Physiology of Respiratory System

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KEY POINTS

- Developmental changes in the respiratory system continue to occur from newborn period through childhood as the alveoli continue to develop. Several prenatal and postnatal processes may affect growth of the lungs
- Breathing is initiated by contraction of the inspiratory muscles, which leads to an increase in the thoracic volume
- Changes in pressure and volume that occur with breathing can be plotted on a pressure-volume curve and the slope of that curve represents the change in volume per unit change in pressure, which is the compliance
- Elastance is the tendency for stretch or distortion, as well as the ability to return to its original configuration after the distorting force is removed
- Airway resistance can be measured during a forced expiratory maneuver into a spirometer
- The alveolar ventilation, oxygen consumption, and carbon dioxide production of the body determine the levels of oxygen and carbon dioxide in alveolar gas. At constant carbon dioxide production, alveolar partial pressure of carbon dioxide (PCO_2) is approximately inversely proportional to alveolar ventilation

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INTRODUCTION

The development of the respiratory system goes through several stages, starting with an outpouching of the epithelial cells lining the laryngotracheal sulcus at the caudal end of the medial pharyngeal groove of the foregut endoderm around 3rd–6th week of gestation (embryonic stage). This stage leads to the formation of the lung buds, trachea, main stem, lobar and segmental bronchi, and developmental anomalies during this period may lead to tracheal, laryngeal, or esophageal atresias, tracheal stenosis, tracheoesophageal fistulae, and bronchial malformations. This is followed by the pseudoglandular stage (6th–16th week), which is characterized by formation of the sub-segmental bronchi and terminal bronchioles, mucus glands, cartilage, and smooth muscle. Defects during this period of development may lead to tracheobronchomalacia, pulmonary sequestrations, cystic adenomatoid malformations, ectopic lobes, diaphragmatic hernias, and congenital pulmonary lymphangiectasia. The canalicular stage (16th–26th weeks) leads to formation of respiratory bronchioles and acini, formation of capillary bed, and type I and type II pneumocyte differentiation. Prematurely delivered newborns born before 26 weeks gestational age, therefore, tend to be surfactant deficient and will always require surfactant replacement and possibly, mechanical ventilatory support. The saccular stage (26th–36th week) prepares the fetus for extrauterine survival with thinning of respiratory epithelium, growth of lung acini,

and maturation of type II pneumocytes. The final alveolar stage continues from 36th week of gestation to mid-childhood until the full complement of about 200 million alveoli has been formed.[1]

With increasing age, there is loss of alveolar elastic recoil, decreased chest wall compliance, increased static lung compliance and decrease in the strength of the expiratory muscles. The residual volume (RV) increases with age, and flow rates such as forced expired volume in 1 second (FEV_1) and forced expiratory flow at 25–75% of forced vital capacity (FVC) ($FEF_{25–75\%}$) tend to decline. There is constant decline of lung function with a drop in FEV_1 by an average of 29 mL/year for men and 25 mL/year for women, starting in the mid-20s. There is large inter-individual and inter-racial variation in this drop and several other patient- and environment-related factors could affect these changes. In addition, there is loss of alveolar surface area and decreased capillary blood volume, which tend to reduce the pulmonary diffusing capacity.

The respiratory system undergoes maturational changes after birth and these have an impact on the way respiratory disorders will present in different age groups. Lungs of the newborn undergo rapid resorption of fetal lung fluid at birth, and presence of adequately functioning surfactant is an important component of this transition. Lack of surfactant due to prematurity (hyaline membrane disease), inactivation (with meconium aspiration), or rarely, due to absence of specific surfactant proteins (congenital surfactant protein B or C

deficiency, *ABCA3* mutations) may lead to difficult transition, including need for mechanical ventilation, as the lungs have low compliance and are unable to allow effective gas exchange to occur at the alveolar level.[1]

MECHANICS OF BREATHING[2,3]

Breathing is initiated by the contraction of the inspiratory muscles that leads to an increase in the thoracic volume. This causes the alveolar pressure to fall below the atmospheric pressure, thus establishing a pressure gradient for airflow. Flow of air continues until alveolar pressure equilibrates with atmospheric pressure. By this time, the inspiratory muscles begin to relax and this leads to a decrease in thoracic volume, causing intrapleural pressure to become less negative and decreasing the alveolar transmural pressure gradient. The increased alveolar elastic recoil (which was generated by stretching of the alveoli during inspiration) then allows the alveoli to return to their preinspiratory volumes. At the end of expiration [at functional residual capacity (FRC)], the inward elastic recoil of the lung is balanced by the outward elastic recoil of the chest wall. Newborns tend to have much lower lung compliance than chest wall compliance (see compliance below), and therefore, have a much lower FRC. They try to maintain their FRC with partial glottic closure towards the end of exhalation, continued diaphragmatic activity in early exhalation and with rapid breathing rates. With conditions that cause respiratory distress, they tend to develop grunting respirations, as they try to maintain their FRC in the face of increased stress on their respiratory system.

The muscles of inspiration include the external intercostal, parasternal intercostal, and scalene muscles that raise and enlarge the rib cage; and the diaphragm, which by descending into the abdominal cavity, elongates the thorax and increases its volume as well. In the supine position, the diaphragm is responsible for about two thirds of the air that enters the lungs, whereas in the standing or seated posture, the diaphragm is responsible for only about one-third to one-half of the tidal volume. This also explains the fact why patients with neuromuscular weakness like spinal muscular atrophy are noted to have paradoxical abdominal movement with breathing, as they rely on their diaphragm alone for inspiration and its downward movement pushes out the abdominal contents with each breath. The accessory muscles of inspiration (sternocleidomastoid) are not involved during normal quiet breathing but may be called into play during forceful breathing seen during exercise, the inspiratory phase of coughing or sneezing; or in patients with respiratory distress.

Expiration is generally a passive process, although forced exhalation (as may occur during exercise, speech, singing, expiratory phase of coughing or sneezing) may involve the use of the internal intercostal muscles and the abdominal muscles—rectus abdominis, the external and internal oblique muscles, and the transversus abdominis. Changes in pressure and volume that occur with breathing can be plotted on a pressure volume curve (Fig. 1) and the slope of that curve represents the change in volume per unit change in pressure, which is the compliance. *Compliance* can be thought of as the ease with which something can be stretched or distorted, and is better understood by the difference in the force required
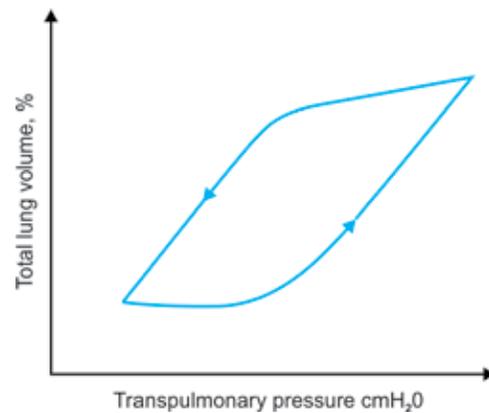

Fig 1: Pressure volume curve

to stretch a large rubber band versus a smaller, stiffer one. The reciprocal of compliance is called *elastance* and it is the tendency to resist stretch or distortion, as well as the ability to return to its original configuration after the distorting force is removed. The compliance of the entire respiratory system is the sum of the individual compliances of the lungs and the chest wall, and these may be affected by several factors. For example, disorders of lung parenchyma, such as pneumonia, will decrease the compliance of the lungs, requiring more pressure change to generate the same change in volume, leading to increased work of breathing. Similarly, severe kyphoscoliosis may limit the excursion of the chest wall and lead to decreased chest wall compliance. Newborns have a more compliant (less stiff) chest wall, leading to lower elastic recoil to balance that of the lungs and thus shifting their static pressure-volume curve to the right.

An understanding of these concepts is important in the management of patients when they are receiving ventilatory support to help determine the optimal settings in accordance with the underlying disease process. By performing an inspiratory breath hold for 1 second in patients on ventilatory support, static compliance is measured and can be followed serially, to help change ventilatory settings as patients start to show improvement. Dynamic compliance, as the name suggests, is the change in the volume of the lungs divided by the change in the alveolar-distending pressure during the course of a breath. With normal breathing, in most cases, the ratio of dynamic compliance to static compliance equals 1. However, with increased airway resistance in the small airways, and increased breathing frequency, this ratio decreases dramatically.

This concept can be further explained by considering two adjacent hypothetical alveoli (Fig. 2) supplied by the same airway where the compliance and resistance can be altered. If the resistances and compliances of the two units were equal, the two alveoli would fill up over the same time courses, but if the compliance of one were half that of the other, then over the same time course, the less compliant one would receive only half the volume. Now, if we double the resistance to airflow to one alveolus while keeping their compliances the same, then the former fills more slowly than the latter. As per Laplace's law, the pressure inside an alveolus (assumed to be spherical in configuration) is determined by the following formula:
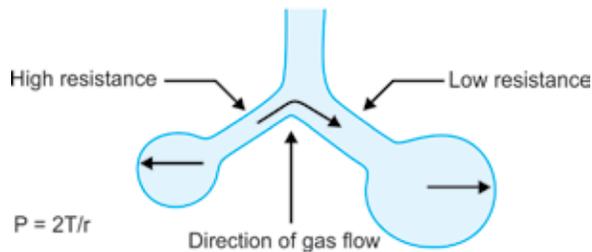
Fig. 2: Relationship of two hypothetical values in terms of their alveolar pressures, compliances, and airway resistance

$$P = 2T/r$$

Where P = Pressure inside an alveolus
    T = Wall tension
    r = Radius.

Thus, the smaller alveolus in the first situation will have higher intra-alveolar pressure than the other and since the alveoli are connected, there will be airflow down the pressure gradient from smaller alveolus to the larger one. The *time constant (τ)* of the respiratory system is the time taken for the volume to be reduced by 63% when the respiratory system is allowed to empty passively and the volume-time profile is measured. The time constants tend to be shorter in infants with normal lungs, but become even shorter in babies in hyaline membrane disease who have stiffer lungs. This also explains how the lungs adapt in various disease pathologies by ensuring that the normal lung continues to remain ventilated and perfused to maintain gas exchange. However, as the number of underventilated alveoli increase, the ventilation-perfusion mismatch becomes apparent. This occurs in patients with asthma, who have increased airways resistance, and have much longer time constants.

Since the lung and chest wall are in series with each other, their compliances add up as reciprocals. The difference between the pressure-volume curve for inspiration and expiration is called *hysteresis*, and is explained in the lungs by the alveolar recruitment and derecruitment as well as the muscles and ligaments of the chest wall. Airways resistance is extremely high at low lung volumes, and decreases with increasing lung volume.

With forced expiration, a positive intrapleural pressure is generated, which combined with the elastic recoil pressure of the alveoli, increases the pressure gradient in the alveoli with regard to the atmospheric pressure. Air starts to move out of the alveoli, but with this increased pressure, there is compression of the smaller airways that lack cartilaginous support and since this happens during exhalation, it is called *dynamic compression of the airways*. At any instant during a forced expiration, there is a point along the airways where the pressure inside the airway is just equal to the pressure outside the airway. At that point the transmural pressure gradient is zero, with pressure above that point being negative. As the forced expiratory effort continues, the *equal pressure point* is likely to move down the airway from larger to smaller airways. Thus, during a forced expiration, when intrapleural pressure becomes positive and dynamic compression occurs, the effective driving pressure for airflow from the lung is the alveolar elastic recoil pressure.

This brings us to the next section, which discusses how the forced expiratory flow rates are useful in assessing airway resistance.

Airway Resistance and Pulmonary Function Testing[1-3]

A significant proportion of the total resistance to airflow is located in the upper airways—the nose, nasal turbinates, oropharynx, nasopharynx, and larynx. Resistance is higher when one breathes through the nose than when one breathes through the mouth. Within the tracheobronchial tree, the smallest airways contribute the most to resistance, and as they are arranged in parallel, their resistances add as reciprocals, so that the total resistance to airflow offered by the numerous small airways is extremely low during normal, quiet breathing. However, resistance is inversely proportional to the radius to the fourth power, so changes in the radii of small airways can cause dramatic changes in airways resistance. The resistance to airflow cannot be measured directly but must be calculated from the pressure gradient and airflow during a breath. The smooth muscle of the airways from the trachea down to the alveolar ducts is under the control of cholinergic parasympathetic postganglionic fibers (causes constriction and increased glandular mucus secretion*)*, and increased adrenergic sympathetic fibers (cause dilation and decreased glandular mucus secretion).

One of the indirect methods of measuring airways resistance is a forced expiratory maneuver into a spirometer—which provides the FVC and FEV_1 (Fig. 3). The part of the curve most sensitive to changes in expiratory airways resistance is the first second of expiration. The volume of air expired in the first second of expiration (the FEV_1), especially when expressed as a ratio with the total amount of air expired during the forced exhalation (which is FVC), is a good index of airway caliber. In normal subjects, the FEV_1/FVC is greater than 0.80; that is, at least 80% of the FVC is expired in the first second. Another measurement is the $FEF_{25-75\%}$, or forced (mid) expiratory flow rate (formerly called the maximal mid expiratory flow rate). This variable is simply the slope of a line drawn between the points on the expiratory curve at 25 and 75% of the FVC, and is more indicative of the airflow in smaller airways. The maximal flow-volume curve that is obtained during a measurement helps distinguish between two major patterns of pulmonary diseases—obstructive diseases and restrictive diseases. Restrictive diseases, which usually entail elevated alveolar elastic recoil, have a normal or above normal FEV_1/FVC ratio,
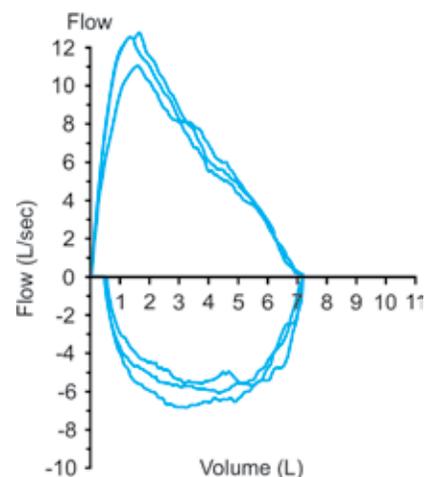

Fig. 3: Flow volume curves obtained by spirometry

since both the FEV_1 and FVC are decreased. Obstructive diseases on the other hand, are often associated with high lung volumes. The RV may be greatly increased if airway closure occurs at relatively high lung volumes. More importantly, the flow-volume curve of a patient with obstructive disease shows inward concavity or "scooping" of mid to lower part of expiratory curve.

Airway response to bronchodilators is frequently assessed to quantify the reversibility of airways obstruction, especially in patients with asthma. This response is considered significant when there is change in FEV_1 that is greater than 12% from baseline. Body plethysmography is used to measure the lung volumes (specifically FRC), and other lung volumes can then be derived from those measurements. The measurement of maximal inspiratory and expiratory pressures (MIPs and MEPs) may help in the management of children with neuromuscular weakness, as declining MIPs suggest progressive respiratory muscle weakness and low MEPs may be a predictor for poor cough and inability to clear the airway secretions in these patients. Other special techniques, like measurement of diffusing capacity of carbon monoxide, also called the transfer factor, may be useful for assessing the intactness of the alveolar capillary unit for the purpose of gas exchange, while techniques like helium dilution or nitrogen washout can help assess static lung volumes or measure ventilation inhomogeneity, respectively. Use of multiple breath washout technique to measure FRC in younger children can be done with tidal breathing. It allows the calculation of lung clearance index (LCI), which is the ratio of the cumulative expired volume of an inert tracer gas (as its concentration drops to $1/40^{th}$ of its initial concentration during washout phase) to the measured FRC. Elevated values of LCI reflect increased ventilation inhomogeneity and small airways dysfunction, and these can be detected much earlier than changes in spirometry. Its advantages include the use of tidal breathing, its reproducibility, its normal values being in a narrow range for most ages, and the results not being affected by height or gender of the subject.

Routine measurement of lung function is important both for initial assessment and for follow-up of lung disease. Many disease processes can have considerable overlap of symptoms and therefore, assessment of flows by spirometry and lung volumes by plethysmography can help differentiate between obstructive and restrictive disease processes.

Measurement of exhaled nitric oxide level can help assess for eosinophilic airway inflammation, with normal levels being less than 20 ppb. Exhaled breath condensates have also been utilized but their use is limited to the research setting. Assessment of lung function on a regular basis can help assess response to therapy, and constitutes an important research tool for determining the clinical effectiveness of newer therapies.

PULMONARY BLOOD FLOW AND VENTILATION-PERFUSION RELATIONSHIPS[1-3]

At resting cardiac output, the diffusion of both oxygen (O_2) and carbon dioxide (CO_2) is normally limited by pulmonary perfusion. The pulmonary vessels are more distensible and compressible than systemic arterial vessels, and also have much lower intravascular pressures. Determinations of the regional distribution of pulmonary blood flow have shown that gravity is another important "passive" factor affecting local pulmonary vascular resistance and the relative perfusion of different regions of the lung. In a person seated upright or standing up, there is greater blood flow per unit volume to lower regions of the lung than to upper regions of the lung. This generated the concept of three different zones in the lung with differences in perfusion and ventilation.

The upper zones of both lungs receive the least blood flow but have higher alveolar pressures (zone 1), whereas the middle zones have higher pulmonary artery pressure than alveolar pressures (zone 2). The lowermost zones of the lungs demonstrates increased blood flow secondary to effect of gravity but has least alveolar pressure due to compressive effect of the overlying lung segments (zone 3). This model was proposed by John B. West and is, therefore, called the West's 3-zone lung model. It is important to realize that the boundaries between the zones are dependent on physiologic conditions and that they are not fixed anatomic landmarks. For example, a patient receiving positive pressure ventilation with positive end expiratory pressure may have substantial amounts of zone 1 because alveolar pressure is always high. Similarly, after a hemorrhage or during general anesthesia, pulmonary blood flow may decrease and majority of the lungs demonstrate zone 1-like conditions. During exercise, as the cardiac output and pulmonary artery pressure increase, any existing zone 1 will be recruited to zone 2, and the boundary between zones 2 and 3 tends to move upward.

Presence of areas of low ventilation-perfusion (V/Q) ratios in which alveoli are underventilated and/or overperfused ("shunt like states") or completely unventilated or collapsed alveoli (absolute shunts) will create a mix of underoxygenated blood with blood draining well-ventilated areas of the lung. About 2–5% of the cardiac output, including venous blood from the bronchial veins, the thebesian veins, and the pleural veins, enters the left side of the circulation directly without passing through the pulmonary capillaries, thus constituting the anatomic shunts. The physiologic shunt, which corresponds to the physiologic dead space, consists of the anatomic shunts plus the intrapulmonary shunts. However, hypoxic pulmonary vasoconstriction tends to divert blood flow away from poorly ventilated areas of the lung by locally increasing vascular resistance, thereby trying to limit the extent of right-to-left shunting. On the other hand, non-uniform perfusion of the lung can be caused by embolus or thrombosis; compression of pulmonary vessels by high alveolar pressures, exudates, edema, pneumothorax, or hydrothorax; collapse or overexpansion of alveoli. These situations create alveolar dead space (as shown Fig. 4, right panel), which increases the V/Q ratio and can cause oxyhemoglobin desaturation. In a perfectly balanced situation where all the ventilated alveolar units are adequately perfused, the V/Q ratio equals 1 (Fig. 4, middle panel) and normal oxyhemoglobin saturations are obtained. However, more commonly, with clinical conditions (such as an acute asthma exacerbation) that cause reduction in alveolar ventilation in relatively large sections of the lung, there is poor ventilation of the affected alveolar units with preserved pulmonary blood flow. This causes the V/Q ratio to be less than 1 (Fig. 4, left panel) and creates a "shunt like state" due to the mixing of poorly oxygenated blood from these underventilated areas of the lung with that from areas where the V/Q relationship is maintained.
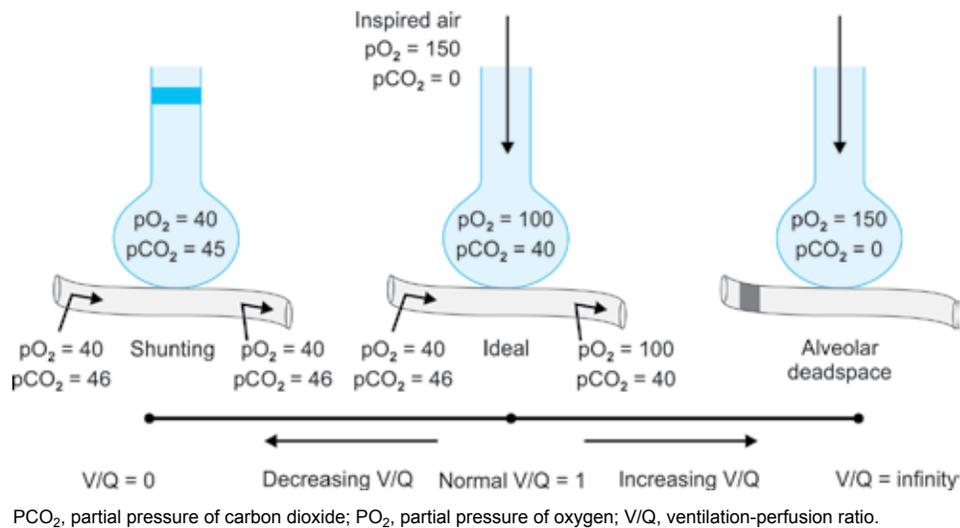
PCO$_2$, partial pressure of carbon dioxide; PO$_2$, partial pressure of oxygen; V/Q, ventilation-perfusion ratio.

Fig. 4: Hypothetical model of ventilation-perfusion relationships

In the clinical setting, it may be useful to estimate the size of this shunt for critically ill children. The shunt equation can be derived from total pulmonary blood flow per minute (Q_t) and the amount of blood flow per minute entering the systemic arterial blood without receiving any O$_2$ (the "shunt flow"—Q_s) is as follows:

The total volume of O$_2$ per unit time entering the systemic arteries = Q_t X CaO$_2$, where CaO$_2$ is the content of oxygen per 100 mL arterial blood

Volume of blood/min that perfuses alveolar-capillary units with well-matched ventilation and perfusion = Q_t – Q_s

The O$_2$ entering the systemic circulation is coming from the well-ventilated and well-perfused alveolar-capillary units = (Q_t – Q_s) × Cc'O$_2$ (where Cc'O$_2$ represents content of O$_2$ per 100 mL of the blood at the end of the normally ventilated and perfused pulmonary capillaries).

Therefore, the shunt equation can be stated as:

O$_2$ delivery to systemic blood = O$_2$ coming from normal V/Q units + O$_2$ from shunted blood flow

or

Q_t × CaO$_2$ = (Q_t – Q_s) × Cc'O$_2$ + Q_s × CvO$_2$ (where CvO$_2$ is the content of O$_2$ per 100 mL of shunted blood)

$$Q_t \times CaO_2 = Q_t \times Cc'O_2 - Q_s \times Cc'O_2 + Q_s \times CvO_2$$

$$Q_s/Q_t = Cc'O_2 - CaO_2/Cc'O_2 - CvO_2$$

The shunt fraction Q_s/Q_t is then multiplied by 100% so that the shunt flow is expressed as a percentage of the cardiac output. This equation can be applied in ICU patients in whom an arterial and mixed venous oxygenation level can be obtained, and the Cc'O$_2$ can be derived from the alveolar air equation.

ALVEOLAR VENTILATION

Alveolar ventilation is the exchange of gas between the alveoli and the atmospheric air. Alveolar ventilation is usually less than the volume of air entering or leaving the nose or mouth per minute (the minute volume) because the last part of each inspiration remains in the conducting airways (the anatomic dead space). The alveolar ventilation, O$_2$ consumption, and CO$_2$ production of the body determine the levels of O$_2$ and CO$_2$ in alveolar gas. At constant CO$_2$ production, alveolar PCO$_2$ is approximately inversely proportional to alveolar ventilation. As air is inspired through the upper airways, it is heated and humidified and the water vapor dilutes this air. Therefore, the true inspired O$_2$ concentration becomes: P$_I$O$_2$ = FiO$_2$ × (P$_B$ – PH$_2$O) = 0.21 (760 – 47) = 149 mmHg at sea level. In healthy people, alveolar PCO$_2$ is in equilibrium with arterial PCO$_2$. Thus, if alveolar ventilation is doubled (and CO$_2$ production is unchanged), then the alveolar and arterial PCO$_2$ are reduced by one-half. If alveolar ventilation is cut in half, near 40 mmHg, then alveolar and arterial PCO$_2$ will double. The alveolar PO$_2$ can be calculated by using the alveolar air equation, which is as follows:

P$_A$O$_2$ = P$_I$O$_2$ – PaCO$_2$/R (where R is the respiratory exchange ratio ~ 0.8). From the P$_I$O$_2$ equation above,

$$P_AO_2 = FiO_2 \times (P_B - PH_2O) - P_aCO_2/R$$

$$P_AO_2 \sim 150 - PaCO_2$$

Normally, there is a difference between the alveolar and arterial PO$_2$s, which is caused by the normal anatomic shunt, some degree of ventilation-perfusion mismatch, and diffusion limitation in some parts of the lung. Larger-than-normal differences between the alveolar and arterial PO$_2$ may indicate significant ventilation-perfusion mismatch, but can also be caused by anatomic or intrapulmonary shunts, diffusion block, low mixed venous PO$_2$, breathing higher than normal oxygen concentrations, or shifts of the oxyhemoglobin dissociation curve. Another useful clinical index in addition to the alveolar-arterial oxygen difference is the ratio of arterial PO$_2$ to the fractional concentration of oxygen in the inspired air. The P$_A$O$_2$/FiO$_2$ should be greater than or equal to 200; a P$_A$O$_2$/FiO$_2$ less than 200 is seen in acute respiratory distress syndrome.

TRANSPORT OF OXYGEN AND CARBON DIOXIDE IN BLOOD[2,3]

Oxygen is transported both physically dissolved in blood and chemically combined to the hemoglobin in the erythrocytes.

At a temperature of 37°C, 1 mL of plasma contains 0.00003 mL O_2/mmHg PO_2. Normal arterial blood with a PO_2 of approximately 100 mmHg, therefore, contains only about 0.003 mL O_2/mL of blood, or 0.3 mL O_2/100 mL of blood. Hemoglobin rapidly combines reversibly with oxygen and each gram of hemoglobin is capable of combining with about 1.34 mL of oxygen. The equilibrium point of the reversible reaction of hemoglobin and O_2 is dependent on how much O_2 the hemoglobin in blood is exposed to and therefore, the PO_2 of the plasma determines the amount of oxygen that binds to the hemoglobin in the erythrocytes. The relationship between the PO_2 of the plasma and the percent of hemoglobin saturation is demonstrated graphically as the oxyhemoglobin dissociation curve (Fig. 5). it is an S-shaped curve, steep at the lower PO_2 and nearly flat when the PO_2 is above 70 mmHg, with S-shape of the curve being due to the fact that it is actually a plot of four reactions (binding of four sites on each hemoglobin molecule to four molecules of O_2) rather than one.

The percent hemoglobin saturation (measured by pulse oximeter) expresses only a percentage of total oxygen binding sites that are occupied by oxygen at a given time, does not relate to the amount or volume of oxygen in blood. Therefore, "percent saturation" is not interchangeable with "oxygen content". As blood in pulmonary capillaries reaches the alveoli, it has a PaO_2 of 40 mmHg, with 75% of the hemoglobin binding sites being saturated. Assuming a hemoglobin concentration of 15 g/dL (for ease of calculation), the oxygen content of blood will be as follows:

Oxygen content of blood = Oxygen bound to hemoglobin + oxygen dissolved in plasma.

15 g/dL of Hb × 1.34 mL O_2/g Hb × 75% sites saturated + 0.003 mL O_2/100 mL blood × 40 mmHg = 15.08 + 0.12 = 15.2 mL O_2/100 mL of blood.

As the blood passes through the pulmonary capillaries, it equilibrates with the alveolar PO_2 of about 100 mmHg, and the hemoglobin becomes 97.4% saturated with oxygen, which yields an oxygen content of:

(15 × 1.34 × 97.4%) + (0.003 × 100) = 19.58 + 0.3 = 19.88 mL O_2/100 mL of blood.

Thus, in passing through the lungs, each 100 mL of blood adds on (19.88 – 15.20) mL O_2, or 4.68 mL O_2, and assuming a cardiac output of 5 L/min, about 234 mL O_2 is added on per minute.

As blood passes from the arteries into the systemic capillaries, it is exposed to lower PO_2s, and the hemoglobin releases oxygen. As the oxyhemoglobin dissociation curve is very steep in the range of 60 to 10 mmHg, a small decrease in PO_2 can result in a substantial further dissociation of oxygen and hemoglobin, unloading more oxygen for use by the tissues. Other factors that affect the oxyhemoglobin dissociation curve include temperature, pH, CO_2, and 2,3-diphosphoglycerate (2,3-DPG) levels.

Low pH and high PCO_2 (which are often seen together) both shift the curve to the right, and is referred to as the Bohr Effect. High temperatures shift the curve to the right, whereas low temperatures allow more oxygen to be dissolved in plasma, and the hemoglobin too does not release its bound oxygen. Red blood cells produce 2,3-DPG during glycolysis, and its binding to the hemoglobin molecule decreases the latter's ability to bind to oxygen, thus shifting the curve to the right. All these factors mentioned above could be favorably affected in metabolically active tissues and help in the release of O_2 where it is needed the most. Presence of fetal hemoglobin (HbF) shifts the curve to the left as it has greater affinity for oxygen relative to adult hemoglobin. This feature of HbF is favorable *in utero* as the fetal hemoglobin's greater affinity for oxygen relative to the maternal hemoglobin promotes transport of oxygen across the placenta by maintaining the diffusion gradient. Abnormal hemoglobin may have either increased or decreased affinities for oxygen (hemoglobin Seattle and hemoglobin Kansas have lower affinities, while hemoglobin Rainier has a higher affinity for oxygen).

The oxyhemoglobin dissociation curve also shows that a change in PaO_2 from 100 to 70 mmHg changes the oxygen saturation from 97.4 to 94.1%. Another way to assess shifts in the curve is by looking at P_{50} which is the PO_2 at which 50% of the hemoglobin present in the blood is in the deoxyhemoglobin
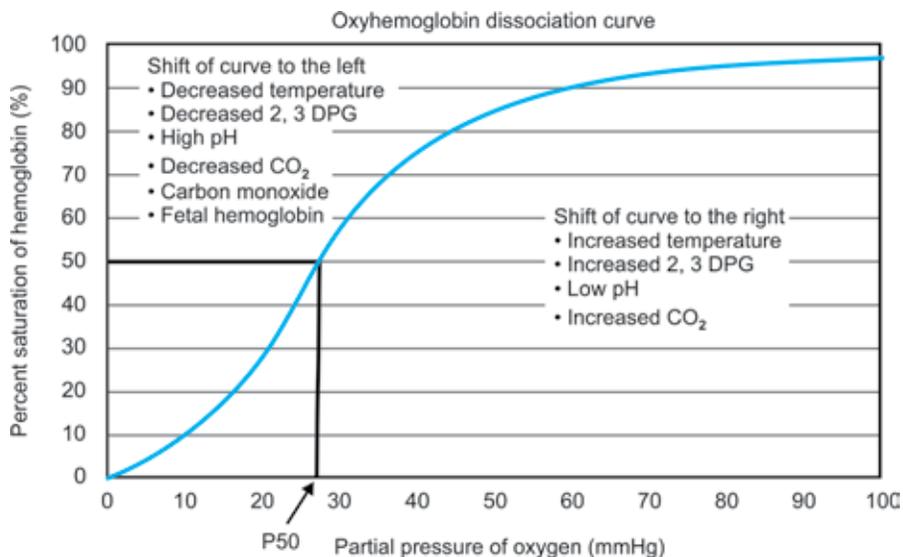

Fig. 5: Oxyhemoglobin dissociation curve

state and 50% is in the oxyhemoglobin state. At a temperature of 37°C, a pH of 7.4, and a PCO_2 of 40 mmHg, normal human blood has a P_{50} of 26 or 27 mmHg. If the oxyhemoglobin dissociation curve is shifted to the right, the P_{50} increases and vice versa.

Cyanosis occurs when more than 5 g Hb/100 mL of arterial blood is in the deoxygenated state. Carbon monoxide has a 200 times greater affinity for hemoglobin than does oxygen and shifts the oxyhemoglobin dissociation curve to the left, thereby preventing the loading of oxygen into the blood in the lungs and also interfering with the unloading of oxygen at the tissues. Nitric oxide can react with oxyhemoglobin to form methemoglobin and nitrate or react with deoxyhemoglobin to form a hemoglobin-nitric oxide complex. Researchers have proposed that the former mechanism can act in regions where the PO_2 is low, and release nitric oxide—a potent vasodilator—producing hypoxia-induced vasodilation in tissues, while the latter (nitric oxide scavenging by hemoglobin) could be responsible for hypoxic pulmonary vasoconstriction in lungs. Myoglobin, a heme protein that occurs naturally in muscle cells, combines chemically with a single molecule of oxygen and its dissociation curve is far to the left of that of normal hemoglobin. This allows O_2 to remain bound to myoglobin in muscle, till exercise produces a drop in local PO_2 when it can be released for use by the muscle tissue.

Carbon dioxide on the other hand is about 20 times more soluble in the plasma than oxygen. About 5–10% of the total CO_2 transported by the blood is carried in physical solution and the total carbon dioxide content of venous blood is about 52.5 mL CO_2/100 mL of blood (2.4 mL CO_2 per 100 mL of blood at 40 mmHg). About 5–10% of the total CO_2 in blood combines chemically with the terminal amine groups in globin to form carbaminohemoglobin, without any enzymes and releases a proton. The remaining 80–90% of the CO_2 transported by the blood is carried as bicarbonate ions, through a reaction catalyzed by carbonic anhydrase (present in erythrocytes, not in plasma).

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

The CO_2 dissociation curve is nearly a straight line within the normal physiologic range of PCO_2. It is shifted to the right at greater levels of oxyhemoglobin (Haldane effect) which means blood can load more CO_2 at the tissues, where there is more deoxyhemoglobin, and unload more CO_2 in the lungs, where there is more oxyhemoglobin.

ALTERATION IN PHYSIOLOGY UNDER VARIOUS CONDITIONS[1,2]

Several physiologic and pathologic states can produce alterations in the working of the respiratory system and it is important to understand the mechanisms involved in these changes. The physiologic changes with exercise, high altitude, and deep sea diving will be discussed in this section.

Exercise increases the metabolism of the involved muscles and places an increased demand for oxygen, while increasing the production of CO_2. Increased respiratory rate and tidal volume increase the alveolar ventilation, but also require increased mechanical work to overcome the elastic recoil of the lungs and chest wall during inspiration, because the lungs are less compliant at higher lung volumes, and because the elastic recoil of the chest wall is inward at high thoracic volumes. The arterial PO_2 and PCO_2 stay relatively constant during even strenuous exercise, although the latter increases once anaerobic metabolism results in lactic acid production. The cardiac output increases linearly with O_2 consumption during exercise, primarily due to autonomically mediated increase in heart rate. The exercising muscles compress the veins, and the deeper inspiratory efforts allow overall increase in venous return to the heart. Studies show more uniform matching of ventilation and perfusion throughout the lung during exercise. The increase in diffusing capacity during exercise is largely a result of the increase in pulmonary blood flow. Recruitment of capillaries, especially in upper regions of the lungs, increases the surface area available for diffusion. Increased linear velocity of blood flow through pulmonary capillaries reduces the time that red blood cells spend in contact with the alveolar air to less than the 0.75 seconds normally seen at rest, decreasing the perfusion limitation of gas transfer. The loading and unloading of both CO_2 and O_2 are enhanced at the tissue level, and prolonged severe exercise may even produce metabolic acidosis secondary to lactate generation. Continued training increases the oxidative capacity of skeletal muscle by inducing mitochondrial proliferation and increasing the concentration of oxidative enzymes and the synthesis of glycogen and triglyceride. These alterations result in lower concentrations of blood lactate in trained subjects than those found in untrained people, reflecting increased aerobic energy production.

There is a decrease in barometric pressure with increasing altitude, which is related to the weight of the air above it. Oxygen constitutes about 21% of the total pressure of dry ambient air, and so the PO_2 of dry air at any altitude is about 0.21 times total barometric pressure at that altitude. The water vapor pressure depends on the temperature and humidity of the air. Since the air entering lungs is warmed to body temperature and completely humidified, the water vapor pressure in the alveoli is 47 mmHg. The alveolar PCO_2 falls at greater altitudes because hypoxic stimulation of the arterial chemoreceptors increases alveolar ventilation. If an unacclimatized person ascends to a moderate altitude, he/she may suffer from a group of symptoms known collectively as acute mountain sickness. The symptoms include headache, dizziness, breathlessness at rest, weakness, malaise, nausea, anorexia, sweating, palpitations, dimness of vision, partial deafness, sleeplessness, fluid retention, and dyspnea on exertion. These symptoms are a result of hypoxia and hypocapnia, and alkalosis or cerebral edema, or both. There is an increase in cardiac output, heart rate, and systemic blood pressure at altitude. These effects are probably a result of increased sympathetic stimulation of the cardiovascular system secondary to arterial chemoreceptor stimulation and increased lung inflation. Hypoxic pulmonary vasoconstriction with engorgement of lungs secondary to pulmonary hypertension may lead to "high altitude pulmonary edema". Long-term compensations to the ascent to high altitude begin to occur after several hours and continue for days or even weeks. Renal compensation for respiratory alkalosis begins within a day, while erythropoiesis begins in 3–5 days. Hypoxic stimulation of the arterial chemoreceptors tends

to be diminished after some time, while the cerebral edema and increased intracranial pressure resolve due to increased reabsorption of cerebrospinal fluid, autoregulation of cerebral blood flow, and a sympathetically mediated vasoconstriction that takes a few days to develop.

The major physiologic stresses involved in diving include elevated ambient pressure, decreased effects of gravity, altered respiration, hypothermia, and sensory impairment. The severity of the stress involved depends on the depth attained; the length of the dive; and whether the breath is held or a breathing apparatus is used. For each 33 feet of sea water (or 34 feet of fresh water) ambient pressure increases by 1 atmosphere. Thus, at a depth of 33 feet of sea water, total ambient pressure is equal to 1,520 mmHg. Since the gas in the lungs is compressible in accordance with Boyle's law, the lung volume is halved at 33 feet depth and is one-third of the original at 66 feet depth if the breath is held for the dive.

CONCLUSION

A thorough understanding of the physiology of the respiratory system is crucial for the evaluation and management of patients with respiratory problems. This chapter gives a very brief overview of some of the key concepts and the interested reader is referred to more exhaustive texts for a detailed description of some of the more advanced concepts in respiratory physiology.

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