# Basics of Gas Exchange

3

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**Educational Aims**

- Understand the physiology of alveolar ventilation.
- Understand the relationship between alveolar ventilation and oxygenation.
- Review the alveolar gas equation.
- Understand the distribution of blood flow and ventilation in the lung.
- Assess the impact of intrapulmonary shunts and dead-space ventilation on gas exchange.
- Review the principles of gas diffusion.
- Understand the physiologic principles of oxygen transport and delivery.
- Understand the relationship between oxygen delivery and consumption.
- Review the interpretation of arterial and venous blood gases.

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## 3.1 Pulmonary Gas Exchange

The ultimate goal of pulmonary gas exchange is adequate tissue oxygen ($O_2$) delivery and carbon dioxide ($CO_2$) elimination. This exchange of gas is a multistep process that begins with ventilation and movement of gas from the atmosphere through the various generations of airways into the alveoli of the lungs. Oxygen quickly diffuses across the alveolar-capillary membrane into red blood cells (RBCs), allowing for transport of $O_2$ to the tissues. The final step in gas exchange occurs in the tissues as oxygen diffuses into cells to meet the metabolic demands of the body. Similarly, $CO_2$ diffuses from the cells into RBCs at the tissue level and is transported to the alveolar capillaries to be exhaled into the atmosphere.

Given the multiple steps involved in gas exchange for both $O_2$ and $CO_2$, there are a number of points in which this process may become disrupted. Despite the complexity of this process, pulmonary gas exchange is generally remarkably effective. This process usually leads to the adequate elimination of $CO_2$ and to the delivery of $O_2$ to tissues and organs well in excess of the body's metabolic demands.

## 3.2 Alveolar Ventilation and Alveolar $PO_2$

The initial step in gas exchange is adequate pulmonary ventilation. Ventilation is ultimately controlled by the amount of gas that reaches the

P.C. Rimensberger (ed.), *Pediatric and Neonatal Mechanical Ventilation*,
DOI 10.1007/978-3-642-01219-8_3, © Springer-Verlag Berlin Heidelberg 2015

alveolar-capillary interface to participate in gas exchange. Each inhalation contains a specific volume of gas, but a portion of this inspired volume is not available for gas exchange since it does not pass beyond the conducting airways. Gas that remains in the conducting airways at the end of inspiration represents the anatomic dead space. This anatomic dead space in combination with any additional alveolar dead space related to lung pathology or mechanical ventilation comprises total physiologic dead-space ventilation (Numa and Newth 1996; Nunn et al. 1959).

Dead-space ventilation has a direct impact on alveolar ventilation. The total quantity of alveolar ventilation is the amount of gas, summed over 1 min, which reaches the capillary bed to potentially participate in gas exchange. Alveolar ventilation is, thus, calculated by subtracting the anatomic dead-space volume from the total inspired volume. The quantity of gas that actually participates in gas exchange is calculated by subtracting the total dead space (anatomic plus alveolar dead space) from the total inspired volume (West 2005a; Numa and Newth 1996; Nunn et al. 1959).

Alveolar ventilation contributes primarily to gas exchange through the control of $CO_2$ elimination. $CO_2$ elimination is determined by the balance between $CO_2$ production and alveolar ventilation. For a constant level of $CO_2$ production, $CO_2$ elimination is inversely proportional to alveolar ventilation. In healthy subjects, the partial pressure of alveolar $CO_2$ ($P_ACO_2$) closely approximates the partial pressure of arterial $CO_2$ ($P_aCO_2$). As alveolar ventilation increases, $CO_2$ elimination increases, and $P_ACO_2$ (and consequently $P_aCO_2$) falls. Adequate $CO_2$ elimination not only prevents respiratory acidosis and acidemia, but also significantly impacts alveolar oxygen levels. The relationship between the partial pressure of alveolar oxygen ($P_AO_2$) and $P_aCO_2$ is a complex one that includes a number of components. This relationship is reflected in the alveolar gas equation as follows:

$$P_AO_2 = P_IO_2 - P_aCO_2 / R$$

In this equation (the alveolar gas equation), $P_AO_2$ represents the alveolar partial pressure of oxygen. Additional variables are defined as follows:

- The first component needed in the calculation of $P_AO_2$ is the $P_aCO_2$. This variable can be measured directly from arterial blood. Alternatively, $P_aCO_2$ can be approximated from alveolar or expired $CO_2$ in the absence of significant lung disease.
- The next element needed to calculate $P_AO_2$ is the $P_IO_2$. $P_IO_2$ is the partial pressure of inspired oxygen and can be calculated using the following formula:

$$P_IO_2 = FiO_2 * \left(P_B - P_{H_2O}\right)$$

- $P_IO_2$ incorporates both barometric pressure ($P_B$) and water vapor pressure ($P_{H_2O}$) based on the universal gas law which relates the partial pressures of a combination of gases to their volumes and temperatures. At sea level, $P_B$ is 760 mmHg, and $P_B$ falls as altitude increases. $P_{H_2O}$ must also be considered since inspired gas is warmed and saturated as it moves through the respiratory system. At a normal body temperature of 37 °C, $P_{H_2O}$ is 47 mmHg. Therefore, for inspired room air gas with an $FiO_2$ of 0.21 at sea level, the $P_IO_2 = 0.21 * (760 - 47) = 150$ mmHg.
- The final component of the alveolar gas equation is the respiratory quotient ($R$). The respiratory quotient is the ratio of $CO_2$ elimination to $O_2$ consumption, but direct measurement of these two variables is often difficult and impractical in the clinical setting, especially in pediatric and neonatal patients. In most circumstances, $R$ can be estimated to be 0.8, but some variability does exist depending on the dietary balance of carbohydrates, protein, and fat.

Bedside calculation of $P_AO_2$ is easily performed using the alveolar gas equation. This calculation provides important clinical data since $P_AO_2$ can be used to determine the alveolar-arterial oxygen gradient ($P_AO_2 - P_aO_2$). This difference between oxygenation at the alveolar level versus that measured in arterial blood allows one to assess for adequacy of tissue oxygenation. Normally, a gradient of 5–15 mmHg exists between the partial pressure of oxygen in the alveolus and arterial blood, but this gradient may increase substantially in a number of pathophysiologic states (Table 3.1).

The $P_AO_2$ calculation provides an important global measure of alveolar oxygenation, but considerable differences in ventilation exist in different regions of the lung. As one travels from the apex of the lung to the base, ventilation per unit of volume increases (Fig. 3.1). This increase in ventilation is largely related to the effects of gravity, which create higher (or less negative, in the spontaneously breathing patient) intrapleural pressures at the base of the lung relative to the apex. In the supine patient, this difference disappears, and a posterior-anterior gradient is produced with more ventilation per unit of lung volume in the posterior (dependent) portion of the lung. This ventilation gradient, coupled with regional blood flow differences within the lung, has important therapeutic implications and can significantly impact mechanical ventilation strategies for a variety of pathophysiologic states (Radford 1955).

**Table 3.1** Causes of hypoxemia

| |
|---|
| 1. Low $FiO_2$ |
| 2. Hypoventilation |
| 3. Ventilation-perfusion mismatch |
| 4. Impaired alveolar-capillary interface diffusion |
| 5. Intrapulmonary shunt |
| 6. Pulmonary artery desaturation |
| 7. Hemoglobinopathies |

## 3.3 Intrapulmonary Shunt

*V*/*Q* matching is an important element in pulmonary gas exchange since only the gas that reaches the alveolar-capillary interface is available for exchange. Under ideal circumstances, pulmonary perfusion (*Q*) would perfectly match the differential ventilation (*V*) of various lung units and create a ventilation to perfusion ratio (*V*/*Q* ratio) of 1. As discussed previously, regional differences exist within the lung, and ventilation is higher in dependent lung units. Similarly, pulmonary perfusion is higher in dependent regions of the lung, but there is a greater change in perfusion across the lung when compared to ventilation. This higher rate of increase in perfusion from nondependent to dependent lung regions leads to imperfect *V*/*Q* matching. The different gradients between ventilation and perfusion across the lung lead to a high *V*/*Q* ratio (>1) in the nondependent regions and a low *V*/*Q* ratio (<1) in the dependent regions (Fig. 3.1). Under normal circumstances, global ventilation is well matched to global perfusion, producing an overall pulmonary *V*/*Q* ratio of approximately 0.8.

A small percentage of pulmonary blood flow in the healthy lung travels through non-ventilated portions of the lung, providing an extreme example of *V*/*Q* mismatching. This blood represents the intrapulmonary shunt and is sometimes referred to as venous admixture. Some degree of

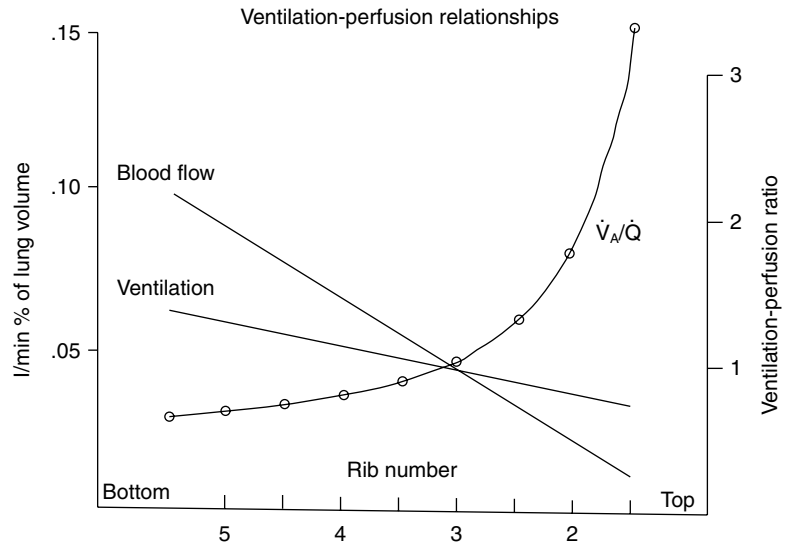


**Fig. 3.1** Distribution of ventilation and blood flow and change in ventilation-perfusion ratio down the upright lung (Excerpted from West (2005b))

intrapulmonary shunting is normal, and the shunt fraction is defined as the percentage of pulmonary blood flow traveling through non-ventilated lung regions. The normal shunt fraction is less than 5 % and is usually closer to 1–2 % of total pulmonary blood flow (or cardiac output) (Cruz and Metting 1987; West 2005b). Within the normal lung, intrapulmonary shunt is caused by three main factors: (1) desaturated bronchial arterial blood that returns directly to the pulmonary veins after $O_2$ delivery to the bronchi, (2) Thebesian veins which return blood directly to the left ventricle after perfusing the myocardium, and (3) alveolar collapse in the bases or most dependent regions of the lung. These portions of the lung are perfused but unable to be ventilated due to the alveolar collapse, thus, creating a *V*/*Q* ratio of 0.

The intrapulmonary shunt fraction can be estimated using the following formula:

$$Q_s / Q_t = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_vO_2}$$

where:

$Q_s$ = shunted fraction of cardiac output (intrapulmonary shunt)

$Q_t$ = total cardiac output

$C_cO_2$ = oxygen content of end pulmonary capillary blood

$C_aO_2$ = oxygen content of arterial blood (systemic)

$C_vO_2$ = oxygen content of venous blood (pulmonary artery)

Clinically, this formula can provide information regarding the adequacy of gas exchange and the magnitude of intrapulmonary shunt as a potential contributor to inadequate oxygenation. Determining the degree of intrapulmonary shunt may assist in the evaluation of therapeutic options and mechanical ventilation strategies (Cruz and Metting 1987; Fink et al. 2005; Furhman and Zimmerman 2006; Marino 1998). When using this formula clinically to calculate the shunt fraction, a few assumptions are usually involved. When calculating $C_cO_2$, the oxygen saturation of hemoglobin ($SaO_2$) is generally assumed to be 100 % due to the fact that in the vast majority of circumstances, blood is fully saturated after traversing the pulmonary capillary. It must be noted that this assumption may not be true in the presence of lung pathology. Furthermore, pulmonary artery catheters are not available in most situations, and mixed venous ($SmvO_2$) or central venous ($ScvO_2$) oxygen saturations can provide a reasonable estimation of hemoglobin saturation in blood returning to the heart for $C_vO_2$ calculations. Lastly, all units for oxygen content should be in mL $O_2$/dL blood.

While a small degree of intrapulmonary shunting is normal, there are a number of circumstances in which the shunt fraction may be significantly increased, thus, worsening *V*/*Q* mismatch. These pathophysiologic states may lead to regional changes in the lung that impact either pulmonary perfusion, ventilation, or both. This increased intrapulmonary shunt and worsening *V*/*Q* mismatch have significant detrimental effects on gas exchange and systemic oxygenation.

Hypoxemia secondary to an intrapulmonary shunt normally does not respond to supplemental oxygen. Increased $FiO_2$ is ineffective in this circumstance because the shunted blood traveling through capillaries adjacent to non-ventilated lung units is not exposed to the increased alveolar oxygen concentrations. Shunted blood remains desaturated and mixes with fully saturated blood as it returns to the pulmonary veins, causing a less than expected response to oxygen administration (Fig. 3.2).

Increasing the shunt fraction does not usually influence $CO_2$ elimination. Transient increases in the concentration of $CO_2$ in shunted blood lead to

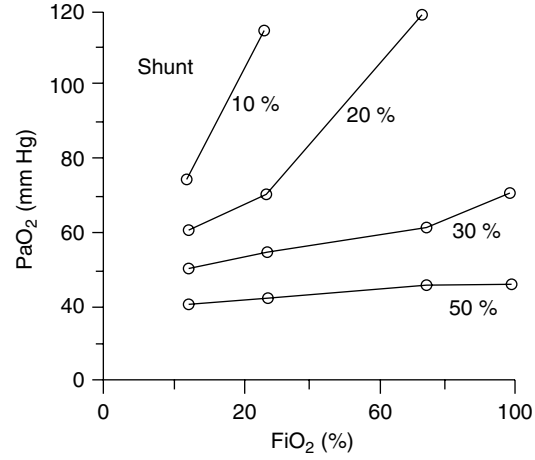


**Fig. 3.2** Response to increasing $FiO_2$ with variation in intrapulmonary shunt fraction (Excerpted from Fink et al. (2005))

an increased ventilatory drive to increase minute ventilation and maintain a normal $P_aCO_2$.

## 3.4 Dead Space

As previously discussed, a certain quantity of dead space exists in healthy lungs due to the portion of inspired gas that remains in the conducting airways and is unavailable for gas exchange. In direct contrast to intrapulmonary shunting, dead-space ventilation represents "wasted" ventilation to areas of the lung that are poorly perfused, or not perfused at all. In these lung units, the *V*/*Q* ratio approaches infinity as perfusion (*Q*) approaches zero. Anatomic dead space is a fixed volume for a given individual and historically has been estimated as 1 mL/lb (0.45 mL/kg) of body weight (Nunn et al. 1959; Numa and Newth 1996; Furhman and Zimmerman 2006; Fink et al. 2005). Most clinicians feel that this estimate is reasonable, but there are recent data that dispute the accuracy of this approximation (Brewer et al. 2008).

In the absence of lung disease, dead space is composed almost entirely of air that remains in the nasopharynx and conducting airways (anatomic dead space), and there is essentially no alveolar contribution. When lung pathology is present, additional alveolar dead space develops. Alveolar dead space is commonly caused by overdistension of healthy lung units during mechanical ventilation. Other potential causes of alveolar dead space include destruction of the alveolar-capillary membrane, poor cardiac output, and pulmonary vascular obstruction. It should be stressed that alveolar dead space is negligible in the absence of lung disease and anatomic dead space predominates. However, depending on the degree of lung injury, alveolar dead space may be of much greater consequence. Overall, total physiologic dead-space ventilation (anatomic plus alveolar dead space) is described as a ratio to total ventilation and expressed as

$$V_D / V_T$$

where $V_D$ is the total volume of dead-space ventilation (including both anatomic and alveolar dead space) and $V_T$ is the total inspired volume for a given breath. The $V_D/V_T$ ratio can be estimated at the bedside using the following modification of the Bohr equation:

$$V_D / V_T = \frac{P_aCO_2 - P_ECO_2}{P_aCO_2}$$

where $P_aCO_2$ is the arterial partial pressure of $CO_2$ and $P_ECO_2$ is the mixed expired concentration of $CO_2$.

In healthy adults, dead-space ventilation is approximately 20–30 % of total ventilation, yielding a $V_D/V_T$ of 0.2–0.3. However, pediatric and neonatal patients may have a larger percentage of dead space due to anatomical differences in head and body size, with normal ratios for $V_D/V_T$ as high as 0.4–0.5 having been reported. In the setting of lung pathology, $V_D/V_T$ may approach 1, and this change is predominantly due to increases in the degree of alveolar dead space. $V_D/V_T$ has important therapeutic implications, and clinicians can quickly estimate this ratio at the bedside using easily available data. Not only can the $V_D/V_T$ ratio be followed as an indicator of the degree of lung injury, but it also may be an important tool in the development of an effective ventilator strategy to optimize *V*/*Q* matching.

## 3.5 Blood-Gas Equilibrium

Adequate matching of ventilation and perfusion depends on diffusion across the interface created at the alveolar-capillary junction. The transfer of both $O_2$ and $CO_2$ is driven by simple diffusion across the alveolar-capillary membrane. As with any gas, this diffusion is governed by Fick's law (West 2005a, Fink et al. 2005, Furhman and Zimmerman 2006, Marino 1998). The Fick principle states that the rate of gas exchange via passive diffusion depends on properties of both the membrane and the gases involved. Gas transfer rates are directly proportional to the surface area and inversely proportional to the thickness of the membrane. In addition, the solubility coefficient of the gases (which depends on both the intrinsic solubility and the molecular weight of the gas) and the difference between the partial pressures of the gases on opposite sides of the membrane

directly contribute to rates of gas transfer. Fick's relationship between these factors can be represented by the following formula:

$$\text{Diffusion Rate} = \frac{K * A * (\text{P1} - \text{P2})}{t}$$

where $K$ is the solubility coefficient (constant) for a given gas, $A$ is the surface area involved in gas exchange, P1 – P2 is the difference between partial pressures across the membrane for a given gas, and $t$ is the thickness of the membrane (distance for diffusion).

The structure of the alveolar-capillary interface in the lung is well suited for remarkably efficient gas exchange. Under normal circumstances, there are approximately 75 $m^2$ of alveolar surface area available for gas exchange in the lung. The membrane separating the pulmonary capillaries and alveoli is in the range of 0.3 um in many places, creating an ideal situation for diffusion. These membrane properties lead to exceptional gas exchange, and it is the rare circumstance that the structure of the alveolar-capillary membrane causes diffusion limitations (Slonim and Pollack 2006; Motoyama and Davis 2006).

Due to these favorable membrane characteristics, most gases are perfusion limited, meaning that their rate of diffusion depends entirely on the amount of available blood passing by the membrane. On average, an individual RBC spends approximately 0.7–0.8 s within the alveolar capillary of the lung. This brief time is approximately three times that which is necessary for complete equilibration of both oxygen and carbon dioxide across the alveolar-capillary interface. Complete transfer of $O_2$ across the membrane usually occurs within 0.25 s, and $CO_2$ equilibrates approximately 20 times faster than $O_2$. This rapid transfer is driven primarily by the large partial pressure gradients that exist between the alveolus and the pulmonary capillary (West 2005b; Slonim and Pollack 2006; Motoyama and Davis 2006).

As blood enters the pulmonary capillary, the $P_aO_2$ is approximately one third of the $P_AO_2$, creating a large gradient to drive gas transfer from the alveolus into the RBC. Normally, diffusion of $O_2$ is complete long before RBCs reach the end of the pulmonary capillary. However, there are two circumstances in which oxygen may become diffusion limited, even in the absence of lung pathology. One situation in which diffusion limitation may occur is when well-trained athletes vigorously exercise. The significant increase in cardiac output that may occur in this setting leads to increased pulmonary blood flow and faster RBC transit time through the pulmonary capillaries. Transit time within the lungs can approach the 0.25 s necessary for oxygen equilibration and can potentially become a limiting factor for diffusion. A second situation in which oxygen may become diffusion limited occurs with substantial decreases in $P_AO_2$, as may be seen at high altitudes. The mechanism for this limitation is a slower rate $O_2$ transfer due to the decreased partial pressure gradient across the alveolar-capillary membrane.

Diffusion limitation may also occur due to the intrinsic properties of certain gases. Carbon monoxide (CO) is diffusion limited because of its strong affinity for hemoglobin. As CO diffuses across the alveolar-capillary membrane, it rapidly binds to hemoglobin within the RBC, creating little change in the partial pressure of CO. This minimal change in downstream partial pressure leads to a persistently large partial pressure gradient across the membrane. Since diffusion is largely driven by this gradient, CO continues to diffuse at a high rate during the entire transit time of the RBC through the pulmonary capillary. CO is one of the few inhaled gases that is diffusion limited in this fashion.

As discussed above, gas equilibration is either limited by perfusion or diffusion in the healthy lung. There are also circumstances in which the structural integrity of the alveolar-capillary membrane may be altered, leading to further limitation of gas exchange. Loss of surface area for gas exchange due to direct lung injury from a variety of causes can lead to impaired gas exchange. Similarly, any increase in thickness of the alveolar-capillary interface can also impair diffusion of gases. There are a number of pathophysiologic processes in the lung that can substantially impair gas exchange by disrupting the blood-gas equilibrium which include parenchymal lung disease, pulmonary edema, interstitial lung disease, pulmonary fibrosis, or impaired cardiac output.

## 3.6 Tissue Oxygenation

Ultimately, the oxygen that diffuses across the alveolar-capillary membrane must be delivered to the tissues to meet the metabolic demands of the body. Tissue oxygenation is dependent on both cardiac output and the amount of oxygen transported in the bloodstream (i.e., arterial oxygen content). Most oxygen transport occurs within the RBCs via binding with hemoglobin (Hgb) (Edwards et al. 1993). Hemoglobin is a complex molecule composed of four polypeptide chains, each of which has a central heme ring. These polypeptide chains occur in varying combinations depending on their amino acid sequences (i.e., alpha, beta, gamma) with the variants each having differing affinities for oxygen binding.

The heme protein of hemoglobin contains iron and can bind $O_2$ only in its ferrous ($Fe^{2+}$) form. The adequacy of oxygen transport from the alveolus to the tissue level depends primarily on this oxygen-hemoglobin relationship, which is graphically represented by the oxygen-hemoglobin dissociation curve (Fig. 3.3).

The shape of the oxygen-hemoglobin dissociation curve is determined by the interaction among the four heme proteins of the Hgb molecule. As oxygen binds to one of the heme moieties, binding affinity to subsequent heme subunits is increased, creating a sigmoidal relationship. This nonlinear, sigmoidal relationship is crucial for oxygen loading at the alveolar-capillary interface and unloading at the tissue level. Under normal circumstances, Hgb saturation is maintained in the range of 97–100 % at any $P_aO_2$ greater than approximately 70 mmHg. There are two other notable points on the oxygen-hemoglobin dissociation curve. First, as $P_aO_2$ falls to approximately 40 mmHg, hemoglobin saturation drops quickly to 75 % due to the steep slope of the oxygen-hemoglobin dissociation curve. This point ($P_aO_2$ of 40 mmHg with a $SaO_2$ of 75 %) represents the usual composition of mixed venous blood as it returns to the heart. A second important point on the oxygen-hemoglobin dissociation curve is the point at which the hemoglobin saturation is 50 % ($P_{50}$). The $P_{50}$ usually occurs at a $P_aO_2$ of 26 mmHg.

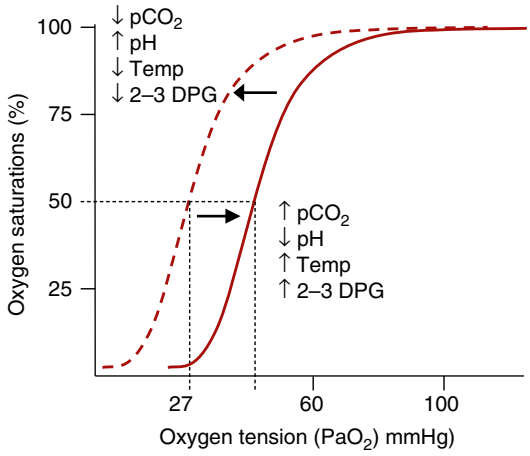


**Fig. 3.3** Oxygen-hemoglobin dissociation curve (Excerpted from West (2005a))

**Table 3.2** Factors affecting the oxyhemoglobin dissociation curve

| |
|---|
| 1. pH |
| 2. $P_aCO_2$ |
| 3. Temperature |
| 4. 2,3-DPG (diphosphoglycerate) |
| 5. Hemoglobin polypeptide subunit composition |

The $P_{50}$ is the reference point often used to discuss shifts in the oxygen-hemoglobin dissociation curve. These shifts may occur due to changes in a number of physiologic variables (Table 3.2). Rightward shift of the oxygen-hemoglobin dissociation curve represents an increase in $P_{50}$ and a decreased $O_2$ binding affinity for Hgb (lower Hgb saturation) for any given $P_aO_2$. The rightward-shifted oxygen-hemoglobin dissociation curve facilitates oxygen delivery and release. Decreases in pH and increases in $P_aCO_2$ shift the oxygen-hemoglobin dissociation curve to the right via the *Bohr effect*. Increased temperature also shifts the oxygen-hemoglobin dissociation curve to the right, further facilitating release of oxygen. The rightward shift of the oxygen-hemoglobin dissociation curve represents a compensatory response to improve oxygen unloading in the setting of acidemia or hyperthermia.

2,3-DPG is a highly charged metabolic byproduct found in RBCs. 2,3-DPG binds deoxygenated hemoglobin and reduces subsequent oxygen

binding affinity, promoting release of oxygen. An increased level of 2,3-diphosphoglycerate (DPG) shifts the oxygen-hemoglobin dissociation curve to the right.

Conversely, leftward shift of the oxygen-hemoglobin dissociation curve represents an increase in $O_2$ binding affinity for hemoglobin at any given $P_aO_2$, favoring oxygen loading and uptake. Increased pH, decreased $P_aCO_2$, decreased temperature, and decreased levels of 2,3-DPG shift the oxygen-hemoglobin dissociation curve to the left and augment oxygen uptake.

The structure of Hgb also can impact the oxygen-hemoglobin dissociation curve. One example of the influence of Hgb structure on oxygen binding affinity occurs in the fetus. In the fetus, a leftward-shifted oxygen-hemoglobin dissociation curve is seen due to the presence of fetal hemoglobin. Fetal hemoglobin contains two gamma chains instead of the beta chains present in normal adult Hgb, which causes an increased affinity for oxygen. These gamma chains have a diminished interaction with 2,3-DPG when compared to adult hemoglobin, shifting the oxygen-hemoglobin dissociation curve to the left. Similarly, hemoglobinopathies are another group of conditions in which the presence of abnormal hemoglobin molecules impact oxygen binding and the location of the oxygen-hemoglobin dissociation curve.

Hgb is the primary determinant of oxygen content in the blood, and the overall content of oxygen in arterial blood ($C_aO_2$) can be determined using the following formula:

$$C_aO_2 = 1.39 * [SaO_2 * Hgb] + 0.003 * P_aO_2$$

where:

$C_aO_2$ (vol % or mL $O_2$/100 mL blood) = oxygen content of arterial blood

$SaO_2$ (%) = oxygen saturation of hemoglobin

Hgb (g/dL) = hemoglobin level

$P_aO_2$ (mmHg) = arterial partial pressure of oxygen

0.003 mL $O_2$/dL blood = constant based on Henry's law relating the volume of a dissolved gas and the partial pressure of that gas

1.39 mL $O_2$ = the amount of oxygen bound by one gram of hemoglobin (may be estimated as 1.32–1.39 mL $O_2$ depending on calculation methods)

$C_aO_2$ is one of the primary determinants of oxygen delivery ($DO_2$) to the tissues. $DO_2$ is the product of $C_aO_2$ and cardiac output (CO) and can be represented by the following formula:

$$DO_2\left(mLO_2/min\right) = C_aO_2\left(mLO_2/dL\,blood\right) * CO\left(L/min\right) * 100$$

In the normal state, $DO_2$ is approximately four times the amount of $O_2$ required by the tissues. This excess oxygen delivery allows the body to compensate for wide variations in $DO_2$ without compromising tissue metabolism and homeostasis.

## 3.7 Metabolic Rate

Metabolic needs of the tissues are quantified as oxygen consumption ($VO_2$). $VO_2$ is the rate of oxygen uptake and utilization by the tissues and can be calculated using a modification of the Fick equation:

$$VO_2\left(mLO_2/min\right) = DO_2\left(mLO_2/min\right) * \left[SaO_2(\%) - SvO_2(\%)\right]$$

where:

$VO_2$ = oxygen consumption

$DO_2$ = oxygen delivery

$SaO_2$ = oxygen saturation of hemoglobin in arterial blood

[1]$SvO_2$ = oxygen saturation of hemoglobin in venous blood

($SaO_2 - SvO_2$) = oxygen extraction by the tissues

Under normal circumstances, $DO_2$ is approximately four times $VO_2$. When $SaO_2$ is 99–100 %, this relationship leads to a $SvO_2$ (or $SmvO_2$) of approximately 75 %, and an overall oxygen extraction ($SaO_2 - SvO2$) of approximately 25 % (West 2005a; Leach and Treacher 1994; Leach and Treacher 2002). As $DO_2$ falls, the body compensates by increasing the extraction of oxygen at the tissue level. This increase in oxygen extraction causes $SvO_2$ (or $SmvO_2$) to fall. In general, the tissues and organs of the body receive an excess supply of oxygen, and, thus, an increased

[1] Ideally, $SvO_2$ for these calculations is a sample of mixed venous blood and reflects $SmvO_2$.

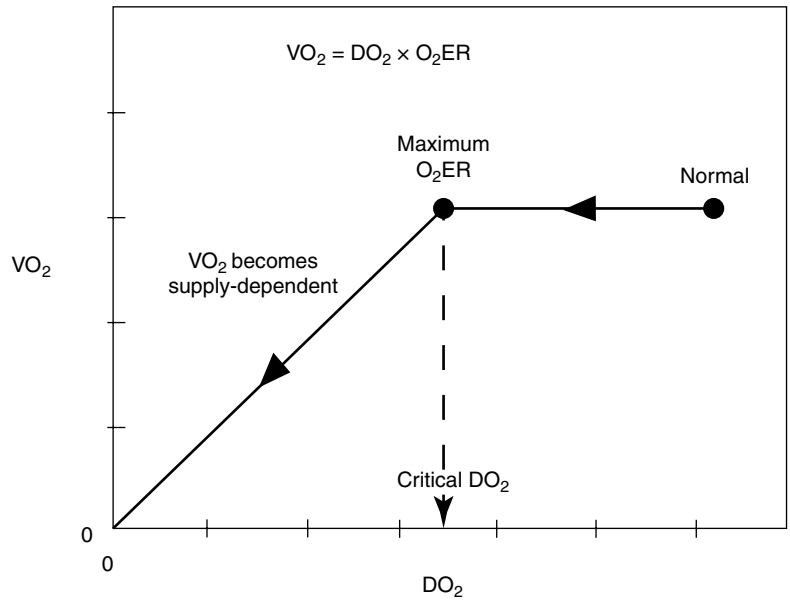


**Fig. 3.4** $DO_2/VO_2$ relationship (Excerpted from Marino (1998))

oxygen extraction does not limit $VO_2$ over a wide range of $DO_2$ (Fig. 3.4).

In healthy patients, $VO_2$ is generally independent of $DO_2$. However, there are a number of pathophysiologic states in which impairment of gas exchange, transport, or utilization may cause $DO_2$ to fall below a critical point (Fig. 3.4). At this point, $VO_2$ becomes dependent on oxygen delivery (Morisaki and Sibbald 2004). This "oxygen supply dependency" is a pathologic state that may be seen in critical illness in which a linear relationship exists between $VO_2$ and $DO_2$. Under these circumstances, any intervention that improves $DO_2$ will subsequently increase $VO_2$ in a linear fashion and improve tissue homeostasis. This relationship provides the physiologic basis for many goal-directed therapies that are routinely implemented in the ICU (Shoemaker et al. 1973; Shoemaker et al. 1988; Taylor et al. 1991; Appel and Shoemaker 1992; Gattinoni et al. 1995).

## 3.8 Interpretation of Arterial and Venous Blood Gases

The relationship between $DO_2$ and $VO_2$ can be affected by the adequacy of pulmonary gas exchange. While there are a number of noninvasive measurements for the assessment of gas exchange, arterial blood gas (ABG) measurement is an important element in the evaluation of oxygenation, carbon dioxide elimination, and metabolic state. ABGs are immediately available in the ICU and are the most common test ordered by ICU providers (Muakkassa et al. 1990). Interpretation of blood gases is a crucial skill for all who care for critically ill patients.

**Table 3.3** Normal arterial blood gas values (room air)

| | |
|---|---|
| pH | 7.35–7.45 |
| $pCO_2$ | 35–45 mmHg |
| $P_aO_2$ | 85–110 mmHg |
| $HCO_3$ | 22–24 mmol/L |
| Base excess | 0 |
| $SaO_2$ | 95–100 % |

ABG analysis involves the direct measurement of pH, $P_aCO_2$, and $P_aO_2$. $SaO_2$ is either calculated based on standard oxygen-hemoglobin dissociation curves or measured directly by co-oximetry. Bicarbonate ($HCO_3$) is determined by the balance between hydrogen ions and partial pressure of $CO_2$ in the blood. Base excess is usually reported as a part of ABG results, and this value reflects the body's metabolic state irrespective of the gas exchange variables. There is a relatively narrow range of normal values for ABG results (Table 3.3), but these measurements may be impacted by equipment, collection technique, temperature, and a number of other metabolic factors.

**Table 3.4** Expected changes in arterial blood gases with acid-base disturbances

| Acid-base abnormality | Primary change | Secondary compensation |
|---|---|---|
| Respiratory acidosis | $PCO_2$ ↑ | $HCO_3$ ↑ |
| Respiratory alkalosis | $PCO_2$ ↓ | $HCO_3$ ↓ |
| Metabolic acidosis | $HCO_3$ ↓ | $PCO_2$ ↓ |
| Metabolic alkalosis | $HCO_3$ ↑ | $PCO_2$ ↑ |

Interpretation of an ABG begins with determination of the primary abnormality in gas exchange. In most circumstances, the pH is a reflection of the primary underlying disturbance. Elevation of pH reflects a primary alkalosis, and low pH indicates acidosis as the primary process. Once the primary abnormality is established, the additional ABG values should be used to determine whether the underlying disturbance is respiratory or metabolic in nature (Table 3.4). For metabolic derangements, the anion gap obtained from basic chemistry values is an important adjunct in establishing an etiology. The normal anion gap is less than 12 and can be calculated using the following formula:

$$\text{Anion Gap} = \text{Na} - \left(\text{Cl} + \text{HCO}_3\right)$$

where Na and Cl are the serum concentrations of sodium and chloride, respectively.

ABGs also reflect the body's compensatory response as it attempts to maintain a normal pH in the face of acid-base abnormalities (Table 3.4). When a primary metabolic disturbance is present (either acidosis or alkalosis), the response of the lungs is relatively immediate as minute ventilation is adjusted to correct pH. However, the renal response required to compensate for primary respiratory acid-base derangements requires 24–48 h to achieve steady state as the proximal tubules of the kidneys alter $HCO_3$ reabsorption.

These compensatory responses occur in a predictable fashion based on the relationship between $P_aCO_2$ and $HCO_3$ in the blood. Given the time course involved in the renal response to respiratory abnormalities, the magnitude of expected compensatory change varies with the acuity of the process. These anticipated changes can be easily calculated (Table 3.5). These calculations are especially important in the context of mixed acid-base disturbances caused by more than one underlying process.

**Table 3.5** Calculation of expected compensatory response with acid-base disturbances

| Primary process | Anticipated change |
|---|---|
| Acute respiratory acidosis | pH change = $0.008 * (PCO_2 - 40)$ |
| Acute respiratory alkalosis | pH change = $0.008 * (40 - PCO_2)$ |
| Chronic respiratory acidosis | pH change = $0.003 * (PCO_2 - 40)$ |
| Chronic respiratory alkalosis | pH change = $0.017 * (40 - PCO_2)$ |
| Metabolic acidosis | $PCO_2$ change = $1.5 * HCO_3 + 8$ |
| Metabolic alkalosis | $PCO_2$ change = $0.7 * HCO_3 + 21$ |

ABGs provide important data regarding the adequacy of gas exchange at both the pulmonary and tissue level, but there are circumstances in which analysis of the venous blood gas (VBG) may also provide helpful additional information. When drawn from the superior vena cava/right atrial (SVC/RA) junction, the VBG represents a sample of mixed venous blood. As discussed previously, the saturation of mixed venous blood ($SmvO_2$) is an important marker for the balance between oxygen uptake and delivery and is used in a number of clinically important calculations including oxygen delivery, oxygen consumption, $Q_p/Q_s$, and the intrapulmonary shunt fraction.

$SmvO_2$ and VBG results are often helpful in the assessment of global gas exchange, but VBG interpretation must be undertaken with caution when the site of sampling is not mixed venous in origin. The pH of venous blood drawn from any site provides a reasonable estimate of acidemia, but substantial differences may exist in the partial pressures of oxygen and carbon dioxide at the local level. These partial pressures may not reliably demonstrate adequacy of oxygenation or ventilation given the variation in oxygen utilization and metabolism by different tissues and organs. VBGs do often provide important adjunctive information regarding gas exchange and metabolic state but should not replace the ABG in the assessment of overall acid-base balance and gas exchange.

Essentials to Remember

- The primary goal of pulmonary gas exchange is tissue $O_2$ delivery and $CO_2$ elimination.
- Alveolar ventilation and oxygenation are related by the alveolar gas equation: $P_AO_2 = F_iO_2 * \left(P_B - P_{H_2O}\right) - P_aCO_2/R$.
- A gradient for *V*/*Q* ratio exists across the lung due to increases in both ventilation and perfusion as one moves from nondependent to dependent regions. In nondependent lung units, the *V*/*Q* ratio is high, and in the dependent areas of the lung, the *V*/*Q* ratio approaches 0.
- Intrapulmonary shunt represents blood flow through non-ventilated lung units, and the normal shunt fraction is <5 % of cardiac output.
- Dead-space ventilation represents "wasted" ventilation to areas of the lung without blood flow.
- Dead-space ventilation is made up of two components: (1) anatomic dead space, which can be roughly approximated as 1 mL/lb (0.45 mL/kg) of body weight, and (2) alveolar dead space, which can be caused by overdistension secondary to mechanical ventilation.
- Dead-space ventilation is often described as it relates to tidal volume ($V_D/V_T$). This ratio is an important indicator of the degree of lung injury and can be easily estimated at the bedside.
- $O_2$ and $CO_2$ diffuse rapidly across the alveolar-capillary interface, making gas exchange limited by diffusion only in rare circumstances.
- The sigmoidal oxygen-hemoglobin dissociation curve is designed for optimal oxygen loading in the lung and unloading at the tissue level.
- Acidosis, elevated $P_aCO_2$, hyperthermia, and increased 2,3-DPG levels shift the oxygen-hemoglobin dissociation curve to the right and facilitate oxygen unloading. Conversely, alkalosis, low $P_aCO_2$, hypothermia, and decreased 2,3-DPG levels shift the oxygen-hemoglobin dissociation curve to the left and facilitate oxygen loading.
- $O_2$ content of the blood depends primarily on hemoglobin and oxygen saturation, and dissolved $O_2$ is a minor contributor to oxygen delivery.
- Oxygen delivery is usually well in excess of oxygen consumption, and $VO_2$ is stable over a wide range of $DO_2$ values.
- ABGs can be utilized to analyze both the primary derangement of gas exchange and the adequacy of the body's compensatory response.

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