas exchange, for example during airway obstruction or external compression by a pneumothorax, experience lower levels of O_2, vasoconstriction of nearby vessels, and subsequently blood flow redirected towards areas of active gas exchange [12].

Dead Space

Understanding that areas of lung perfusion and ventilation are unequal brings up an important concept of ventilation called "dead space." Areas that are well ventilated, but poorly perfused, are central to this concept. Three types of dead space exist: physiologic, anatomical, and device related (Fig. 2.2).

Physiologic dead space is best seen at the apex of the lung or West zone 1. At rest these areas receive adequate movement of gases in and out of alveoli, however with minimal blood flow. This is normal physiology and varies based on cardiac output as previously described. The ratio of dead space to perfused alveoli can be calculated by the formula:

$$\frac{\text{Dead space}}{\text{Perfused}} = \frac{\left(\text{Alveolar partial pressure carbon dioxide}\right) - \left(\text{Exhaled partial pressure carbon dioxide}\right)}{\left(\text{Arterial partial pressure carbon dioxide}\right)}$$

Because it is nearly impossible to measure the partial pressure of CO_2 at the alveolar level, the arterial partial pressure of CO_2 is substituted instead [13].

Anatomical dead space exists within the airways where gases are transmitted from the atmosphere to alveoli but no gas exchange occurs. This includes all the volume from the trachea to the terminal bronchioles. The amount of anatomical

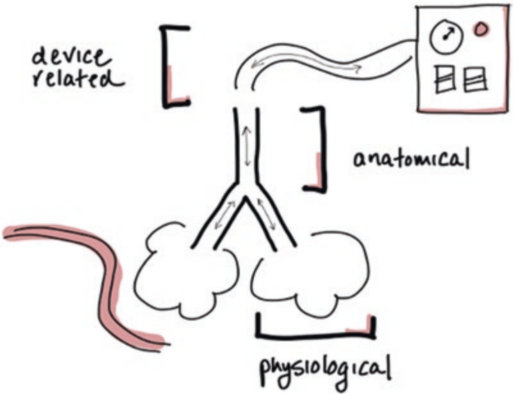


Fig. 2.2 Dead space may exist as related to the device, patient anatomy, or patient physiology

dead space is based on sex and height, and can be estimated at 1 mL/kg of ideal body weight [14].

Lastly, device- or apparatus-related dead space can exist. Mechanical ventilation requires tubes for delivering gases which exist outside of the body. These tubes contain a volume of gas that is considered dead space. This volume is generally clinically insignificant; however, it can become a problem with long circuits or small patients [15, 16].

Shunt

A related concept representing the opposite of “dead space” is “shunt” where blood travels from pulmonary to systemic circulations without gas exchange. This can occur within the lung where blood bypasses beyond areas of ventilated alveoli [17]. Additionally, blood can be “shunted” from pulmonary to systemic circulations at extrapulmonary locations which are seen in utero and congenital heart disease [18]. However, this extrapulmonary shunt physiology is complex and beyond the scope of this chapter.

A-a Gradient

As blood interfaces at the alveolar/endothelial basement membrane, gas exchange occurs. This process is primarily driven by diffusion. The volume of gas diffused is based on a number of factors including area, properties of gas, carrying capacity of blood/hemoglobin content, membrane thickness, and difference in partial pressures of gas from alveoli ($\mathrm{Pa}_{\mathrm{Alv}}$) to arterial ($\mathrm{Pa}_{\mathrm{Art}}$). These factors can be summarized in the following relationship [19]:

$$\text{Volume gas} = \frac{\text{Area} \times \text{Gas properties} \times \text{Hemoglobin content}}{\text{Thickness}} \times \left(\mathrm{Pa}_{Alv} - \mathrm{Pa}_{\mathrm{Art}}\right)$$

The only part of this equation that is clinically relevant is the difference in alveolar to arterial partial pressures of gas or “A-a gradient” and their relative relationship to diffusion. Generally, this value is less than 10, but when elevated it can be helpful in diagnosing lung pathology [20].

For example, administering increasing amounts of O_2 to a patient with substantial shunt will result in a widened A-a gradient secondary to the relatively small area O_2 has to diffuse into the blood [21]. This is in contrast to instances where a diffusion limitation occurs such as with increased membrane thickness or decreased carrying capacity of the blood where administration of O_2 narrows the A-a gradient [22].

V/Q Mismatch

An additional cause of an increased A-a gradient that narrows with O_2 administration is "V/Q mismatch" or ventilation/perfusion mismatch [23]. Simplistically, this physiological condition represents areas of imbalanced ventilation and perfusion. This occurs under normal circumstances, described in previous sections by "West zones" where bases or zone 1 receives more perfusion than ventilation and apices or zone 3 experiences more ventilation than perfusion [24]. With approximately 4 L/min of ventilation and 5 L/min of perfusion to the lungs, the overall average V/Q ratio is 0.8 [25].

Pathologically this overall lung ratio can be decreased in instances of reduced ventilation such as obstructive lung disease, or increased with reduced pulmonary blood flow seen in pulmonary emboli [26].

Carbon Dioxide

The most important gas that diffuses at the alveolar/endothelial membrane and is central to ventilation is CO_2. This by-product of cellular respiration is used as a surrogate for the adequacy of ventilation, and its interaction with water is unique in that it contributes significantly to maintaining normal body pH.

The solubility of CO_2 into water is represented by the formula from Henry's law [27]:

$$\text{Dissolved carbon dioxide} = 0.0301\, mM\,/\,\text{mmHg} \times \text{Partial pressure of carbon dioxide}$$

With a normal partial pressure of this gas ranging from 35 to 45 mmHg, the total amount diffused in water is very small at approximately 1.2 mM.

However, CO_2 undergoes chemical change with water into the unstable intermediate of carbonic acid and then stable product bicarbonate, a weak acid. This reaction is represented in the equation $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO3^-$. As a weak acid, bicarbonate obeys the principles of the Henderson-Hasselbalch equation with its relationship to pH explained in the formula [28]

$$pH = 6.1 + \log\left[\frac{HCO3-}{\text{Pa}_{CO2} \times 0.0301}\right]$$

Using this formula, at physiologic pH of 7.4 with a partial pressure of CO_2 of 40 mmHg, approximately 24 mM of bicarbonate is soluble in water.

With this conversion to bicarbonate, a nearly 20 times increase in the capacity of water to carry CO_2 is seen beyond that of just dissolved gas. The acid base properties of this reaction also allow for relatively large amounts of CO_2 in the form of bicarbonate to be transported with small changes in pH. However, these small changes become clinically significant as normal physiologic pH is tightly regulated between 7.35 and 7.45 [29]. Increases in the partial pressure of CO_2 beyond 45 mmHg can lower pH beyond physiological limits. The opposite is also true with decreases in the partial pressure of this gas to less than 35 mmHg, increasing pH to values outside of physiological limits.

The rate at which CO_2 is eliminated via ventilation is represented by the alveolar ventilation equation, which is a derivation of the ideal gas law. In this equation, minute ventilation, volume of CO_2, and partial pressure of CO_2 are related to each other in the following formula [30]:

$\text{Minute ventilation} = \frac{\text{Volume}\, CO_2}{\text{Pa}_{CO_2}} \times K$, where K equals 863 at a body temperature of 37 °C and 1 atmosphere.

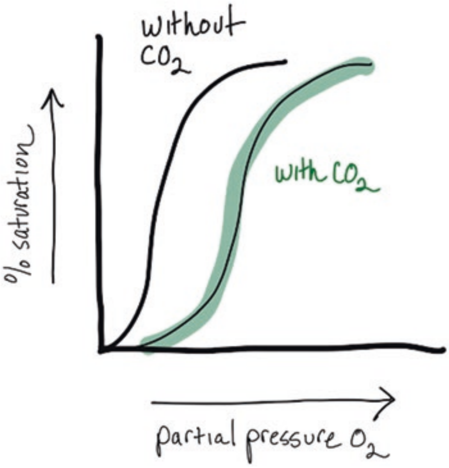
The inverse relationship between minute ventilation and partial pressure of CO_2 is clinically useful in adjusting ventilation to match CO_2 production. For example, to halve a given partial pressure of CO_2, minute ventilation would have to double [31].

Bohr Effect

Emphasizing its importance to ventilation, the impacts of CO_2 extend beyond those of its influence on acid-base balance, and its clinical use to assess the adequacy of ventilation. At the tissue level, this gas has significant effects on the availability of O_2. The Bohr effect describes the elegant relationship between increasing levels of CO_2 and increased availability of O_2 gas that can be used in cellular respiration (Fig. 2.3) [32].

The mechanism of this process is a result of changes to the oxygen-hemoglobin dissociation curve, discussed in the below section. CO_2 reversibly interacts with the

Fig. 2.3 Graphical representation of the Bohr effect



protein structure of hemoglobin, decreasing its affinity to O_2. This effectively shifts the overall oxygen-hemoglobin dissociation curve to the right [32].

The effect of this interaction is twofold. At the tissue level where CO_2 levels are high, it causes O_2 molecules to be "released" from hemoglobin. This stands in contrast to the conditions at the alveolar level where CO_2 gas is rapidly removed, increasing the affinity of hemoglobin to O_2. The overall net effect is an increase in the efficiency of oxygen transport to tissues [32].

O_2 Delivery to Tissues

Once in the blood, O_2 is carried in two forms: dissolved O_2 and O_2 that is reversibly bound to hemoglobin. During its journey to the tissues, dissolved O_2 accounts for roughly 2% of the total O_2 content in the blood while the remaining 98% of O_2 is reversibly bound to hemoglobin. Hemoglobin is a globular protein that contains four subunits. Each hemoglobin subunit is able to bind and transport one molecule of O_2 for a total of four molecules of O_2 per hemoglobin molecule. As we will go on to later explore, O_2 is able to dissociate from the hemoglobin molecule under different conditions. This dissociated O_2 is what exerts the partial pressure of O_2 within the blood, leading to important implications for O_2 delivery and gas exchange within the peripheral tissues.

The amount of dissolved O_2 in the blood abides by Henry's law regarding the concentrations of dissolved gases. In the context of blood as a solution, Henry's law states

$$Cx = Px \times \text{Solubility}$$

where Cx = concentration of dissolved gas (mL gas/100 mL blood), Px = partial pressure of gas (mmHg), and solubility = solubility of gas in blood (mL gas/100 mL blood per mmHg).

Henry's law demonstrates that the concentration of dissolved gas is directly proportional to the partial pressure of the gas and the solubility of the gas in the blood. The dissolved O_2 is solely responsible for exerting the partial pressure of O_2 in the blood. The partial pressure of O_2 is a crucial factor when it comes to establishing the gradient for oxygen's eventual exchange in the lungs and peripheral tissues.

Similar to the lungs, the capillaries within the peripheral tissues have thin membranes that allow for the rapid and efficient exchange of gases. O_2, bound to hemoglobin within the blood, is released for utilization by O_2-deprived tissues. At the same time, CO_2 is rapidly diffused from the peripheral tissues back into the capillaries for eventual removal by the lungs. In both ventilation and oxygenation, gas exchange occurs as a result of the underlying properties and laws that drive the movement of gases. We will now explore the underlying forces that drive the process of gas exchange.

The diffusion of O_2 and CO_2 in gas exchange is driven primarily by Fick's law for the diffusion of gases. Fick's law defines how the volume of gas transferred per unit time is affected by factors such as the diffusion coefficient of a specific gas, surface area for diffusion, partial pressure difference, and thickness of the membrane and it is represented by the following equation:

$$\dot{\mathrm{V}}\mathrm{x} = \frac{\left(D \times A \times \Delta P\right)}{\Delta x}$$

where $\dot{V}_{\mathrm{x}}$ = volume of gas transferred per unit time, D = diffusion coefficient of the gas, A = surface area, ΔP = partial pressure difference of the gas, and Δx = membrane thickness.

This law states that the volume of gas transferred per unit of time is directly proportional to the diffusion coefficient of the gas, surface area available for diffusion, and partial pressure difference of the gas. Conversely, the volume of gas transferred per unit of time is inversely proportional to the thickness of the membrane. The main driving force for the volume of gas transferred per unit time is the partial pressure difference of the gas across the membrane. As previously mentioned, the partial pressure of O_2 in the blood is exerted by the amount of freely dissolved, non-bound O_2 in the blood. In the context of O_2 diffusion in the lungs and peripheral tissues, the larger the gradient of partial pressure of O_2 across the membrane, the larger the volume of gas transferred per unit time.

Haldane Effect

The removal of CO_2 from the tissues is another key component of gas exchange. CO_2 exists in the body in three forms: dissolved CO_2, carbaminohemoglobin (CO_2 bound to hemoglobin), or bicarbonate. As mentioned previously, CO_2 binds to hemoglobin as carbaminohemoglobin at a site different from O_2 and decreases hemoglobin's affinity for O_2. This effect is known as the Bohr effect. Alternatively, O_2 affects hemoglobin's affinity for CO_2 in a process known as the Haldane effect. When less O_2 is bound to hemoglobin, the affinity for CO_2 is increased. The Bohr and Haldane effects operate in tandem at the peripheral tissues. As the amount of CO_2 increases, hemoglobin's affinity for O_2 decreases (Bohr effect), and as the amount of O_2 on hemoglobin decreases, hemoglobin increases its affinity for CO_2. At the molecular level, the Bohr and Haldane effects lead to an efficient system for delivery of O_2 with concurrent removal of CO_2.

Oxyhemoglobin Dissociation Curve

The O_2-hemoglobin dissociation curve demonstrates how hemoglobin saturation with O_2 varies with changes in the pressure of O_2. As mentioned previously, hemoglobin is a globular protein with four subunits, each of which can bind one molecule of O_2 for a total of four molecules of O_2 per molecule of hemoglobin.

The sigmoid shape of the O_2-hemoglobin dissociation curve demonstrates an important concept related to the hemoglobin molecule called positive cooperativity. The hemoglobin molecule is structured in such a way that its affinity for a molecule of O_2 increases as each molecule binds. This means that as the first molecule of O_2 binds to hemoglobin, there is a stronger affinity for a second molecule of O_2 to bind, and so on.

The curve also demonstrates why O_2 has a preference for binding to hemoglobin in the lungs and a preference for dissociating in the peripheral tissues. As you move from right to left along the curve, the hemoglobin saturation percent increases as the partial pressure of oxygen (PO_2) increases. The systemic arterial blood has a PO_2 of roughly 100 mmHg which correlates to 100% hemoglobin saturation. As the pulmonary capillary blood also has a PO_2 of 100 mmHg, hemoglobin becomes nearly 100% saturated with O_2 in the lungs. Alternatively, in the peripheral tissues, mixed venous blood has a PO_2 of roughly 40 mm Hg meaning that the hemoglobin saturation will be lower as demonstrated by the curve and the O_2 will have a higher propensity to be off-loaded. Let us now explore how changes in certain factors lead to shifts with the O_2-hemoglobin dissociation curve.

There are four main factors that tend to shift the O_2-hemoglobin dissociation curve to the right or the left. These factors are P_{CO2}, pH, temperature, and 2,3-diphosphoglycerate (2,3-DPG). Shifts of the curve to the right demonstrate a decreased affinity for O_2 to hemoglobin. When tissues are in highly metabolic states, they produce CO_2 as waste, leading to a subsequent drop in the pH of that area. CO_2 binds to hemoglobin at a site different from O_2. As previously described, the binding of CO_2 to hemoglobin leads to increased O_2 dissociation from hemoglobin and this is known as the Bohr effect. Additionally, metabolic tissues produce heat, leading to an increase in temperature. This increase in temperature leads to a decrease in oxygen's affinity for hemoglobin, leading to an increase in O_2 dissociation from hemoglobin. The increased CO_2, decreased pH, and increased temperature indicate that tissues are utilizing O_2 through metabolic cellular respiration. As a result, more O_2 is needed and the O_2-hemoglobin dissociation curve shifts to the right. Lastly, 2,3-DPG indicates hypoxic tissue as it is a by-product of glycolysis. Rates of glycolysis increase during anaerobic conditions leading to an increase in the production of 2,3-DPG. When 2,3-DPG binds to hemoglobin, it decreases the affinity for O_2 to hemoglobin and leads to a subsequent off-loading of O_2 in these hypoxic tissues. Shifts in the O_2-hemoglobin dissociation curve to the left demonstrate an increased affinity for O_2 binding and are caused by the same factors described above. These factors shift the curve to the left for the exact opposite contextual reason that shifts the curve to the right.

Hypoxemia vs. Hypoxia

Hypoxemia and hypoxia both refer to lack of O_2. However, hypoxemia is more specifically decreased arterial PO_2 while hypoxia is decreased O_2 at the tissue level. As mentioned previously, O_2 contained in atmospheric air travels through the respiratory tract to the alveoli where it is diffused into the pulmonary capillaries. Hypoxemia is defined as decreased arterial PO_2, indicating either an issue with the actual inspiration of O_2 or an issue somewhere along the respiratory tract. Causes of hypoxemia include high altitude, hypoventilation, diffusion defects across the membranes, ventilation/perfusion (V/Q) defect, and right-to-left shunts.

Approximately, 2% of O_2 in the blood is found as dissolved O_2. This dissolved O_2 is able to exert a partial pressure known as PaO_2. The remaining 98% of O_2 is bound to hemoglobin. The percentage of hemoglobin sites that are saturated is known as the SaO_2. O_2 content in the blood, denoted by CaO_2, is calculated by adding the amount of dissolved O_2 with the amount of O_2 bound to hemoglobin. CaO_2 can be better represented by the following equation:

$$CaO_2 = \left(Hb \times 1.34 \frac{\mathrm{ml\,O_2}}{gm\,Hb} * SaO_2 \right) + \left(\mathrm{PaO_2} \times 0.003\,\mathrm{ml\,O_2\,/\,mmHg\,/\,dl} \right)$$

where Hb = hemoglobin, 1.34 = oxygen-combining capacity, SaO_2 = oxygen saturation, PaO_2 = partial pressure of arterial oxygen, and 0.003 = solubility coefficient of oxygen at body temperature.

Lastly, O_2 delivery (D_{O2}) is calculated using cardiac output and O_2 content of the blood (CaO_2). It is represented by the following equation:

$$\mathrm{D_{O2}} = \mathrm{Q} \times CaO_2$$

where DO_2 = oxygen delivery in mL/min, Q = cardiac output in L/min, and CaO_2 = oxygen content.

The O_2 delivery equation demonstrates that DO_2 is directly proportional to cardiac output and O_2 content within the blood. As cardiac output or O_2 content of the blood increases, O_2 delivery will also increase. Decreased cardiac output or O_2 content will lead to subsequent decreased O_2 delivery.

Altitude Effects on Gas Exchange

Altitude is defined as height in relation to sea or ground level, and with increases, there is a decrease in atmospheric pressure. Atmospheric pressure refers to the total pressure of the total components of air at a specific height. While changes in atmospheric pressure with altitude have no direct effect on O_2 concentration within inspired air, it reduces the overall partial pressure of O_2 which is the main driver of gas exchange as discussed earlier. With this decreased partial pressure of inspired O_2, the partial pressure of O_2 in the alveoli and subsequently the artery is decreased compared to sea level. Interestingly, the alveolar-arterial gradient is actually increased compared to sea level due to gas exchange and diffusion not being limited to ventilation-perfusion matching. This is because blood traveling through the lung capillaries is inadequately oxygenated as a result of reduced drive pressure which in turn causes hypoxic vasoconstriction and thus longer time for gas exchange to occur. Exercise at high altitudes can lead to hypoxia due to the larger role of V/Q matching with inability to maintain slow transit time due to higher cardiac output. Over time, the body can acclimate to the changes in gas exchange at higher altitudes. However, if the rise in altitude is too rapid, then the hypoxia and resulting pulmonary hypertension can lead to pulmonary edema and altitude sickness [33].

Normal Physiologic Parameters

In this chapter, the authors have introduced fundamental topics in lung anatomy and physiology. The subsequent tables are intended to serve as a reference of normal physiologic parameters for arterial blood gas (Table 2.1), PaO_2 (Table 2.2), arterial pH and $PaCO_2$ in men (Table 2.3), arterial pH and $PaCO_2$ in women (Table 2.4), respiratory parameters for adults (Table 2.5), and venous blood gas values (Table 2.6).

Table 2.1 Normal arterial blood gas values [34]

Parameter	Normal range
pH	7.36–7.44
$PaCO_2$	35–45 mmHg
PaO_2	80–100 mmHg
SaO_2	95–97%
HCO_3	22–26 mEq/L
Base excess	±3 mmol/L

Table 2.2 PaO_2: Altitude- and age-adjusted normal values [35]

	0 m	1000 m	2000 m
Age	PaO_2	PaO_2	PaO_2
19–24	102.1–103.5	86.7–88.2	74.2–75.6
25–34	99.6–101.8	84.3–86.5	71.7–73.9
35–44	97.1–99.4	81.8–84.0	69.3–71.5
45–54	94.7–96.9	79.4–81.6	66.8–69.0
55–64	92.2–94.5	76.9–79.1	64.4–66.6
65–74	92.0–89.8	74.5–76.7	61.9–64.1
75–84	87.3–89.5	72.0–74.2	59.5–61.7

Table 2.3 Arterial pH and $PaCO_2$ in men [35]

Altitude	pH	$PaCO_2$
0 m	7.42 (7.38–7.46)	38.3 (33.0–43.7)
1000 m	7.43 (7.39–7.47)	35.1 (29.8–40.5)
2000 m	7.44 (7.40–7.48)	32.5 (27.1–37.8)

Table 2.4 Arterial pH and $PaCO_2$ in women [35]

Altitude	pH	$PaCO_2$
0 m	7.43 (7.39–7.46)	37.2 (31.8–42.5)
1000 m	7.44 (7.40–7.47)	34.0 (28.6–39.3)
2000 m	7.45 (7.41–7.48)	31.3 (26.0–36.7)

Table 2.5 Normal values for respiratory parameters for average adult [36–38]

Parameter	Normal value
End tidal CO_2	30–35 mmHg
Dead space (Vd)	150 mL
Tidal volume (Vt)	500 mL
Vd/Vt	28–33%
Minute ventilation (VE)	5–8 L/min
Arterial oxygen content (CaO_2)	19–20 ml O_2/dl blood
Oxygen delivery (DO_2)	900–1100 mL/min
Oxygen consumption (VO_2)	200–250 mL/min
Mixed venous oxygen saturation (SvO_2)	65%

Table 2.6 Normal venous blood gas values

Parameter	Normal value
pH	7.31–7.41
pCO_2	40–50 mmHg
pO_2	36–42 mmHg
SO_2	60–80%
Bicarbonate	22–26 mEq/L
Base excess	±3 mmol/L

Conflicts of Interest None

Financial Disclosures None

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