Respiratory System Physiology

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Key Points

1. Spirometry, lung volumes, diffusion capacity and exercise testing can be performed preoperatively in order to better understand a patient's pulmonary mechanics and identify those at high risk for postoperative complications.
2. The equation of motion of the respiratory system helps in understanding the components that are involved in ventilation. It divides the components into elastic and resistive loads.
3. The pressure volume curve can provide helpful information regarding the resistance and compliance of the respiratory system in an invasively ventilated patient.
4. Compliance of the respiratory system is a sum of lung compliance and the chest wall compliance and is affected by lung, chest wall, or abdominal cavity pathology.
5. The surface tension is the force present at air-liquid interface, which tends to minimize the surface area of a liquid. Surfactant reduces the surface tension, and with this allows homogenous ventilation and avoids atelectasis of lung at low lung volumes.
6. The major determinant of airway resistance is the radius of the airway. A decrease in radius will increase the airway resistance to a power of 4.
7. A major determinant of gas exchange is ventilation, perfusion, and its distribution. Dead space occurs when ventilation is higher than perfusion. Shunt occurs when perfusion is higher than ventilation.
8. Diffusion of a gas through the alveolo capillary membrane is dependent on the distance for diffusion, the pressure gradient, molecular weight, the thickness of the membrane, and solubility coefficient of the gas.
9. The lung serves other functions besides gas exchange. It serves as a filter for both the circulation (emboli) and inhaled particles. It has the ability to metabolize endogenous compounds and secrete hormones.
10. Perioperative smoking has effects systemically. This will affect not only the physiologic characteristics of the patients, but their outcomes.

18.1 Introduction

The lungs are in the chest cavity, surrounded by chest wall, bones, and muscles. The lungs have a resting size (volume), which depends on the elastic characteristics of the lung and the chest wall. In this interaction between the chest wall and the lungs, the lungs recoil inward (always trying to collapse), while the chest wall is trying to expand outward. This relation ends in a resting volume where the distending pressure of the chest wall balances with the collapsing pressure of the lung end in the resting volume or functional residual capacity. This is easily recognized after thoracotomy, the chest wall opens (outward) while the lungs collapse rapidly (no more negative pressure in the pleural cavity). The activity of the respiratory muscles, the habitus of the patient, and lung characteristics will affect this relationship. We use several physiological tests to evaluate this relationships.

We can assess the entire respiratory system physiology with three tests: (1) spirometry, (2) lung volumes, and (3) diffusion capacity. More complex tests, such as the cardiopulmonary exercise studies or ventilation perfusion studies are also useful for some specific cases (eg, lung resection). For most cases, the history and physical, spirometry, and a pulse oximetry will provide sufficient information on the status of the respiratory system to allow the anesthesiologist to understand the condition and expectations of the patient.

18.1.1 Spirometry

A spirometry is a device that measures the volume (flow) of inspired and expired air in terms of time. The values generated by the patient are compared to "normal" or predicted values, which are calculated using population-based equations using the patient's age, height, smoking status, gender, and race [1].

◘ Figure 18.1 depicts the different lung volumes measured with spirometry. The Y axis represents the lung volumes, from being completely deflated (as if the thorax was open and the lung compressed to contain zero air) to completely inflated (total lung capacity; the lung cannot have any more air in it at maximal inspiratory pressure). ◘ Figure 18.1 initially displays a patient breathing at rest. This is called the tidal volume or tidal breathing. You can see that there is lung volume above and below the tidal volume; this is the "reserve" the patient can inhale or exhale. To measure it, the patient is instructed to take the deepest breath possible. The volume generated is the inspiratory capacity (if measured from end expiration) or the inspiratory reserve volume (if measured from the top of the tidal volume). To measure the expiratory reserve, the patient is asked to exhale as much as possible to the point where no further air comes out in spite of maximal effort (this is the expiratory reserve volume). Indeed, there is still air in the lungs; however, this air cannot come out due to the elastic recoil from the chest wall and negative pleural pressure. This "remnant air" is called the residual volume. The curve demonstrates the vital capacity, which entails the amount of air exhaled after a maximal inspiration (we add *forced*, as we ask the patient to "forcefully" exhale). The functional residual capacity is the expiratory reserve volume plus the residual volume, which is the amount of air that remains in the lungs at end tidal breathing.

◻ Fig. 18.1 This Fig depicts the pressure volume curve of lung (P_L), chest wall (P_{CW}) and total respiratory system (P_T). The diagram indicates the direction and magnitude of the elastic forces of lung (*blue line*), chest wall (*red line*) and total respiratory system (*black dashed line*) at various lung volumes. At total lung capacity (*TLC*) the PCW is positive, trying to return to its resting state. The volume of lung and chest wall at zero pressure is different: lung has to be expanded and chest wall has to be compressed to reach resting volume. At resting volume (*FRC*), the inward elastic recoil of lung is equal to outward elastic recoil of chest wall. The residual volume is the lowest lung volume that the chest wall will allow to occur [2]
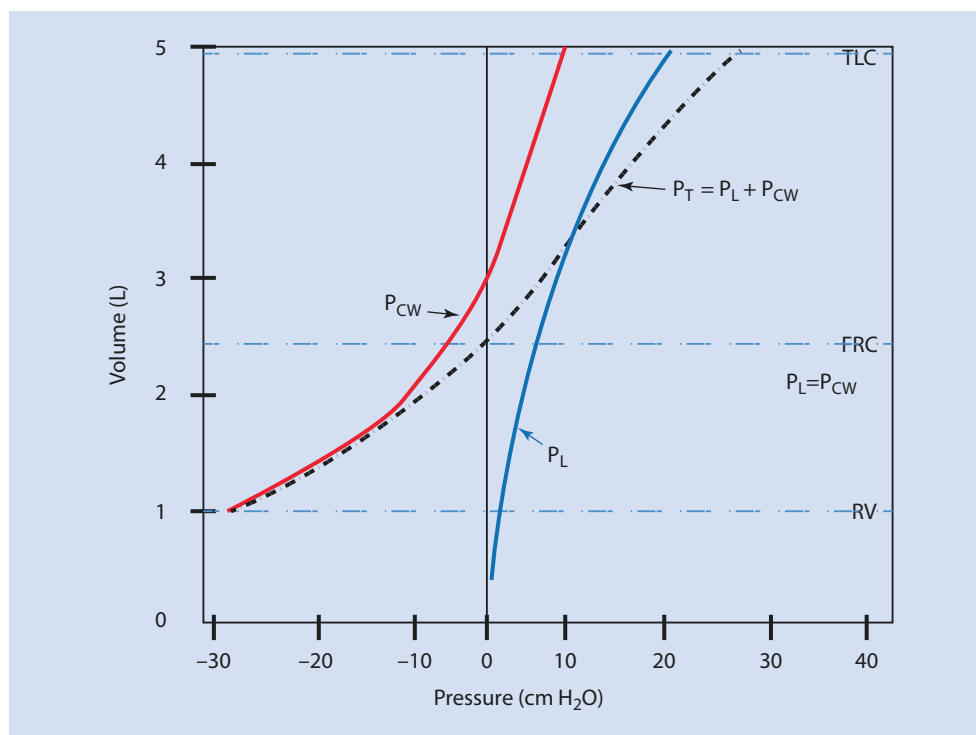
In summary, the lung has four basic lung volumes that constitute both inspiratory and expiratory phases and are as follows [2, 3, 4]:

1. Inspiratory reserve volume (IRV)
2. Tidal volume (Vt)
3. Expiratory reserve volume (ERV)
4. Residual volume (RV)

When two or more volumes are combined, they constitute four distinct lung capacities that are as follows [2, 3, 4]:

1. VT + IRV = inspiratory capacity (IC)
2. RV + ERV = functional residual capacity (FRC)
3. VT + IRV + ERV = vital capacity (VC)
4. IRV+ VT + ERV + RV = total lung capacity (TLC)

A typical spirometry tracing that displays the measured lung volumes is depicted in ◻ Fig. 18.2. Although the report will contain a large amount of numbers, the spirometry will only yield three values of interest for the anesthesiologist. The FVC (forced vital capacity), the FEV1 (forced expiratory volume in 1 s) and the ratio FEV1 to FVC. The absolute values are reported as percent of the predicted.

When interpreting a spirometry, the first thing to check is that the patient values entered are correct as this will affected the predicted values. The next value to read is the FEV1/FVC ratio, which is a marker of obstruction. If the value is below the lower limit of normal for the patient, then the patient has obstructive airway disease (eg, asthma, chronic obstructive pulmonary disease [COPD], tracheal stenosis) [5]. If there is obstruction, the next value to see is the FEV_1. This will help gauge the degree of obstruction present. The lower the value

the worse the obstructive physiology (in general, an FEV_1 <50% predicted represents severe obstruction) [1]. The last value to see is the forced vital capacity (FVC). The FVC is subject to many influences (lung and chest wall elastance, pleura, airway resistance, patient effort, duration of effort). A reduction in FVC is interpreted as restriction (ie, the lung cannot expand as much), however, this can be due to decreased muscle strength, large abdomen displacing the diaphragm, pleural disease, spinal deformity, poorly compliant chest wall, or a poorly done test. A decreased FVC requires clinical correlation, and if further clarification is needed to confirm restriction, then performing lung volumes is the necessary next step. In the setting of severe airflow obstruction, the FVC may be reduced [1].

18.1.2 Lung Volumes

We obtain all the lung volumes and capacities to better identify the type of physiological derangement the patient has. There are 3 methods available: (1) the plethysmography (body box), (2) the helium dilution technique, and (3) the nitrogen washout [2, 3, 4]. These techniques are used to measure the FRC and TLC (as these cannot be measured by spirometry alone). Each technique has its details and caveats, which can be read in pulmonary physiology books. In brief, plethysmography is based on Boyle's Law, which states that, under isothermal conditions, when a constant mass of gas is compressed or decompressed, the gas volume decreases or increases and gas pressure changes such that the product of volume and pressure at any given moment is constant [2, 4].
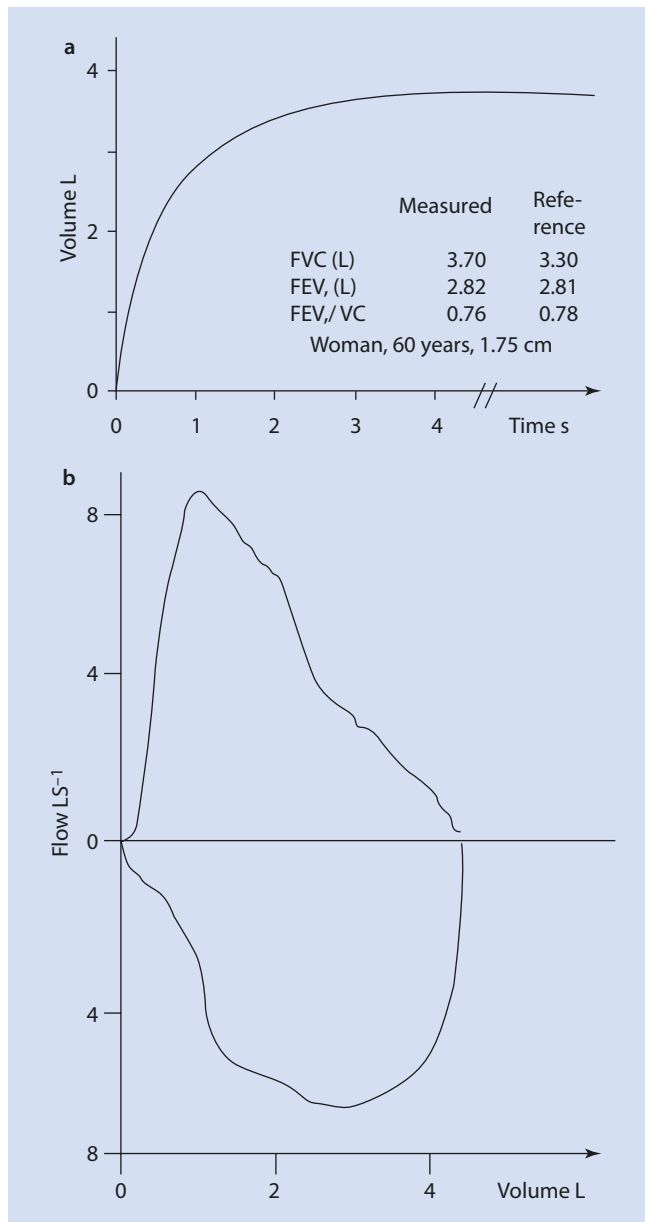
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Fig. 18.2 **a** Depicts volume of air expired as a function of time in seconds with included examples of measured and expected values for FVC, FEV_1, and FEV1/FVC ratio. **b** Flow volume curve obtained with spirometry with expiration above the x-axis and inspiration below x-axis (Reprinted with permission from Madsen et al. [31])

By placing the patient in a tightly enclosed box, we can measure the change in volume and pressure and calculate the FRC. The nitrogen washout and helium dilution rely on the volume of distribution of a known gas in order to determine FRC [5].

In the helium dilution technique, patients are attached to a spirometer that includes a known concentration of helium in a known volume. After several breaths the concentration of the helium is distributed over an increased volume (that includes the patient's lung volume) and allowed to reach a new equilibrium. The final exhaled concentration can thus be measured and the FRC can be calculated based on the dilution of the gas [5].

Similarly, in the nitrogen washout technique the patient is attached to a spirometry and allowed to breathe in 100% FiO_2 while measuring exhaled volumes and nitrogen concentration at timed intervals. With each breath the exhaled concentration of nitrogen is decreased until after several minutes (approximately 7 min) the entire concentration of the nitrogen in the lung has been washed out [5]. Once this happens FRC can be determined using a formula. A reduction on TLC below the lower limit of normal is consistent with restriction.

18.1.3 Diffusion Capacity

We measure the pulmonary diffusion capacity of carbon monoxide (DL,CO) to gain insight into gas exchange. CO is used due to its similarity to oxygen in both molecular weight and solubility coefficients. CO has an affinity for hemoglobin that is 210 greater than oxygen and thus able to maintain a very high pressure gradient across the alveolo-capillary interface as only the free unbound gas contributes to this gradient [6]. Therefore, in theory, the diffusion of CO would be a reflection of the alveolo-capillary interface itself (see later section in the chapter: Diffusion). The most common method for measuring DL,CO is by the single breath method. This test is done by having patients completely exhale to the level of RV followed by maximal inhalation of a gas mixture containing 0.3% CO to the level of the TLC [5]. The subject then holds their breath for 10 s followed by quick forceful exhalation. After the initial portion of gas is expired, which accounts for dead space, a sample of expired air is collected to calculate DL,CO [5]. It is measured in ml/min/mm Hg, using the volume of inhaled CO compared to exhaled volume of CO.

DL,CO is not only a manifestation of the alveolo-capillary interface, it depends upon a number of physiological factors (eg, age, sex, height, hemoglobin, lung volumes, carboxyhemoglobin, and exercise and body position). To account for these changes, it is often reported with corrections to the absolute value using hemoglobin DL,hb and lung volumes DL_{VA}.

18.1.4 Exercise Testing

In exercising healthy individuals, the supply of oxygen by the pulmonary system (minute ventilation) and the oxygen delivery by the cardiovascular system (cardiac output) are increased to provide oxygen to meet the demand of the skeletal muscle mitochondria. A cardiopulmonary exercise test is a physiological study that can identify defects in pulmonary ventilation, cardiovascular function, or skeletal muscle function. In complex patients, it can provide insight into the specific clinical limitations causing cardiopulmonary limitation. Exercise studies are also used to estimate preoperative morbidity and mortality in high-risk procedures [7].

Exercise testing is done with a metabolic cart connected via a non-rebreathing valve to a patient. The patient undergoes progressive exercise load over 10–15 min on either a stationary cycle or treadmill [5]. The metabolic cart measures the fractions of inspired and expired O_2 and CO_2, oxygen consumption (VO_2), CO_2 production (VCO_2), and minute ventilation (Ve) [7, 8].

The VO_2 is measured breath by breath during the exercise test. It reflects the amount of oxygen your body uses per kilogram per minute. In essence, it is the ability of a patient to deliver and use oxygen. Initially, during exercise VO_2 increases linearly and is matched by linear increases in CO_2 production, which reflects the increased skeletal muscle function [8]. The linear increase in VO_2 continues until a maximum level is reached (VO_2 max) and represents the patient's aerobic capacity. If the patient continues to exercise after the VO_2 max, it results in shifting of the skeletal muscle from aerobic to anaerobic metabolism. Anaerobic metabolism results in increased lactic acid, which is converted into lactate and CO_2. The point where in the VCO_2 is higher compared to VO_2 is the anaerobic threshold (AT) [5].

VO_2 max is usually lower in women compared to men and increases with exercise training. Impairment in aerobic function is defined as abnormally low VO_2 max compared to predicted. A low VO_2 max can be due to decreased cardiac output, decreased oxygen level, decreased hemoglobin, or muscle condition/function/size. The patterns of cardiac, pulmonary and muscle interaction help define the physiological defects. In addition to identifying exercise limitations, cardiopulmonary exercise testing can also be used to help gain insight in certain patient populations preoperatively. For example, a VO_2max <15 ml/kg/min is associated with high-risk patients for thoracic surgery. An anaerobic threshold >11 ml/kg/min is associated with decreased perioperative mortality after surgery [7, 8]. As a consequence, several protocols include cardiopulmonary testing to assess candidacy for surgery (lung volume reduction, heart transplantation, and high-risk lung resections.

18.2   Lung Mechanics: Compliance and Resistance

The respiratory system can be characterized by two physiological characteristics: (1) compliance and (2) resistance. These terms are further defined below. The best way to understand the characteristics of respiratory systems in our opinion is by using the equation of motion (the equation has been simplified for clarity). This equation illustrates the forces and their interaction during breathing:

$$P\,\mathrm{mus} + P\,\mathrm{vent} = \left(\mathrm{volume} \times \mathrm{elastance}\right) + \left(\mathrm{flow} \times \mathrm{resistance}\right)$$

$$(18.1)$$

Where P_{mus} is the pressure generated by respiratory muscle activity and P_{vent} is the pressure difference across the respiratory system (ie, transrespiratory pressure = pressure at the airway opening minus pressure on the body surface) generated by a mechanical ventilator. Pressure, volume, and flow are variables (ie, change with time) while elastance and resistance are considered to be constant. The first evident conclusion is that the pressure from the respiratory muscles and/or the mechanical ventilator has to overcome the loads from the elastic component (elastance × volume) and the resistive component (resistance × flow) [3, 4].

18.2.1   Compliance

Elastance is the constant of proportionality between volume change and change in transrespiratory pressure (or the slope of the volume-pressure curve) [4, 5]. In practice it may be calculated as the change in pressure difference across the system divided by the change in lung volume (ie, tidal volume, V_T) between two points in time when flow throughout the respiratory system is zero and $P_{mus} = 0$ (ie, the patient is paralyzed):

$$E_{RS} = \frac{\Delta P_{vent}}{\Delta V_T}$$

$$(18.2)$$

Compliance is the reciprocal of elastance (elastance = 1/compliance) [3, 5]:

$$C_{RS} = \frac{\Delta V_T}{\Delta P_{vent}}$$

$$(18.3)$$

With this understanding, now we know that compliance describes the ability of change in pressure to distend the respiratory system and is expressed in mL/cmH$_2$O. The respiratory system is not only comprised of lungs, it also includes the chest wall and abdomen. We need to recognize that a compliance obtained at the bedside includes this components [3, 9]. That is:

$$C_{RS} = \frac{C_L \times C_{CW}}{C_L + C_{CW}}$$

$$(18.4)$$

Where C_{RS} is the respiratory system compliance, C_L is the total lung compliance and C_{CW} is the chest wall compliance. The compliance calculated by the ventilator is C_{RS}. In order to ascertain C_L and C_{CW} we need to know the transmural pressures (pressures across the lungs and the chest wall). This means that we need to measure the pressure in the pleural space (or its surrogate, esophageal pressure) [9]. Hence the pressure across the lungs (transpulmonary pressure, P_{TP}) is the pressure at the airway opening minus esophageal pressure and trans-chest wall pressure, P_{TCW}, is esophageal pressure minus pressure on the body surface. Then C_L and C_{CW} are calculated by substituting P_{TP} or P_{TCW} into Eq. 18.3.

Lung Compliance

The factors responsible for lung compliance are the elastin and collagen fibers present in lung parenchyma and the
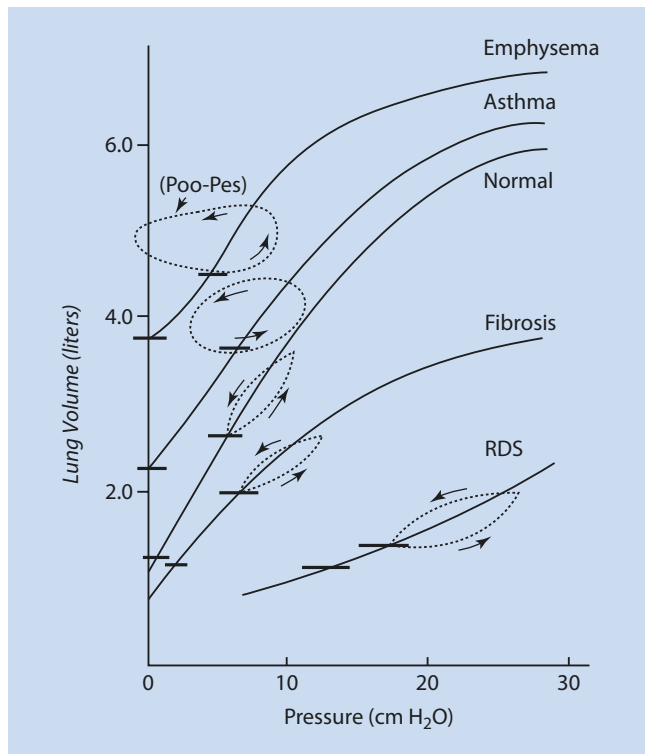
Fig. 18.3 This Fig compares the compliance curve of normal lung with various lung pathology. Note, that in emphysema and asthma the lungs are more compliant (ie, a small change in pressure causes a large change in volume) while in fibrosis and RDS (respiratory distress syndrome) the lung are less compliant (ie, a large in pressure is needed for small change in volume) (Reprinted with permission from Hildebrandt [32])

Fig. 18.4 Depicts the pressure volume curve during inspiration and expiration. Note the difference in lung volume at same pressure in inspiration and expiration limbs. This phenomenon is called hysteresis [3, 5, 10] (Reprinted with permission from Nurok and Topulos [33])

Fig. 18.5 Depicts 2 alveoli (A and B) with different radius. If the pressure inside both alveolus is same, the surface tension changes with change in alveolar radius to maintain stability. In this case, surfactant will lower the surface tension in alveoli B, reducing the pressure inside and prevent it from collapsing (Reprinted with permission from Haitsma [34])

alveolar surface tension [3, 6]. To better understand the elastic components we see a pressure/volume curve of the lung under different conditions. Figure 18.3 compares the compliance curve of a normal lung with compliance curve of lung with different pathology.

The curves labeled fibrosis and RDS (respiratory distress syndrome) represent low lung compliance (ie, a small change in volume for a large in change pressure). The curves labeled asthma and emphysema represent a lung with higher compliance (ie, a large change in volume for a small change in pressure) from loss of elastic tissues. Figures 18.3 and 18.4 highlight that the compliance of lung depends on the FRC from where the change in volume occurs. In Fig. 18.4 we can see that at the beginning or at the end of the inflation curve, minimal change in volume occurs with a large change in pressure. On the steeper part of the curve, a large change in volume occurs with less change in pressure. Clinically, this phenomenon is observed in patients with acute respiratory distress syndrome (ARDS) with too little positive end-expiratory pressure (PEEP) (under recruited) or very high PEEP (over distended). The other clinical condition is severe COPD, where the FRC is elevated due to air trapping and loss of elastic structures and is close to TLC, thus small changes in volume require high amounts of changes in pressure.
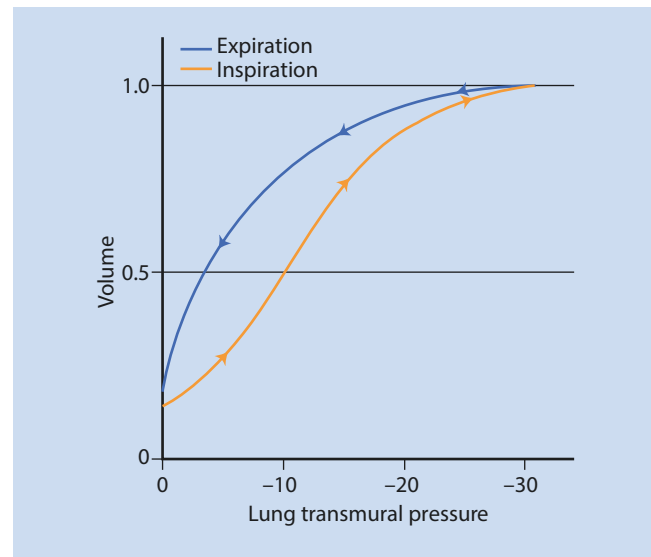
Surface Tension

The surface tension is a little bit counterintuitive and requires us to understand the Laplace law (Fig. 18.5). Surface tension is the force present at the air-liquid interface caused by the

attraction of the particles in the surface layer of a liquid, which tends to minimize the surface area [6, 11]. In other words, liquids have an inherent elastic tendency to acquire the least surface area possible (ie, a drop of water is circular in order to have the least surface area). The **Laplace equation** states that:

$$P = \frac{2T}{r}$$ **(18.5)**

Where, P is the pressure within the alveoli (dyn/cm^2), T is the surface tension inside the alveoli at air-liquid interface (dyn/cm), and r is the radius of the alveoli (cm).

Following this formula, for a constant surface tension, smaller alveoli will have higher pressure. The high pressure in smaller alveoli will force it to empty itself in large alveoli and collapse (atelectasis) while larger alveoli with less pressure would have preferential ventilation. This phenomenon is not observed under normal conditions due to presence of pulmonary surfactant. The presence of pulmonary surfactant reduces the surface tension forces and results in lower pressure inside the alveoli [5, 6, 11]. Surfactant prevents atelectasis and allows even distribution of ventilation. The clinical correlate is ARDS in adults or RDS in premature neonates, where the absence of surfactant results in collapse of smaller alveoli and decreased total lung compliance.

The pulmonary surfactant is produced by type II pneumocytes and released by exocytosis in response to high-volume lung inflation, increased ventilation rate, or endocrine stimulation [6, 11]. It is composed of 90% lipid in the form of phospholipids with the remainder of it being protein and carbohydrates. Dipalmitoyl phosphatidyl choline is the main constituent. The hydrophobic fatty acids project into the gas phase, while the hydrophilic end lies in the alveolar lining fluid. The surfactant gets packed densely together during exhalation, when alveoli assume a smaller radius exerting a greater effect in reducing surface tension and preventing the alveoli from collapsing.

Hysteresis

The difference in shape between the inflation and deflation limbs of the pressure volume curve is called hysteresis (◘ Fig. 18.4). That is, there is a higher lung volume, per unit of pressure, at any given point during deflation compared to inflation. Hysteresis is mostly due to the presence of pulmonary surfactant and its effect on surface tension forces at the air-liquid interface. The other factor responsible for hysteresis is opening of closed alveoli during inspiration [2, 5]. These alveoli remain open during exhalation, explaining why more than the expected pressure is required during inflation. The loop becomes progressively broader as the tidal volume increases or, in ARDS, due to loss of surfactant.

Chest Wall Compliance

The chest wall is composed of visceral pleura, rib cage, muscle (including the diaphragm), fat, and skin. The abdominal cavity also contributes to the chest wall compliance; this becomes evident in conditions such as ascites, abdominal compartment syndrome, or obesity.

To measure the chest wall compliance, one needs to measure pleural pressure by placing a pleural catheter (rarely done, if ever) or using surrogate of pleural pressure (classically using an esophageal catheter) [9]. The gradient between the pressure at the airway opening and the pleural pressure will provide the transpulmonary pressure, which is a reflection of the lung compliance. The chest wall compliance then will be the total respiratory system compliance minus the lung compliance. The contribution of the chest wall to the respiratory system compliance ranges from 20% to 50% in normal to severe ARDS patients. Normal chest wall compliance is 200 ml/cm H$_2$O.

Static and Dynamic Compliance

Static compliance is measured in absence of any air flow in the entire respiratory system with no muscle activity (muscle paralysis). Because, in some conditions we can only hold it for a few seconds before we have to let the subject breathe, the system never reaches true static condition and thus is called quasi-static compliance. There are different methods to measure compliance [10]:

- **The Super Syringe**: In this method, a known amounts of gas (volume) is pushed into the lungs, and the pressure change is measured after flow has stopped. This is mainly used when trying to build a pressure volume curve. Another alternative is to use a very slow flow to increase the volume gradually while measuring the pressure change. Because the flow is low (<9 L/min), the resistive component is essentially eliminated.
- **Single Occlusion Test**: This is the most commonly used method at the bedside. An end inspiratory pause is performed in patients receiving mechanical ventilation. The pressure will decay to form a plateau, commonly known as plateau pressure (P$_{plat}$).
- **Multiple Occlusion Test:** Airway occlusions are performed several times at different points of expiration. This allows the building of a volume/pressure curve.

Dynamic compliance is measured during an active breath, but the changes in volume and pressure are measured between points in time when flow at the airway opening is zero. This can be done by hand, but a ventilator uses linear regression. Because there may still be flow among lung units even when flow at the airway is zero (ie, pendelluft) the pressure difference may be larger than under true static conditions [3, 10]. Hence dynamic compliance tends to be lower than static compliance to the degree that the mechanical properties in the lungs are heterogeneous.

18.2.2   Resistance

Resistance opposes the flow of gas in and out the respiratory system. Resistance is defined as the constant of proportionality between pressure (P) and flow ($\dot{V}$) in a flow conducting system and is usually expressed in units of cm H$_2$O/ (L/s) [3, 5]:

$$R = \frac{\Delta P}{\Delta \dot{V}}$$

The total respiratory system resistance is the result of airway (natural and artificial) and tissue resistance [3, 12]. The lung parenchyma and chest wall viscoelastic resistance to motion gives rise to tissue resistance. The contribution is minuscule and in clinical practice they are essentially ignored. Thus this section focuses on airway resistance.

The airway caliber, nature of the gas flow, viscosity, and density of the gas determine airway resistance. Under normal conditions, the most decisive of them is airway caliber [3, 5]. Poiseuille's equation illustrates the relationship between airway caliber, laminar flow and viscosity:

$$\dot{V} = \frac{\Delta P \pi r^4}{8 \mu L} \qquad \textbf{(18.6)}$$

Where, Δ(Delta) P is the pressure gradient across the flow path (airway), L is the length of the flow path, μ is a dynamic's viscosity, $\dot{V}$ is the flow, r is a radius, and π(pi) is a mathematical constant. This equation demonstrates that the pressure gradient is directly proportional to gas flow. Because of this, for any flow rate, the pressure gradient divided by the flow rate equals a constant, called resistance:

$$\text{Resistance} = \frac{\Delta P}{\dot{V}} \qquad \textbf{(18.7)}$$

The equation can be rewritten to show the factors affecting resistance:

$$\text{Resistance} = \frac{8 \times \text{length} \times \text{viscosity}}{\pi \times (\text{radius})^4} \qquad \textbf{(18.8)}$$

Airway Caliber

The Poiseuille's equation demonstrates that the major determinant of resistance is the airway radius. In normal subjects, the larger airway contributes to 80% of total airway resistance, while the rest stems from the smaller airways [2, 4, 6]. Although this seems counterintuitive (because the radius of the airway is the main contributor to resistance), the increase in cross-sectional area as the airways divide (bronchial subdivisions) compensates for the small diameter, such that because of the increased cross-sectional area of the distal airway, the resistance to flow as a matter of fact is reduced [3]. In conditions such as airway edema, obstructive lung disease, or secretions where there is a decrease in airway radius, the airway resistance exponentially increases and so does the workload on respiratory muscles.

The airway caliber is also dependent on lung volume. Resistance is inversely proportional to lung volume. As lung volume decreases, there is a decrease in airway volume and thus in transmural pressure. This can result in closure of smaller airway and increased airway resistance [2, 3]. During forced expiration, high intrathoracic pressures can exceed the transmural pressure resulting in their collapse and increased resistance. The larger airway, due to presence of cartilage, has higher structural integrity and is less prone to collapse by changes in lung volume.

The airway caliber is mainly regulated by the autonomic system innervating the smooth muscle in the bronchus. The parasympathetic nervous system innervates via vagal nerve and plays a critical role in maintaining the airway caliber. The afferent fibers in the bronchial epithelium are stimulated by noxious stimuli and cytokines [5, 6]. These stimuli cause the efferent fibers to release acetylcholine, which acts on muscarinic receptors (M3) leading to bronchoconstriction. As a counterbalancing measure, there are ß(beta)2 receptors in bronchial epithelium that are responsive to circulating catecholamine. The activation of ß(beta)2 receptors causes bronchodilation as seen during stress, exercise, and with drugs.

Density, Viscosity, and Turbulent Flow

The other contributors to resistance, as demonstrated by the Poiseuille's equation, are the characteristics of the gas (density and viscosity) and the nature of the flow (turbulent vs. laminar). From the equation one can note that resistance, during laminar flow, is directly proportional to gas viscosity. Thus, helium (a low density, high viscosity gas) will not improve gas flow in conditions of laminar flow. However, in a condition where there is turbulent flow (ie, asthma or upper airway obstruction), helium does improve flow [5, 13]. This described by the Reynolds number (dimensionless unit):

$$\text{Reynolds number} = \frac{\rho d v}{\eta} \qquad \textbf{(18.9)}$$

Where, ρ(rho) is the density of the gas, d is the diameter of the tube, v us the linear velocity of the gas, and η(eta) is the viscosity. It is known that turbulent flow occurs when the Reynolds number is greater than 2000. At that point, the pressure gradient to generate flow is proportional to the gas density but independent of viscosity. As a consequence, helium (low-density gas) improves flow in asthma or airway stenosis.

In laminar flow, the gas flows in an orderly fashion as a series of concentric cylinders, which slide over each other forming the shape of a cone as they advance (Fig. 18.6). The

Fig. 18.6   a Shows a laminar flow with convex front. The arrows denote the direction and magnitude of air flow. **b** Turbulent flow with a square front (Reprinted with permission from Chatterjee and Fisher [35])
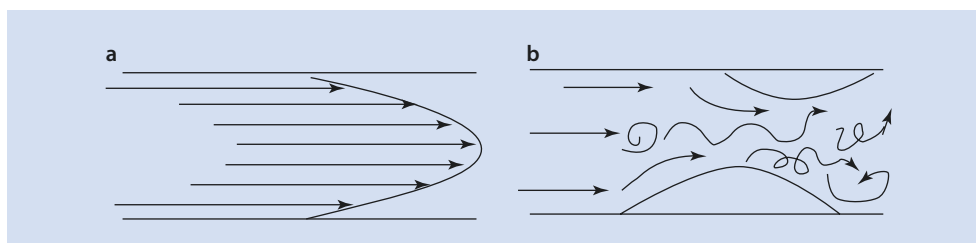
peripheral column of air in contact with wall is stationary while the center column of air slides over them. This greatly reduces the frictional forces acting on the airflow and hence the airway resistance is least with laminar flow. As can be seen from the diagram of laminar flow (▪ Fig. 18.6a), the center column of air will reach alveoli faster. During turbulent flow, the gas flows in a chaotic pattern with a square front (▪ Fig. 18.6b). This increases frictional forces acting on the flow and hence the resistance.

Measurement

In clinical practice, estimation of total respiratory system resistance (including the artificial airway) is often done during mechanical ventilation while delivering volume-controlled breath (at constant flow) with an end inspiratory pause (see ▪ Fig. 18.7). In light of Eq. 18.7 we can rearrange Eq. 18.1 to get:

$$R_{RS} = \frac{\Delta P_{vent}}{\Delta \dot{V}} \tag{18.10}$$

The pressure gradient, ΔP_{vent} is the peak pressure minus the plateau pressure. The flow gradient, " $\dot{V}$, is the set constant inspiratory flow relative to flow during the pause (ie, zero). The peak airway pressure constitutes both the elastic and resistive component. After occlusion there is a sharp drop in peak pressure followed by slow decline until it reaches plateau pressure. The plateau pressure constitutes the elastic component (as there is no flow). Thus ΔP_{vent} is the pressure required to overcome the resistance at the set flow.

As with compliance, modern ventilators can use linear regression to calculate resistance under dynamic conditions [2, 5].
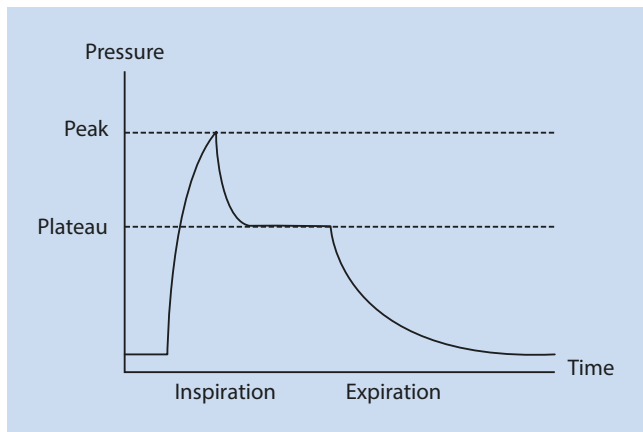
▪ **Fig. 18.7** The pressure time curve on constant flow with end inspiratory pause. The ∆(Delta)pressure between the peak and plateau pressure, is the pressure required to overcome the resistive load, while the ∆(Delta)pressure between plateau and PEEP is pressure required to overcome the elastic load (Reprinted with permission from Rimensberger [36])

18.2.3 Work of Breathing

Work of breathing is the external work (diaphragm or ventilator) required to move air in and out of lungs by overcoming the elastic and resistive forces opposing it (▪ Fig. 18.8). Under normal conditions, the work of breathing is completely performed by the respiratory muscles. During respiratory failure, when respiratory muscles are unable to meet the demands, this work is partially or completely accomplished by the use of invasive or non-invasive mechanical ventilation.

Work occurs when force acting on an object causes displacement of the object in direction of force:

$$\text{Work} = \text{Force} \times \text{Distance} \tag{18.11}$$

Pressure is the force acting on a unit area of an object and volume is the product of area and distance. They can be expressed as:

$$\text{Pressure} = \frac{\text{Force}}{\text{Area}} \tag{18.12}$$

$$\text{Volume} = \text{Area} \times \text{Distance} \tag{18.13}$$

Rearranging the equation:

$$\text{Pressuret} \times \text{Volume} = \text{Force} \times \text{Distance} = \text{Work} \tag{18.14}$$

Hence, work occurs when a change in pressure causes a change in volume and can be calculated from the pressure volume curve:

$$\text{Work} = \int \text{PdV} \tag{18.15}$$

∫PdV = Integral of applied pressure over a change in volume.

If you observe, the resting volume of lung and chest wall (ie, the volume at zero pressure) is different for lung and chest wall (▪ Fig. 18.8). The resting volume for lung is just above the residual volume. Hence, work is done to increase the lung volume to FRC. While the resting volume of the chest wall is above the FRC, the chest has to compress to FRC. This work done on chest wall is stored as kinetic energy and utilized during normal tidal breathing [3, 14].

When the lung compliance is decreased (eg, ARDS, pulmonary edema), the lung elastance curve is shifted to the left, requiring increased work of breathing. The increased work of breathing observed in obstructive lung disease is due to increased resistive component (ie, diagonally hatched area) [3, 14].

The work of breathing can also be expressed as O_2 cost of breathing, which is the amount of oxygen consumed by the diaphragm and respiratory muscle during ventilation. The O_2 cost of breathing in normal individuals is 0.5–1.0 mL of O_2
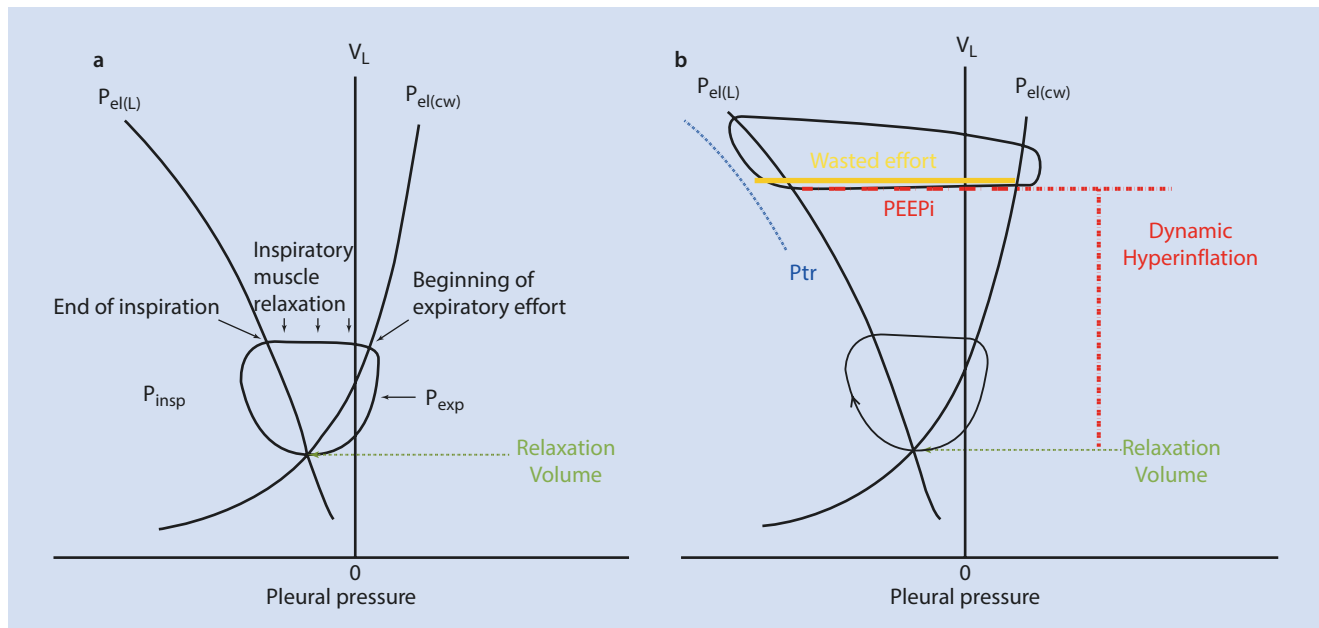
◘ Fig. 18.8 **a** In normal subjects inspiration starts from the relaxation volume of the respiratory system, where the passive pressure-volume curves of the lung [$P_{el(L)}$] and chest wall [$P_{el(cw)}$] intersect. Inspiratory muscle action results in pressure development (P_{insp}) on the left of the pressure-volume curve of the chest wall [$P_{el(cw)}$]. Inspiratory flow, and thus increases in volume (V_L) take place on the left of the pressure-volume curve of lung and coincide with the beginning of inspiratory muscle action. Inspiration ends on the pressure-volume curve of the lung and the inspiratory muscles relax (so that pressure returns on the pressure-volume curve of the chest wall). In the case shown, expiration is active so that pressure develops on the right of the pressure-volume curve of the chest wall due to activity of expiratory muscles (P_{exp}). This returns volume back to the relaxation volume of the respiratory system.

b In COPD patients with dynamic hyperinflation, inspiration starts from an increased end-expiratory lung volume. Inspiratory muscle action has to overcome the intrinsic positive end expiratory pressure [PEEPi, red dashed line, horizontal distance between the $P_{el(L)}$ and $P_{el(cw)}$] before it results in inspiratory flow and thus increases in volume. In mechanically ventilated patients, inspiratory muscle action has to overcome PEEPi plus the trigger sensitivity (Ptr) before it results in inspiratory flow and thus increases in volume (V_L). When the magnitude of inspiratory muscle action is less than the sum of PEEPi + Ptr this inspiratory effort (orange line) cannot trigger the ventilator and consequently does not result in inspiratory flow and thus increases in volume (VL). This inspiratory effort is called ineffective or wasted (Reprinted with permission from Vassilakopoulos [37])

per liter of ventilation, which is less than 5% of the total body oxygen consumption. During increased respiratory demand, the oxygen consumption by respiratory muscle can exceed 30% of the total body oxygen consumption.

18.3 Ventilation Perfusion

The primary function of respiratory system is exchange of oxygen and carbon dioxide. This depends on the gas inhaled and perfusion of the lungs. The ventilation and perfusion are not equally distributed throughout the lung normally, giving rise to a mismatch (V/Q = 0.8).

18.3.1 Ventilation

Ventilation involves convective movement of gas from the atmosphere into alveoli through the airways. Airways are divided into two zones (see ◘ Fig. 18.9):
1. **Conducting zone**, where there is no exchange of gas. It includes mouth, nose, trachea and bronchi up to the terminal bronchioles.

2. **Respiratory zone**, where the airway participates in gas exchange. It includes the respiratory bronchioles, alveolar sacs, alveolar ducts, and alveoli.

Minute Ventilation
Minute ventilation is amount of air entering the respiratory tree in a minute and is calculated as a product of respiratory rate (RR) and tidal volume (V_T). In literature and most mechanical ventilators, usually the exhaled minute ventilation is reported:

$$MV = RR \times V_T \tag{18.16}$$

For a healthy adult breathing 10 breaths/min and having a V_T of 500 mL:

$$MV = 10\,bpm \times 500\,mL = 5L / min \tag{18.17}$$

A fraction of gas remains in the conducting airways and will not participate in gas exchange. The fraction of V_T that participates in gas exchange is called "alveolar volume." The fraction of wasted breath in the conducting airway is called "dead space volume," and it is estimated as 2 mL/kg of ideal body weight. Thus:

Fig. 18.9 Schematic representation of airway branching in adult human lung. Note that the airway branches a total of 21–25 times from trachea to alveoli. The exchange of gases occur in respiratory bronchioles and alveoli (Reprinted with permission from Tu et al. [38])
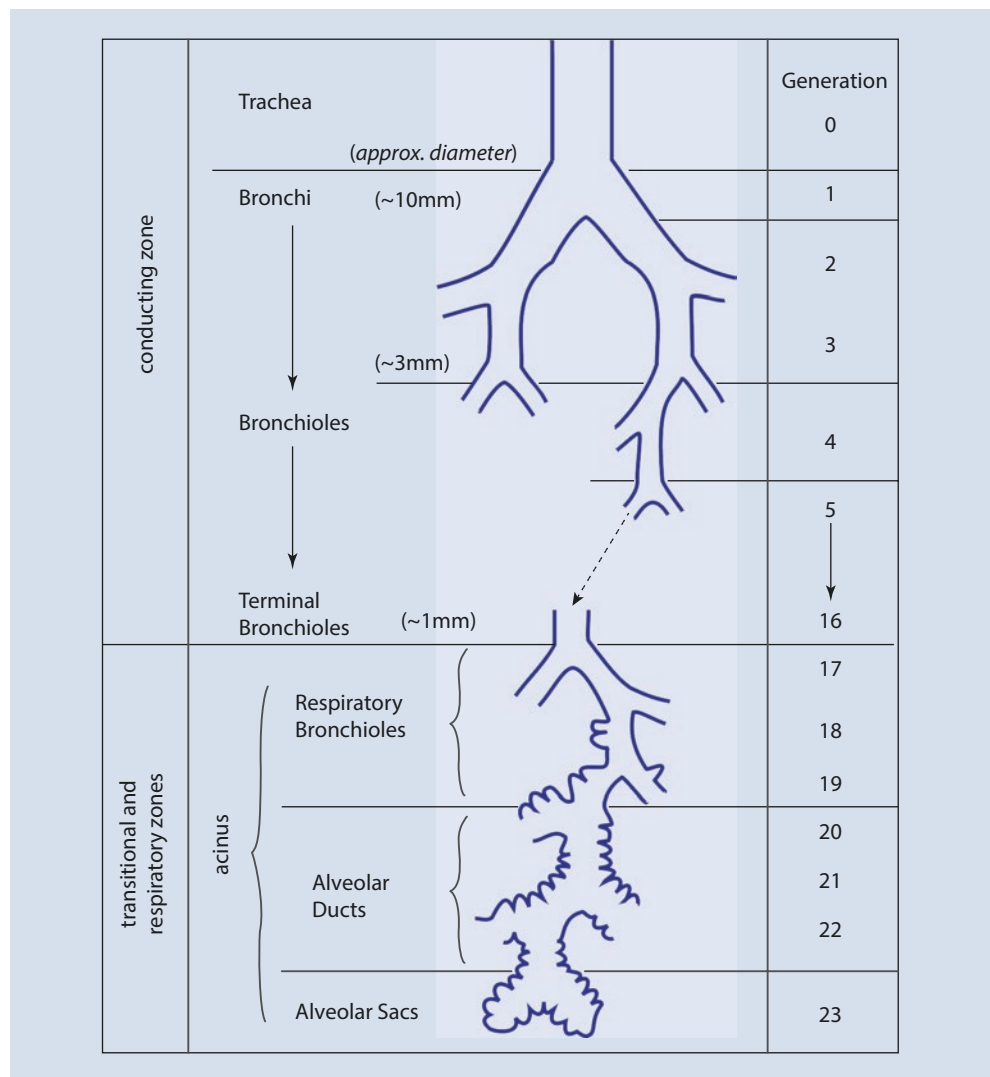
$$V_T = V_D + V_A$$

VD = Dead space volume

VA = Alveolar volume

As a consequence we can also calculate the alveolar minute ventilation as:

$$\text{Alveolar Minute Ventilation} = RR \times V_A$$

Dead Space

As stated above, dead space is the portion of the tidal volume that does not participate in gas exchange. Dead space occurs due to conducting airways (anatomical dead space) or form ventilation perfusion mismatch (alveolar dead space).

Anatomic Dead Space

The anatomic dead space—consisting of the nasopharynx, oropharynx, and the upper respiratory tract—does participate in exchange of oxygen and carbon dioxide and is denoted by $V_{D\ anat}$. It averages approximately 2 mL/kg of ideal body

weight and is affected by age, posture, end inspiratory lung volume, tidal volume, and respiratory rate [5].

The actual anatomic dead space can be calculated using the Fowler's method, also referred to as the single breath nitrogen washout test [3]. A patient is attached to a spirometer with 100% FiO_2 and instructed to take multiple deep breaths. The entire respiratory system along with dead space is filled with 100% FiO_2. The O_2 in respiratory zone engages in exchange of gases, while the O_2 in the conducting zone does not. Upon expiration the amount of exhaled nitrogen concentration is measured. The initial part of exhaled air comes from upper airway. As no exchange of gases occurred, the exhaled air will not contain any nitrogen. As exhalation progresses the gas from alveoli start entering the airways and mixing with oxygen. The concentration of nitrogen rises sharply till a plateau is reached. This plateau represents the equilibrium of the exhaled nitrogen in the alveolar space when all the dead space volume has been washed out. Anatomic dead space can then be calculated as the area to the left of the curve after the plateau is reached (Fig. 18.10).
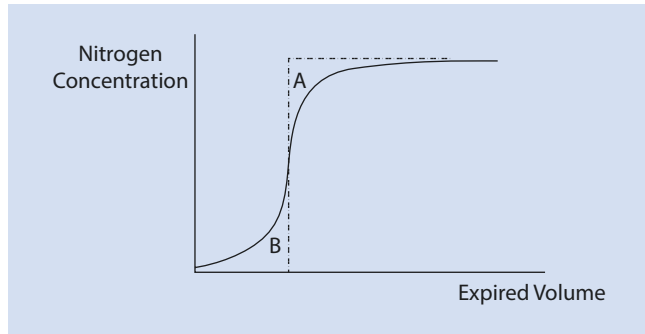
Fig. 18.10 Fowler's method to determine the physiological dead space. The N_2 concentration is on Y-axis and expired volume on X-axis. The deadspace volume is represented by the volume where the AB line intercepts the x axis (Reprinted with permission from Sinha et al. [39])

Alveolar Dead Space

Absence or insufficient perfusion to a ventilated alveoli results in them being unable to undergo gas exchange [4, 5]. This constitutes alveolar dead space and is denoted by $V_{D\ alv}$. It is seen in normal healthy lung at the apices of lung with adequate ventilation but minimal perfusion in upright position. Under normal circumstances, alveolar dead space is very small and not of any clinical significance. It assumes clinical importance during pulmonary hypoperfusion from low cardiac output states or pulmonary embolism.

Physiologic Dead Space

Physiological dead space is the sum of alveolar dead space and anatomic dead space. It is usually expressed as a fraction of tidal volume denoted as $V_{D\ phy}$:

$$V_{D\ phy} = V_{D\ anat} + V_{D\ alv}$$

Any factor that increases either the anatomical dead space or alveolar dead space will increase physiological dead space. Physiologic dead space is measured clinically by the modified Bohr's equation and assesses the functional ability of lungs to eliminate carbon dioxide:

$$\frac{V_D}{V_T} = \frac{PACO_2 - PECO_2}{PACO_2} \quad (18.18)$$

V_T = tidal volume
V_D = dead space volume
P_ECO_2 = Partial pressure of CO_2 in mixed expired air
P_ACO_2 = Partial pressure of CO_2 in alveolus
In normal healthy lungs, alveolar and arterial PCO_2 are the same and hence the equation can be modified as:

$$\frac{V_D}{V_T} = \frac{PaCO_2 - PECO_2}{PaCO_2} \quad (18.19)$$

$PaCO_2$ = partial pressure of CO_2 in arterial blood.
Any increase in physiological dead space will decrease the efficiency of lung to remove carbon dioxide from the body. Physiologic dead space increases in several conditions; classic examples are heart failure, pulmonary embolism, or increased anatomical dead space from insertion of artificial airway.

Distribution of Ventilation

The volume of air entering the lungs with each breath is not distributed equally in each lung units. This happens due to presence of multiple forces encountered by air as they move in the respiratory tree. These forces can be divided into gravitational and non-gravitational forces.

Gravitational Forces Affecting Ventilation

Gravitational forces play a key role in how the gas is distributed in the lungs. Due to the weight of the lung, the alveoli in the dependent region are smaller compared to the nondependent region and are on the steeper part of the pressure volume curve. A small change in pressure causes a large change in volume at FRC and hence the dependent areas receive higher ventilation. Thus, while standing, the ventilation per unit volume of lung is greatest in the bases and decreases as we move toward the apex. In supine, increased ventilation occurs in the dependent region; ie, the posterior region compared to anterior lung regions [3, 5].

The preferential ventilation of the dependent lung zones occurs with concomitant increases in perfusion to the same region, so the ventilation/perfusion ratios are not greatly altered on changing posture. This is important to understand, as any local disease (eg, pneumonia, atelectasis) of the dependent region will increase V/Q mismatch and affect gas exchange. This knowledge can also be utilized to alter the gas exchange in our favor. In a patient with unilateral lung disease, placing the healthier lung in a dependent position may improve the gas exchange by matching ventilation to perfusion.

Non-Gravitational Forces Affecting Ventilation

The distribution of ventilation also depends on the local mechanical properties of the lung units; ie, resistance and compliance [3, 15]. A simple way to understand the effect of the respiratory system characteristics on distribution of ventilation is to use the time constant. The time constant describes the time (in seconds) that it takes for an exponential function of time to change by 63% of its original value. To translate into clinical practice, we must remember that to describe the respiratory system we use a single resistance and a single compliance. (This is for simplicity. Although we can understand that different areas of the lung, and even single alveoli, have different values). These, when exposed to a change in pressure (step increase or decrease) in the airway opening, will lead to a change in alveolar pressure in an exponential function of time. That is, for a step change in airway pressure, the time constant is the time in seconds that it takes to inflate or deflate 63% of the alveoli (ie, the lung). Alveolar pressure reaches its steady state at 5 time constants.

The formula to calculate the time constant is:

$$\text{Time constant} = \text{Resistance}(cm\,H_2O\,/\,L\,/\,s) \times \text{Compliance}(L\,/\,cm\,H_2O)$$
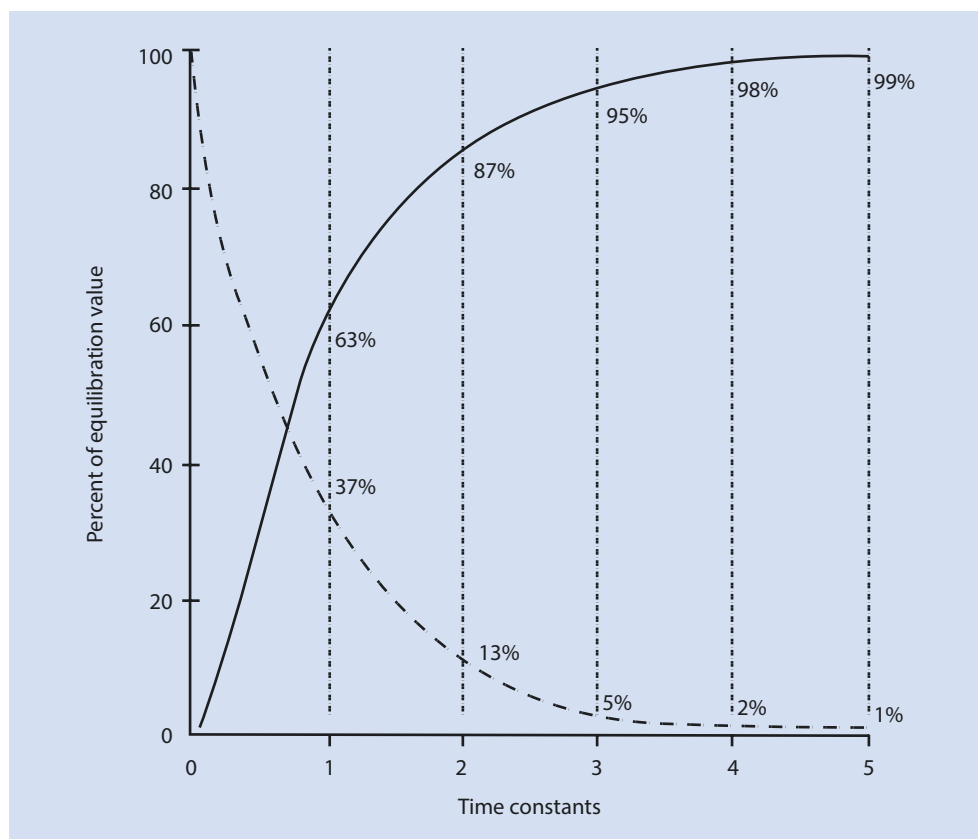
(Be aware that compliance is usually presented in mL/cmH$_2$O, so you may need to multiply by 1000.)

If resistance or compliance increases, the time constant of that region increases and as a consequence it takes longer to inflate/deflate, resulting in unequal ventilation [3, 10] (Fig. 18.11). Another example is when respiratory frequency is increased in a patient with increased time constant. They might not be able to completely empty the lung before the next inspiration begins. This is observed in COPD as dynamic hyperinflation.

18.3.2 Perfusion

The pulmonary circulation is a low pressure and high capacitance system mainly determined at the level of the pulmonary capillaries. The pulmonary capillaries are composed of alveolar and extra-alveolar vessels. The alveolar vessels are capillaries around the alveoli and exposed to alveolar pressure, whereas the extra-alveolar vessels are more influenced by lung volume status [2, 5]. The caliber of these vessels is determined by the radial traction of the surrounding alveolar walls on vessel. Extra-alveolar vessel resistance falls with lung inflation whereas alveolar vessel (capillary) resistance rises with lung inflation. Similar to ventilation, gravitational and non-gravitational forces affect the distribution of blood flow.

Distribution of Perfusion

Gravitational Forces Affecting Perfusion
Gravity plays a very important role on distribution of blood flow. The average length of a healthy adult lung upright is 30 cm, providing a hydrostatic pressure difference of 30 cm of H$_2$O or 23 mm Hg from apex to the base. In upright position, the blood flow is highest in the dependent region and varies with posture as observed with ventilation.

Non-Gravitational Forces Affecting Perfusion
The pulmonary vascular resistance is high at high and low lung volume and lowest at FRC (see Fig. 18.12). This is due to the effect of lung volume on alveolar pressure and traction on extra alveolar vessels [3, 16]. At low lung volume, the extra-alveolar capillaries are collapsed due to lack of radial traction from the supporting lung tissue. As the lung volume increases, the vascular resistance falls with opening of extra-alveolar vessels. At high lung volume, the increased alveolar pressure causes collapse of alveolar capillaries along with stretching and distortion of extra-alveolar vessels, causing a rise in vascular resistance. In positive pressure ventilation, the increase in resistance is much more at high lung volume due to significant increase in alveolar pressure compared to arterial or venous pressure.

Fig. 18.12 This diaphragm shows the effect of lung volume on pulmonary vascular resistance. At low lung volume, the extraalveolar vessels are compressed and at higher lung volumes the alveolar vessels are compressed increasing the pulmonary vascular resistance at both extremes of lung volume (Reprinted with permission from Jaeger and Blank [41])
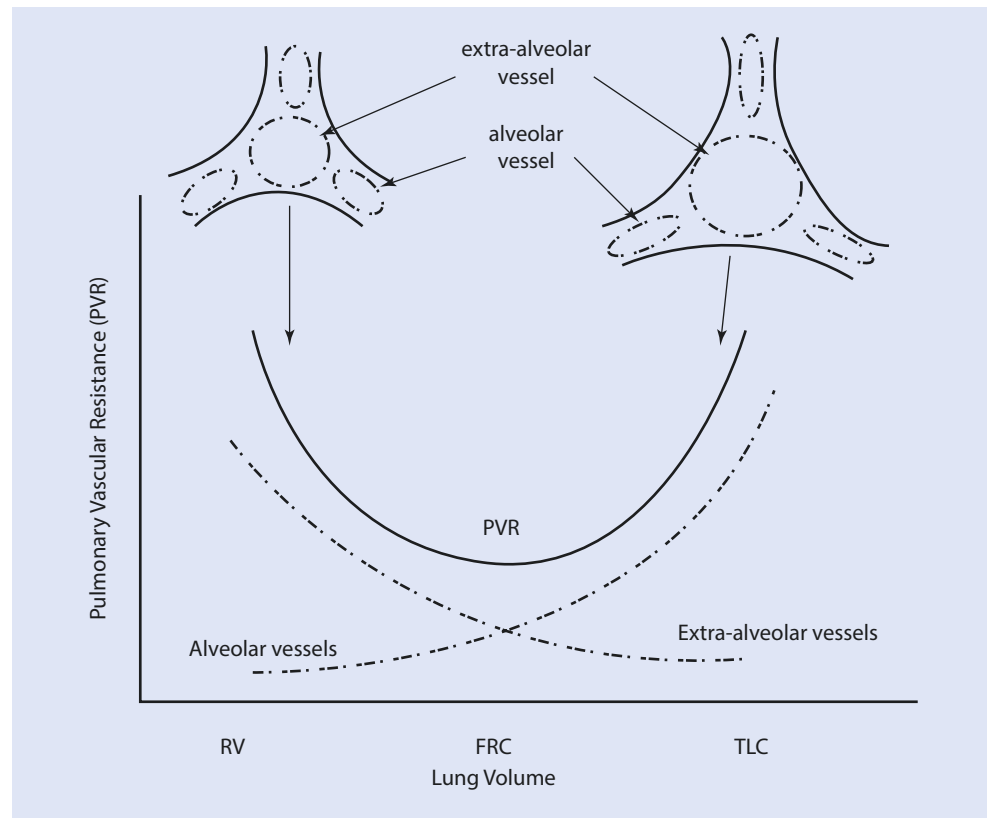
18.3.3 West Lung Zone

To better explain the blood flow based on the alveolar, pulmonary arterial and venous pressure, John West et al. in 1964 divided the lung into three zones [16]:

- **Zone 1** is a lung region where alveolar pressure > arterial pressure > venous pressure. The high alveolar pressure causes the arterioles and alveolar capillaries to collapse, resulting in markedly decreased to no flow.
- **Zone 2** is a lung region where arterial pressure > alveolar pressure > venous pressure. The flow in this zone is described by arterial alveolar pressure difference. As we go down on zone 2, the hydrostatic effect causes the arterial pressure to increase but alveolar pressure remains constant resulting in linear increase in flow. This effect is described as "waterfall" effect.
- **Zone 3** is a lung region where arterial pressure > venous pressure > alveolar pressure. The flow is dependent on arterial venous pressure difference. The blood flow increase in zone 3 is only partially because of increased hydrostatic pressure and more from increased transmural pressure causing distension and recruitment of pulmonary capillaries.

18.3.4 Hypoxic Vasoconstriction

Another mechanism that affects perfusion distribution is hypoxic vasoconstriction. A drop in alveolar PaO_2 in a region of lung is associated with contraction of the local pulmonary arterioles, leading to increased local vascular resistance and decreased blood flow to that region. This limits the ventilation perfusion mismatch and maintains arterial PO_2. The vasoconstriction is affected by alveolar PaO_2 and not arterial PaO_2.

The mechanism is not fully understood, but a multitude of local mediators are suspected to be the cause [17]. The vasoconstriction effect to hypoxia is non-linear, as no effect is observed when alveolar PO_2 is above 100 mm Hg. The vasoconstriction becomes prominent when alveolar PO_2 mm Hg falls below 70 and at lower levels no blood flow is observed.

18.4 Diffusion

Simple diffusion is the process where there is gas exchange across the alveolo-capillary membrane in both directions. This process depends on the diffusion of molecules from either the gas to fluid phase or vice versa based on pressure gradients. Several basic concepts, or laws, govern the process.

Dalton's law (partial pressures) states that the total pressure of a gas in a mixture is equal to the sum of all the individual partial pressures. That is, the partial pressure of each gas is the pressure it would exert if it occupied the entire volume alone [3]. This principle allows for the definition of the different partial pressures at various points along the respiratory tract:

$$\text{Partial Pressure of Gas} = \text{Barometric pressure} \\ \times \text{fractional concentration of gas}$$

Henry's law (solubility) states that when a liquid and a gas are in equilibrium, the amount of gas in solution is directly proportional to the partial pressures of the gas if temperature is constant. In the gaseous state only the concentration of the gas determines the partial pressure; the partial pressure of a gas in a liquid is also determined by the solubility coefficient of the gas. This is based on the principle that some molecules, based on their chemical properties, have different interactions with the fluids they are dissolved in. Recall that only unbound gas accounts for its partial pressure in a fluid; as such, oxygen bound to hemoglobin, does not exert a partial pressure [3, 4]:

$$\text{Partial pressure of gas dissolved in liquid} = \frac{\text{Concentration of dissolved gas}}{\text{solubility coefficient}}$$

Graham's law (diffusion) states that the diffusion of a gas is inversely proportional to the square root of its molecular weight. An example is CO_2 (molecular weight is 44) vs. O_2 (molecular weight is 32), thus CO_2 has a greater molecular weight and diffuses slower than oxygen in the gaseous state.

18.4.1 Calculated Atmospheric, Tracheal Air, Alveolar Air

With the aforementioned formulas the individual partial pressure of gases at atmospheric air can be determined by applying the known concentration of major gases (N_2 78.62%, O_2 20.84%, CO_2 0.04%, H_2O 0.5%) multiplied by the total atmospheric pressure (760 mm Hg). Once air is inspired into the trachea, air is exposed to the moist mucosa of the airway and becomes humidified, which increases the partial pressure of H_2O (47 mm Hg at 37 ° C) and thus dilutes the concentration of the other gasses, since the sum of their combined total cannot exceed atmospheric pressure. Example:

$$(760 - 47) \times \text{Fractional concentration } O_2 = 149 \, \text{mm Hg } O_2$$

Alveolar air concentration changes due to the fact that oxygen is constantly being absorbed by the pulmonary capillaries down the concentration gradient and with each breath small amounts of atmospheric air is added with addition of O_2. The overall concentration of O_2 in the alveoli is thus dependent on the rate of absorption into the blood as well as the rate of addition of new O_2 that can vary extremely based on metabolic demands. In addition, the diffusion of CO_2 from the pulmonary capillaries into the alveolar air further changes their composition.

Respiratory Membrane

In addition to the pressure gradients, molecular weight and solubility are determinants for diffusion. **Fick's law** summarizes the factors, and their impact, on the rate of diffusion [3, 6]:

$$D \alpha \frac{\Delta P \times A \times S}{D \times \sqrt{MW}} \tag{18.20}$$

Where, D is diffused gas flow, Δ(Delta)P is the pressure gradient across the gas-liquid interface, A is cross sectional area, S is the solubility of the gas, d is the distance for diffusion, and MW is the molecular weight of the gas. Now it becomes evident that the diffusion of a gas is proportional to the pressure gradient, solubility, and cross-sectional area; and inversely proportional to the distance for diffusion and the square root of the molecular gas. If we set the diffusion of O_2 as 1, the relative rates of diffusion of other gases follow. We can observe now that CO_2 diffuses faster that oxygen even though the molecule is larger because the solubility coefficient is much higher than oxygen.

18.4.2 Preoxygenation, Apneic Oxygenation, and Diffusion Hypoxia

Pre-oxygenation prior to endotracheal intubation has long been practiced in order to delay peri-intubation desaturation [18]. This is performed by administration of high concentrations of oxygen prior to intubation. The increase in the partial pressure of alveolar O_2 in relation to N_2 causes a "nitrogen washout" from the alveoli. This acts as a reservoir of oxygen and delays desaturation during intubation.

Apneic oxygenation refers to the administration of oxygen (via nasal cannula) during the period of apnea after induction and paralysis. During this period of apnea, air is entrained from the environment into the alveoli while oxygen reservoirs are depleted by extraction into the pulmonary circulation [19]. If time for successful intubation is greater than that of the oxygen reserves, desaturation will occur. The time to desaturation has been shown to delay even further with the administration of oxygen by nasal cannula [20].

Diffusion hypoxia (Fink or "third gas" effect) refers to the effect that a soluble gas has on the partial pressures of oxygen in the alveoli. Recall that the administration of any gas will affect the partial pressure of other gases and that highly soluble gases will diffuse rapidly. Thus, during administration of a soluble gas (the most commonly cited is nitrous oxide) the gas will diffuse faster than oxygen. As a consequence the partial pressure of O_2 and CO_2 will increase. However, once the gas is no longer administered (postoperative period) it will be released from the tissues (due to pressure gradients) and will be eliminated through the lung. As the gas enters the alveoli, it will decrease the partial pressure of other gases (ie, oxygen, CO_2, etc.) and thus the patient may become hypoxemic and hypoventilate [20].

The "second gas" effect was noted during the administration of inhaled anesthetics in conjunction with inhaled nitric oxide. Again, the rapid absorption of the nitrous oxide leads to relatively higher partial pressures of other gases. However this is relevant when the other gas is other anesthetic agent.

18

18.5 Transport of Gasses

18.5.1 Transport of Oxygen

The transport of oxygen occurs mainly as a free dissolved oxygen and bound to hemoglobin.

Free Dissolved O_2

Similar to other fluids, blood is also subject to having gases dissolved into it upon exposure. Once equilibrated the partial pressures of the gas in air will balance with the blood. Henry's law helps us define the amount of oxygen that the blood may carry:

$$\text{Concentration of dissolved } O_2$$
$$= \text{Solubility coefficient of oxygen}$$
$$\times \text{Partial pressure of } O_2 \text{ in blood}$$

Now, if the partial pressure of oxygen is 100 mm Hg, the solubility coefficient of O_2 in blood is 0.0031 ml O_2/mmHg O_2/dL blood (this is a constant, assuming 37 °C) then the total concentration of oxygen is 0.3 ml O_2/dl. If we consider a normal resting cardiac output of 5 L/min, the total delivery of oxygen from dissolved O_2 alone would be equal to 15 ml O_2/min (that is 6% of the normal adult O_2 consumption at rest, 250 ml O_2/min). Therefore, oxygen delivery is dependent on alternative transport methods to sustain even normal function at rest.

Oxyhemoglobin

Given the poor content of the dissolved oxygen in blood, the transport of oxygen is dependent on the reversible binding to hemoglobin (approximately 98% of the total oxygen delivery). In the oxygen-bound state, hemoglobin is referred to as oxyhemoglobin and conversely in the oxygen-free state is referred to as deoxyhemoglobin.

Hemoglobin consists of four subunits. Normal adult hemoglobin (Hemoglobin A, HbA) is comprised of two alpha and two beta subunits, each of which contains one heme molecule. Each heme molecule can reversibly bind to one molecule of O_2, up to a total of four for each molecule of hemoglobin [2]. At any given point, the total number of O_2 molecules that is bound is expressed as % saturation of hemoglobin. If on average all hemoglobin molecules in the blood are completely saturated with four molecules of O_2, then the % saturation would be 100%.

The total amount of O_2 content in the form of oxyhemoglobin can be determined by multiplying the hemoglobin level by the % saturation and the amount of O_2 carried by 1 g of hemoglobin (1.34 ml O_2/g Hg). The total O_2 content of blood is calculated by adding the amount of O_2 carried by oxyhemoglobin to the amount of O_2 carried dissolved in blood:

$$O_2 \text{ Content} = \begin{bmatrix} (\text{Hb}) \times (O_2 \text{ \%Saturation}) \\ \times 1.34 \, \text{ml} \, O_2 \, \text{mm Hg} \end{bmatrix} + [\text{Partial Pressure of } O_2 \times 0.003] \quad (18.21)$$

Oxygen Hemoglobin Dissociation Curve

The oxygen hemoglobin dissociation curve is formed by the % saturation in the y-axis and the partial pressure of oxygen on the x axis (◘ Fig. 18.13). The sigmoidal or S-shape of the Hb-O_2 dissociation curve is reflective of the avidity of hemoglobin for
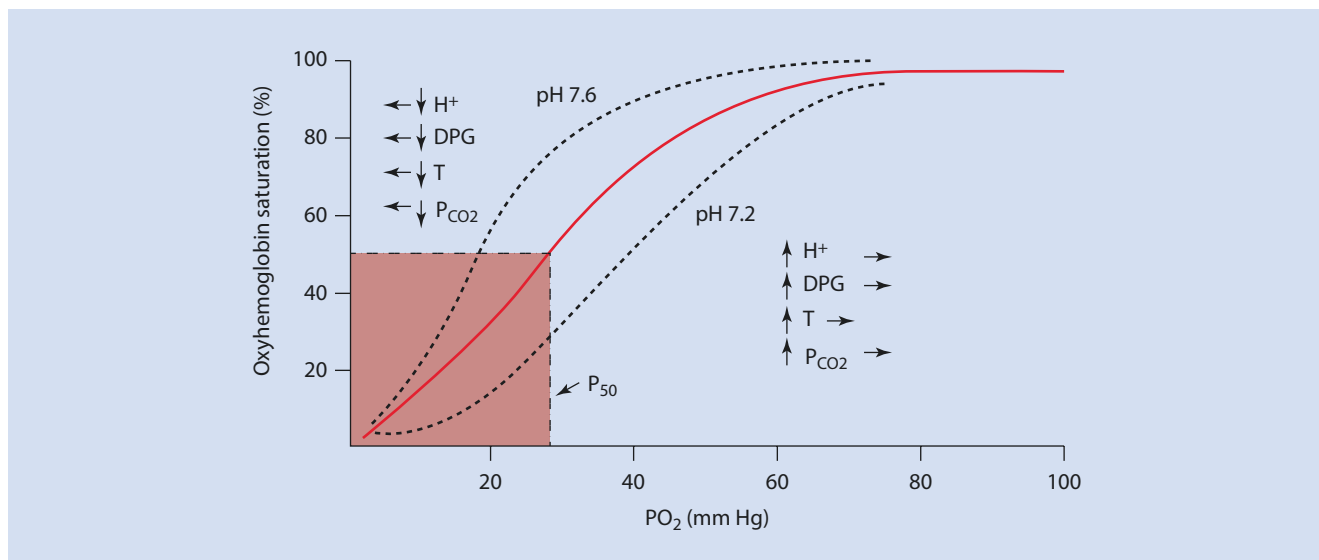
◘ **Fig. 18.13** The solid line, depicts the characteristic Hemoglobin Oxygen Dissociation Curve which is created by plotting oxygen saturation on the y-axis as a function of partial pressures of O_2 on the x-axis. The sigmoidal or S-shape curve of the hemoglobin oxygen dissociation curve represents the steep incline/decline in the oxygen saturation with relatively minimal changes in PO_2, which occurs in order to maximize loading/unloading of oxygen. Increases in H+, DPG, Temp, and P_{CO_2} (conditions favored in peripheral tissues) lead to a right shift in the curve which favors offloading of O2 in peripheral tissues. Conversely, decreases in H+, DPB, Temp, and P_{CO_2} (conditions found in lung) results in a left shift which results favors loading of O_2 (Reprinted with permission from Sullivan and Nkromah [42])

O$_2$. As 1 molecule of O$_2$ binds to a heme particle, it causes a conformational change that results in an increased affinity for adding a second molecule of O$_2$. With each further additional O$_2$ molecule, affinity increases further until the hemoglobin molecule is maximally loaded to nearly 100%. The result is a steep portion of the curve where there is rapid rises in % saturation with minimal changes in partial pressures of oxygen. When approximately 90% of the hemoglobin is saturated, any further changes in partial pressure results only in minimal increases in O$_2$ saturation. The opposite effect also occurs during the unloading of oxygen, where the unloading of 1 molecule also causes conformational changes that quickly favors further oxygen unloading with minimal changes in partial pressures. The sigmoidal shape of the curve ultimately leads to efficient loading and unloading of oxygen in areas of high and low partial pressures respectively.

The % saturation of hemoglobin is mainly dependent on partial pressures of O$_2$; however, these values are not fixed and can be affected by multiple variables. This is evident by evaluating the P50, which is the partial pressure for which hemoglobin is 50% saturated on the O2-Hb dissociation curve. There are some conditions (increased temperature, increased PaCO$_2$, and low pH) that decrease the affinity of hemoglobin for oxygen (favor unloading) (see ◘ Fig. 18.13). All of the conditions that result in a right shift occur in the peripheral tissues at times when metabolic activity, specifically of skeletal muscle, is increased requiring higher oxygen demands. The decreased affinity and further unloading of oxygen as a result of this right shift helps to provide this demand. All of the conditions that result in a right shift occur in the peripheral tissues at times when metabolic activity, specifically of skeletal muscle, is increased, requiring higher oxygen demands. The decreased affinity and further unloading of oxygen as a result of this right shift helps to provide this demand.

Another factor that causes right shift in the dissociation cure is the increase in 2,3–diphosphoglycerate (2,3 DPG), which is a byproduct of glycolysis inside red blood cells. Its concentration increases during times of hypoxia and binds to B subunits on hemoglobin [3, 4]. This interaction causes a conformational change in hemoglobin resulting in decreased affinity of O$_2$ and results in increased unloading of O$_2$.

Once hemoglobin has left the peripheral tissues it returns to the pulmonary capillaries where partial pressures of CO$_2$, temperature, and 2,3-DPG levels are lower relative to the peripheral tissues. The environment of the pulmonary capillaries also is associated with a higher pH. These relatively opposite values causes the opposite effect on hemoglobin, resulting in conformational changes that increase the affinity for hemoglobin. This results in a decrease in P50 and an overall left shift of the curve (favoring loading). This in effect optimizes the loading of oxygen back to hemoglobin.

18.5.2   Transport of CO$_2$

CO$_2$ is produced as a result of metabolic activity. It diffuses from the tissue to the venous blood, leading to a marginal increase from 40 to 45 mm Hg in arterial partial pressures of CO$_2$. The transport of CO$_2$ in the blood occurs in 3 methods: (1) dissolved in the blood, (2) bound to proteins, and (3) as carbonic acid.

Dissolved CO$_2$

Similar to oxygen, a small portion of this gas is transported back in the free dissolved state. The venous blood contains about 3 mL/dL of carbon dioxide. Now consider a normal resting cardiac output of 5 L/min. The total delivery of carbon dioxide to the lung from dissolved CO$_2$ alone would be equal to 150 ml CO$_2$/min. However, because of carbon dioxide's high solubility and diffusing capacity, only about 25 mL will be exhaled. This amount contributes very little to the total amount of CO$_2$ content of the blood (approximately 5% of the total CO$_2$ transported) [2, 4].

CO$_2$ Bound to Amine Groups

Another small portion of the CO$_2$ entering the venous system binds to amine groups of various plasma proteins as well as amine groups on hemoglobin, causing a loose reversible bond resulting in carbaminohemoglobin. The amount of CO$_2$ transported in the form of carbaminohemoglobin also makes up a small portion of the total transported—roughly equal to 15–20%.

CO$_2$ Transported as Carbonic Acid

The remainder of the 70–80% of transported CO$_2$ occurs in the form of bicarbonate (HCO$_3$-). Carbon dioxide and water diffuse into the red blood cell. There they form carbonic acid, in a reaction accelerated by the red cell carbonic anhydrase. Almost immediately, the carbonic acid dissociates into bicarbonate and hydrogen ions. Bicarbonate is transported across the membrane in exchange for chloride ions (AKA as the chloride shift). The H+ molecule binds to deoxyhemoglobin, which acts as a significant acid-base buffer in venous blood. Once back into the oxygen rich environment of the pulmonary circulation this H+ is released and replaced with oxygen. The free H+ molecule combines with HCO$_3$- where the reverse reaction that occurs in the peripheral tissue occurs, resulting in free CO$_2$ that diffuses across the alveolar membrane and eventually expires.

The transport of CO$_2$ in all forms at various partial pressures also can be plotted resulting in a CO$_2$ dissociation curve. The x-axis on this curve represents the total content of CO$_2$ in all forms plotted at partial pressures (y-axis). As the partial pressure of CO$_2$ increases from 40 mm Hg in the pulmonary capillaries to 45 mm Hg in the peripheral tissue, the total CO$_2$ content increases. Compared to the Hb-O$_2$ dissociation curve, the CO$_2$ curve results in a near linear appearance as the increase in CO$_2$ binds to hemoglobin and amino groups on proteins.

Bohr Effect

CO$_2$ is produced in the peripheral tissues as a result of ongoing metabolic activity. The increase in CO$_2$ when combined with H$_2$O, catalyzed by carbonic anhydrase

results in a net increase in H+ that is buffered by attaching to B subunits on hemoglobin. The increase in CO_2 as well as H+ results in a right shift of the Hb-O_2 association curve as well as an increase in P50 resulting in decreased affinity for O_2. The changes to the curve, as a result of increases in CO_2 and H+, are referred to as the Bohr effect [2, 4]. These changes ultimately help provide increases in O_2 supply in times of increased metabolic activity and thus increases in CO_2 and H+.

Haldane Effect

When CO_2 that is transported bound to hemoglobin is returned to the pulmonary circulation where partial pressures of O_2 are 100 mm Hg, the binding of O_2 to hemoglobin is favored. The O_2 binding results in hemoglobin that is slightly more acidic. The more acidic hemoglobin has less affinity for CO_2 on the amine groups and also results in less affinity for buffered H+ molecules. The displaced H+ molecules, catalyzed by carbonic anhydrase, combine with HCO_3^- and produce CO_2. Converse to the Bohr effect, where increases in CO_2 results in off-loading of O_2 from hemoglobin, increases in partial pressures of O_2 results in the off-loading of CO_2. This is referred to as the Haldane effect and similar to the Bohr effect is essential in transport of CO_2. The changes that occur in the setting of increased O_2 causes a downward shift in the CO_2 dissociation curve and a net increase in CO_2 offloading [3, 4].

18.5.3 Systemic Effects of Hypoxia and Hyperoxia

Hypoxemia results in deleterious effects, most notably cellular injury when the supply of oxygen is below the cellular demand. The threshold for cellular injury depends on the tissue. The most sensitive is the central nervous system. The mechanism of injury is a consequence of no longer being able to produce adenosine triphosphate (ATP) in order to provide the energy necessary for cellular function. This results in decreases in cellular pH that ultimately lead to cell death and tissue ischemia. In order to overcome these clinical situations, oxygen delivery is increased either by providing supplemental O_2 or by giving red blood cell transfusions if indicated. However, there are deleterious effects of elevated levels of O_2 with supplemental oxygen. The excess O_2 delivered by supplemental therapy can lead to the formation of oxygen free radicals resulting in systemic inflammation and tissue destruction. The threshold for which this occurs, however, is unknown. In order to prevent this from occurring, generally the least amount of oxygen that is needed in order to maintain cellular function should be delivered. In addition to the possibility of oxygen toxicity, acute administration of oxygen also results in increases in displacement of CO_2 from hemoglobin leading to changes in blood pH levels (Haldane effect). This effect is more marked in patients with hypercapnia and decreased pulmonary function (COPD).

18.5.4 Systemic Effects of Hypocarbia and Hypercarbia

There are adverse systemic effects that are a consequence of both decreased and elevated levels of CO_2. As discussed previously, the partial pressure of CO_2 is maintained in a relatively narrow margin between the arterial and venous blood system. Increases in levels of CO_2 beyond the normal arterial range of 40 mm Hg have several systemic effects. Most notable is: as levels of CO_2 increase, the CO_2 combines with H_2O, catalyzed by carbonic anhydrase, resulting in the HCO_3^- as well as H+. The net acid produced results in acidic blood pH (respiratory acidosis) that can cause significant impairment in skeletal and cardiac contractility, as well as metabolic changes. The CNS is also sensitive to increases in CO_2, which causes increases in cerebral blood flow and intracranial pressure as well as increased respiratory rate by triggering central receptors. These effects, if acute, can result in altered mental status, referred to as CO_2 narcosis. Conversely, low CO_2 levels have the opposite effects on the CNS, resulting in decreases in cerebral blood flow by vasoconstriction, which can also quickly result in CNS dysfunction. Also, with decreased levels of CO_2 the opposite reaction with HCO_3^- occurs in order to maintain blood levels in normal ranges. This can result in depletion of H+ molecules leading to alkalotic blood pH (respiratory alkalosis). This can also cause dysfunction in cellular metabolic function of skeletal muscle.

18.6 Control of Ventilation

18.6.1 Respiratory Center

The respiratory center is a collection of neurons in the pons and medulla. This group of neurons generates uninterrupted rhythmic discharges similar to the pacemaker in the heart. The signal is transmitted via the phrenic nerve to the diaphragm and to the external and internal intercostal muscles via the by thoracic spinal cord. These groups of neurons are called: (1) dorsal respiratory group, (2) ventral respiratory group, and (3) pneumotaxic center.

Dorsal respiratory group neurons are located in the dorsal region of the medulla in the nucleus of tractus solitarius and mainly control inspiration. The sensory stimulus is carried from peripheral chemoreceptors, baroreceptors, and other receptors in the lung via the vagal and glossopharyngeal nerves to the tractus solitarius. These neurons discharge inspiratory neuronal action potentials mainly to the diaphragm in a "ramp" signal form. In a ramp signal, the action potential begins weakly and increases steadily until it reaches peak and then ceases abruptly, ending inspiration. The expiration occurs from elastic recoil followed again by an inspiratory ramp signal, and this cycle continues during normal quiet breathing. The pneumotaxic center transmits signal to inspiratory neurons and controls the rate and depth of breathing. The ventral respiratory group remains inactive during normal quiet breathing. It controls inspiration and active expiration by abdominal muscles.

18.6.2   Receptor

The main goal of the respiratory center is to maintain normal arterial PCO_2, PO_2, and H+ concentration in arterial blood. There are numerous central and peripheral receptors that continuously monitor their concentration in arterial blood and regulate the respiratory center to maintain their concentration. Chemoreceptors are specialized nerve endings that are highly sensitive to changes in PCO_2, PO_2, and H+ concentration.

1. **Central chemoreceptors** are a group of nerve endings present on the ventral surface of the medulla and collectively are called "chemosensitive area" or "medullary chemoreceptors." They monitor H+ concentration of cerebrospinal fluid (CSF) and brain interstitial fluid. The blood brain barrier (BBB) and blood CSF barrier is not permeable to blood H+, but CO_2 diffuses very easily through these barriers and enters the CSF. In CSF, CO_2 combines with water to form carbonic acid, which rapidly dissociates into H+ and HCO-. This H+ stimulates the chemoreceptors, which in turn activates the ventral respiratory neurons and controls inspiration and alveolar ventilation [21].

2. **Peripheral chemoreceptors** are a group of nerve endings present in the arterial wall bilaterally at the bifurcation of carotid arteries (carotid bodies) and on the aortic arch (aortic bodies). A few chemoreceptors are also found in thoracic and abdominal arterial wall. They are highly sensitive to changes in PO_2 and to a lesser extent in PCO_2 and H+ in arterial blood [22].

3. **Proprioceptive Receptors; Respiratory Muscles and Reflexes.** There are numerous receptors present in the respiratory tract, which are stimulated by the presence of chemicals or irritants and protect the lungs [3, 5]. There are also receptors that monitor the lung volume and regulate respiration accordingly. Here we highlight some:
   - **Cough Reflex**: Cough reflex is mediated by C-fiber receptors with a primary aim of removing foreign bodies from the respiratory tree. It can be initiated from both the upper and lower respiratory tract.
   - **Hering-Breuer Reflex**: As the lung volume increases, it activates slowly adapting pulmonary stretch receptors present in lung interstitial tissue. These receptors inhibit phrenic nerve output and prevent overinflation of the lungs. It increases respiratory frequency so minute alveolar ventilation is unaffected.
   - **Sigh Reflex**: Sigh is a slow deep inspiration followed by a prolonged expiration and acts as a stimulus for surfactant release. Sighs open up closed alveoli and prevent atelectasis. Yawn is an exaggerated sigh and takes lung volume to total lung capacity for that breath.

   - **Lung "J" receptors** are sensory nerve endings found on the alveolar walls close to pulmonary capillaries. They are activated by the presence of pulmonary capillary engorgement or pulmonary edema and are considered to be the genesis of the sensation of dyspnea.

18.6.3   Voluntary Center

The voluntary control originates from the cerebral cortex and innervates the respiratory muscle via the corticospinal tract, bypassing the respiratory center in the medulla, and controls both inspiration and expiration (◘ Fig. 18.14). The voluntary control can alter the inspiratory or expiratory time, intensity, or pattern. The limbic system and hypothalamus also exert some effect, as evidenced by hyperventilation in response to pain or emotional stimuli.

18.6.4 CO_2 and O_2 Response Curves

The goal of the respiratory system is to maintain an appropriate concentration of CO_2, O_2, and H+ in arterial blood. The respiratory system is extremely sensitive to any changes in their concentration and alters breathing frequency or pattern to meet its goal.

#### Acute Carbon Dioxide Response

A rise in $PaCO_2$ causes an equal rise in CSF and brain interstitial fluid CO_2 concentration, as blood brain barrier and blood CSF barrier is permeable to CO_2. This CO_2 dissociates and increases H+ concentration and decreases pH in CSF. This activates the respiratory center and increases both the depth and rate of respiration and brings PCO_2 back to normal value [3, 21].

The peripheral chemoreceptors also respond to increase in arterial PCO_2. The response to rising PCO_2 is much stronger (7 times stronger) by the central chemoreceptors but quicker by peripheral chemoreceptors (5 times quicker). Their main function is to increase ventilation rapidly to increasing $PaCO_2$ followed by a stronger and sustained effect by central chemoreceptors.

Chronic Carbon Dioxide Response

The stimulation of the respiratory center is greatest in the first few hours of $PaCO_2$ rise. The effectiveness in stimulation of the respiratory centers decreases to one-fifth in 1–2 days, as the blood and CSF pH is corrected by addition of bicarbonate by the kidneys [3, 6]. The bicarbonate neutralizes H+ in CSF and brings pH closer to normal value with an elevated steady-state arterial PCO_2.

18

Fig. 18.14 The image shows the peripheral chemoreceptors **a** aortic bodies and **b** carotid bodies (CB). They are a group of nerve endings present in the arterial wall, which detects changes in PO_2 and transmits the signal to central receptors. (IX) glossopharyngeal nerve, X vagus nerve, IC internal carotid, PA pulmonary artery and AA ascending aorta (Reprinted with permission from Santos et al. [43])
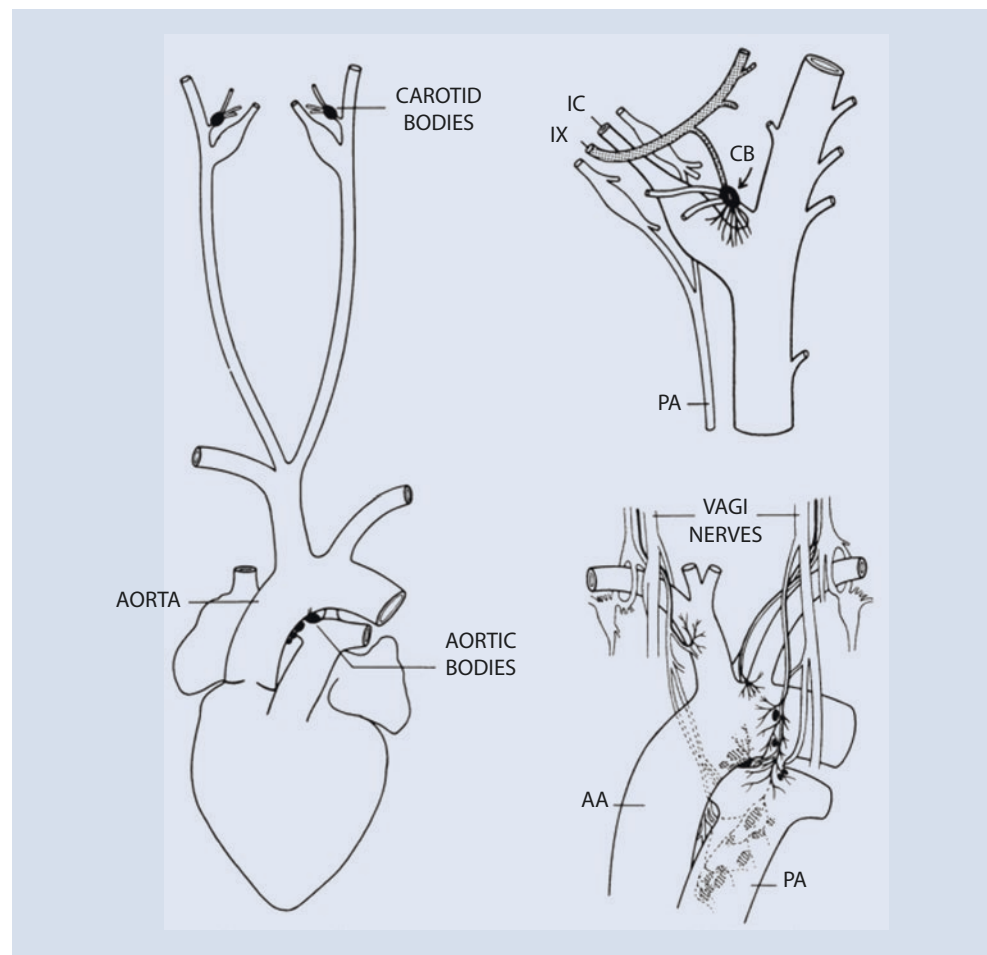
Acute Oxygen Response

Hemoglobin maintains adequate oxygen delivery to tissue for an arterial PaO_2 ranging between 60–1000 mm Hg. The alveolar ventilation may decrease significantly without any change is observed in PaO_2. Hence, the primary stimulus for respiration and alveolar ventilation is arterial $PaCO_2$. When PaO_2 falls below this critical level, it activates the respiratory center indirectly [23].

The carotid and aortic bodies have specialized glandular cells called glomus cells, which act as chemoreceptors [3, 22]. They have O_2-sensitive potassium channels, which are inactivated in absence of adequate oxygen causing depolarization of cells and opening of voltage-gated calcium channels. The increase in intracellular calcium concentration causes release of neurotransmitter and activation of afferent neurons. ATP or dopamine may be the key excitatory neurotransmitter released by glomus cells.

Chronic Oxygen Response

The response to chronically low oxygen state has been best studied in mountain climbers. The alveolar ventilation is initially increased due to hypoxia, but as $PaCO_2$ decreases from hyperventilation it has an inhibitory effect on the respiratory center

[24]. After 2–3 hours as central chemoreceptors lose their sensitivity to low $PaCO_2$, the alveolar ventilation often increases to 400–500% of normal. At normal or less than normal, alveolar ventilation does not increase until PaO_2 drops below 60 mm Hg. When $PaCO_2$ is held constant at a higher level, there is linear increase in ventilation with decreasing PaO_2 level.

18.7 Non-Respiratory Functions of Lungs: Metabolic, Immune

The lung is primarily an organ involved in gas exchange. However, the importance of lung in the cardiorespiratory system accepting the entire right heart cardiac output and its constant exposure to environment necessitates it to perform additional functions to maintain a normal internal milieu.

18.7.1 Pulmonary Circulation as a Physical Filter

Thrombus, gas, and fat emboli formed in the body may enter the systemic circulation and cause devastating consequences

in the coronary or cerebral circulation. The respiratory system acts as a physical barrier to various particle emboli and clears them. The effective clearance occurs due to the presence of a robust proteolytic system and endogenous anticoagulants. The pulmonary endothelium is rich in plasmin activator, which converts plasminogen into plasmin, which in turn converts fibrin into fibrin-degradation products. The pulmonary endothelium also contains thromboplastin, which converts prothrombin to thrombin and promotes coagulation.

18.7.2   Clearance of Inhaled Particles

The respiratory tree is in direct contact with atmosphere and constantly exposed to particles, pathogens, and chemicals present in inhaled air. The size of inhaled particle also affects their interaction with the respiratory system. Particles <1 μ(mu)m undergo diffusion by Brownian motion and are simply exhaled with minimum contact with airway. Particles 1–3 μ(mu)m are either exhaled or deposited on alveolar walls by sedimentation and ingested by alveolar macrophages. Particles >3 μ(mu)m and particularly >8 μ(mu)m undergo inertial impaction and rarely reach beyond the pharynx [6].

The respiratory tree is lined by a pseudo-stratified ciliated columnar epithelium from the posterior two-thirds of the nose to the respiratory bronchioles. This is composed of two layers—the cilia arising from the columnar epithelium and the overlying mucous layer—and acts as the first line of defense. The mucous layer is formed by mucin, which is a highly viscous mucopolysaccharide secreted by goblet cells in the epithelium and mucous cells of the submucosal glands [25]. Mucin is secreted in response to direct chemical irritation, inflammatory cytokines, and vagal stimulation. The ciliated epithelial cells propel this mucous layer cephalad at an average rate of 4 mm/min [3]. The effective function of mucociliary escalator depends on the periciliary fluid volume; controlled by amiloride-sensitive Na^+Cl^- pump, also known as cystic fibrosis transmembrane regulator protein.

18.7.3   Clearance of Pathogens

The majority of inhaled pathogens are cleared by ciliated nasal epithelium, swallowed, or gets trapped by the mucous layer and removed by mucociliary escalator as discussed previously. If the particle enters deeper into the bronchioles or alveoli, then the defense mechanisms are surfactant, macrophages, and cytokines. Surfactant has a key role in innate defense against inhaled pathogens; as the surfactant protein A and D are directly bactericidal [3, 5, 6]. Airway lining fluid contains defensins, which are antimicrobial peptides, and lysozyme with direct bactericidal activity. Immunoglobulins (Ig) are secreted by alveolar lining cells. The most predominant of them is secretory IgA in the larger airways and IgG in the alveoli. They act as an opsonin and induce complement activation and antigen recognition. They also activate the alveolar macrophages resulting in recruitment of large numbers of phagocytic cells.

18.7.4   Metabolism of Endogenous Compounds

The lung may activate or inactivate certain endogenous compounds as they pass through the pulmonary circulation. Angiotensin is converted to vasoactive angiotensin II by angiotensin-converting enzyme (ACE), which is mostly present on the vascular surface of pulmonary endothelium. This is also responsible for removal of bradykinin, which along with angiotensin II, provides a substantial role for the lungs in blood pressure control. The lung is also a major site of synthesis, metabolism, uptake, and release of arachidonic acid metabolites [26].

18.7.5   Drug Delivery and Elimination

The lung acts as an effective route for drug delivery for both topical action in the respiratory system or for systemic effect. The advantages are rapid onset of action, high concentration in the respiratory airway with minimal systemic side effect, and needle-free drug delivery for medications with poor oral bioavailability.

A particle size of 3 μ(mu)m is optimal for alveolar delivery. Other factors influencing pulmonary uptake are lipophilicity, protein binding, ventilation, perfusion, oxygenation, ageing, lung pathology, and co-administration of other drugs. Nitrofurantoin, bleomycin, and amiodarone are taken up by alveolar cells and may result in fatal lung toxicity.

Lung plays an important role in elimination of drug by metabolism or by retention in lung tissue acting as a reservoir and releasing the drug slowly. Certain inhaled drugs—such as theophylline, salmeterol, and budesonide—undergo significant metabolism in the lung due to high cytochrome P_{450}. This characteristic of medications has been used to minimize systemic side effects with improved airway selectivity.

18.7.6   Endocrine Lung

The airway mucosa contains pulmonary neuroendocrine cells and innervated cell clusters called neuroepithelial bodies constituting "pulmonary neuroendocrine system." They secrete peptide in response to hypoxia and cause central nervous system activation [27]. The lung is a rich source of nitric oxide, which regulates airway smooth muscle, pulmonary vascular resistance, and platelet function. It also secretes heparin, endothelin, and eicosanoids on exposure to allergens resulting in immune and cardiovascular response.

18.8   Perioperative Smoking

18.8.1   Physiologic Effects

Smoking has long been associated with adverse postoperative outcomes for a multitude of reasons. In general, smoking

causes a systemic pro-inflammatory state by increases in interleukin (IL)-1, IL-8, tumor necrosis factor-alpha (TNF-α), as well as others. The increase in systemic inflammation leads to a decrease in the ability to recruit local inflammation that is imperative in the wound reparative process. The increase in systemic inflammation also leads to vascular endothelial injury as well as platelet dysfunction [28]. In addition, the increase in pro-inflammatory cytokines has adverse effects on the ability of neutrophils and macrophages to produce bactericidal enzymes. Active smoking is also associated with tissue vasoconstriction and thus less delivery of peripheral oxygen. The decrease in oxygen delivery and increase in vasoconstriction also limits the ability to deliver necessary cells involved in tissue repair as well as promoting more ischemia to areas that have already sustained injury as a result of surgical trauma. The overall results are increases in rates of infection as well as delays in wound healing.

In addition to wound healing and infection, smoking is also associated with increased trends in pulmonary and cardiovascular complications. Smoking results in ciliary dysfunction, which acts as a primary defense mechanism for mucous and bacterial clearance. Increase in mucous production is also a result of ongoing inflammation in the bronchopulmonary tree that can also increase infection rates in the setting of decreased clearance. As a result, the postoperative pulmonary complications are increased compared to non-smokers, especially in those with underlying pulmonary disease. The increased rates in cardiovascular outcomes in the setting of long-term smokers is likely a consequence of vascular injuries that have been associated with increased postoperative cardiovascular events.

18.8.2 Cessation of Smoking

Many of the adverse effects that lead to increase in postoperative complications as a result of smoking can be minimized with the cessation of smoking. The most immediate of which is within hours of smoking cessation, the vasoconstrictive effects of smoking and thus peripheral O_2 delivery are returned to normal, in the absence of already present vascular disease [29]. Within 2–4 weeks of cessation, platelet dysfunction, neutrophil, and macrophage dysfunction are also improved as a result of decreases in oxidative stress. This leads to improvement in overall vascular endothelial function and bacterial fighting ability. However, the changes that result in an overall decrease in tissue proliferation and synthesis do not appear to reverse to the level of non-smokers. As evident in studies showing rates of complications in former smokers, although less than active smokers, they are still higher compared to never smokers [30]. While the timeframe for the ideal duration of cessation is unestablished, some studies have suggested that maximal outcomes in preventing complications as a result of smoking is at least 8 weeks. However, there is evidence that suggests some benefit compared to ongoing smoking with cessation as little as 1–2 weeks [30].

The overall effects of smoking cessation not only have improved clinical outcomes postoperatively but also proven financial/economic benefits to the healthcare system. This provides an excellent opportunity in the perioperative timeframe to discuss and advocate smoking cessation.

18.9 Questions and Answers

? Questions (choose the most appropriate answer)

1. The Total Lung Capacity is the addition of the following:
   A. VT + IRV + ERV
   B. IRV + VT + ERV + RV
   C. VT + IRV
   D. RV + ERV
2. A reduced FEV1/FVC ratio is the manifestation of restriction
   A. True
   B. False
3. DL,CO is affected by the following, EXCEPT:
   A. Hemoglobin
   B. Lung volumes
   C. Age
   D. Body position
   E. PaO_2
4. The anaerobic threshold is the result of
   A. A boost of the aerobic metabolism
   B. A manifestation of mitochondrial dysfunction
   C. The moment where aerobic metabolism shifts to anaerobic metabolism
   D. The maximum level VO2 can attain
5. Compliance of the lung will be decreased in the following conditions, EXCEPT
   A. Lung fibrosis
   B. Obesity
   C. Pleural thickening
   D. ARDS
6. The main determinant of airway resistance is
   A. Density of the gas
   B. Viscosity of the gas
   C. Length of the airway
   D. Caliber of the airway
7. Alveolar dead space increases in the following conditions:
   A. Increase in ventilation in relation to the local perfusion
   B. Decrease in ventilation in relation to the local perfusion
   C. Increase in perfusion in relation to local ventilation
   D. Increase in perfusion with proportional increase in local ventilation
8. To improve ventilation-perfusion matching in a patient with unilateral lung disease on mechanical ventilation
   A. You should sit the patient up
   B. Keep the patient supine

    C. Don't change the patient position, gravity has minimal effects on the V/Q matching
    D. Place the healthy lung down

9. Henry's law states that the total pressure of a gas in a mixture is equal to the sum of all the individual partial pressures
    A. True
    B. False

10. You should expect to see diffusion hypoxia at
    A. The beginning of the case when you are administering nitrous oxide
    B. At the end of the case when you are decreasing sevoflurane
    C. In the postoperative period
    D. 24 h after surgery

11. The Haldane effect can lead to hypercapnia in patients that are exposed to oxygen and already had chronic hypercapnia
    A. True
    B. False

12. The Hering-Breuer effect consists of:
    A. C-fiber receptors with a primary aim or removing foreign body from the respiratory tree
    B. Slow deep inspiration followed by a prolonged expiration and act as stimulus for surfactant release
    C. Pulmonary capillary engorgement leading to sensation of dyspnea
    D. Receptors inhibit phrenic nerve output and prevent over inflation of the lungs

13. The lung has effect on the following compounds passing through the lung, EXCEPT
    A. Angiotensin I
    B. Serotonin
    C. Bradykinin
    D. Dopamine
    E. Adenosine

✔ **Answers**

1. **B**. The lung has four basic lung volumes that constitute both the inspiratory and expiratory phases and are as follows: Inspiratory reserve volume (IRV), Tidal volume (V_T), Expiratory reserve volume (ERV), and residual volume (RV). When two or more volumes are combined they constitute four desiccant lung capacities that are as follows: V_T + IRV = Inspiratory capacity (IC), RV + ERV = Functional residual capacity (FRC), V_T + IRV+ ERV = Vital capacity (VC), and V_T+ IRV + ERV + RV = Total lung capacity (TLC).

    The TLC is the volume of air present in the lung at the end of maximal inspiratory effort (see ◘ Fig. 18.1) and can be calculated from the summation of all four basic lung volumes as above.

2. **B**. Vital capacity is the volume of air exhaled after maximal inspiration (from the point of TLC). If the expiration is performed with maximal effort then it is referred to as forced vital capacity (FVC). The forced expiratory volume in 1 s (FEV_1) represents the total amount of the FVC that is expired in the first second; and in patients with healthy non-diseased lungs the normal value is roughly 80%. In other words, 80% of the total FVC should be exhaled in 1 s. Reductions when compared to standard values of the FEV1/FVC ratio represents obstructive lung disease (asthma, COPD, tracheal stenosis). In restriction lung disease, both FEV_1 and FVC are decreased proportionally with near normal values the FEV_1/FVC ratio.

3. **E**. DL,CO (pulmonary diffusion capacity of carbon monoxide) is used clinically as a surrogate for gas exchange. CO is similar to oxygen in both molecular weight and solubility, hence diffusion of CO would be a reflection of the alveolo-capillary interface itself. But certain physiological factors (eg, age, sex, height, hemoglobin, lung volumes, carboxyhemoglobin, and exercise and body position) affects the diffusion of CO. This physiological factors are considered during calculation of DL,CO and reported.

4. **C**. Cardiopulmonary exercise testing can be performed to help identify defects in pulmonary ventilation, cardiovascular function, or skeletal muscle function in patients with undifferentiated shortness of breath or limitations in exertional capacity. It can also be performed in the preoperative setting to help identify high risk patients for surgical interventions. It is performed by having patients exercise while connected to a metabolic cart that evaluates certain parameters that include heart rate, minute ventilation, O_2 consumption, and CO_2 production. Normally during exercise O_2 consumption and CO_2 production are increased linearly and reflect increased metabolic demand and production of the tissues, respectively. However, there is a point in time at which CO_2 production is greater than O_2, which reflects the transition into anaerobic metabolism. The increase in CO_2 is a result of increased production of lactic acid that is converted to CO_2. This point is known as the anaerobic threshold.

5. **B**. Compliance is the change in volume per unit change in transmural pressure. The compliance measured at bedside is total compliance of respiratory system and is affected by compliance of lung, chest wall, and abdominal cavity. If you recall:

$$C_{RS} = C_{lung} + C_{CW}$$

    Obesity decreases the total respiratory system compliance by decreasing the chest wall compliance with little to no effect on lung compliance.

6. **D**. Recall the equation for resistance is:

$$Resistance = \frac{8 \times length \times viscosity}{\pi \times (radius)^4}$$

The airway resistance depends on the length of the airway, viscosity of the gas, and radius of the airway. If the other conditions remain constant, a decrease in radius of airway caliber by ½, will increase the resistance by 16-fold. Hence, caliber of the airway has the most significant effect on the resistance of system.

7. **A.** Alveolar dead space are the alveoli that are ventilated but do not contribute in gas exchange due to decreased or absent perfusion. A classic example is pulmonary embolism, where a blood clot partially or completely obstructs the pulmonary circulation. The alveoli downstream are ventilated but not perfused. These alveoli act like conducting airways and are called alveolar dead space.

8. **D.** The ventilation and perfusion are both affected by gravitational forces, as both flow to dependent regions of the lung. Hence, in a patient with unilateral lung disease, placing the healthy lung in a dependent position (ie, down in lateral position) will increase the blood flow to the healthy lung, optimize V/Q matching, and improve oxygenation. The exception to this strategy is unilateral lung disease with excessive secretions or hemorrhage. In such a situation, the diseased lung should be placed in the dependent position to prevent overflowing of secretions or blood to the healthy lung.

9. **B.** Dalton's law (partial pressures) states that the total pressure of a gas in a mixture is equal to the sum of all the individual partial pressures. That is, the partial pressure of each gas is the pressure it would exert if it occupied the entire volume alone. This principle allows for the definition of the different partial pressures at various points along the respiratory tract. Henry's law refers to solubility and states that when a liquid and a gas are in equilibrium, the amount of gas in solution is directly proportional to the partial pressures of the gas if temperature is constant.

10. **B.** Diffusion hypoxia (Fink or "third gas" effect) refers to the effect that a soluble gas has on the partial pressures of oxygen in the alveoli. Recall that the administration of any gas will affect the partial pressure of other gases and that highly soluble gases will diffuse rapidly. Thus, during administration of a soluble gas (most commonly cited is nitrous oxide) the gas will diffuse faster than oxygen. As a consequence the partial pressure of O_2 and CO_2 will increase. However, once the gas is no longer administered (postoperative period) it will be released from the tissues (due to pressure gradients) and will be eliminated through the lung. As the gas enters the alveoli, it will decrease the partial pressure of other gases (ie, oxygen, CO_2, etc.) and thus the patient may become hypoxemic and hypoventilate once other gases are decreased at the end of a case.

11. **A.** The Haldane effect refers to the CO_2 carrying capacity of hemoglobin in the presence of oxygen (CO_2 hemoglobin dissociation curve). In the presence of oxygen, hemoglobin has a decreased affinity for CO_2, which results in offloading of CO_2 and thus an increase in unbound or dissolved CO_2. In patients with lung disease, specifically COPD with hypercarbia at rest, supplemental O_2 results in offloading of CO_2 by the hemoglobin. These patients, as a result of their underlying lung disease, are not able to increase minute ventilation in order to decrease this excess of dissolved CO_2, which ultimately can lead to increases in partial pressures of CO_2.

12. **D.** The Hering-Breuer reflex occurs due to presence of slow-adapting stretch receptors present in smooth muscle of smaller airways and lung interstitial tissues. They are activated during large inspiration, whereby they inhibit phrenic nerve output and prevent lung over inflation.

13. **D.** Angiotensin I is activated during its passage through pulmonary circulation, while serotonin, bradykinin and adenosine are inactivated. Dopamine passes through the pulmonary circulation unchanged.

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