# Chapter 3
# Gas Exchange


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The main function of the respiratory system is to remove $CO_2$ from and add $O_2$ to systemic venous blood brought to the lung. Tissue demands of $O_2$ supply and $CO_2$ removal requires the process of matching perfusion and alveolar ventilation ($V_A$), diffusion of gases across the alveolar capillary membrane, $O_2$ delivery ($DO_2$) and consumption ($VO_2$). These processes are schematically represented in (Fig. 3.1).

## 3.1 Alveolar Gas Equation

The total pressure of atmosphere ($P_{ATM}$) at sea level is 760 torr or mm Hg. $P_{ATM}$ is also sometimes expressed in kilopascal unit. 1 kilopascal is approximately 7.5 torr. $P_{ATM}$ decreases progressively at higher altitude (Table 3.1). The total atmospheric pressure is the sum of pressures exerted by each of its component gases. With increasing altitude, $P_{ATM}$ decreases while the fraction of $O_2$ ($FiO_2$) remains constant. At temperature of 37°C (98.6°F), and 100% humidity, water vapor exerts pressure of 47 torr regardless of the altitude. Alveolar air is 100% humidified, therefore the inspired gas is also assumed to be fully saturated with water. To subtract the contribution of water vapor, 47 torr is subtracted from the atmospheric pressure to account for the pressure exerted by gases alone. Our atmosphere contains 20.93% (≈21%) oxygen at any altitude. Thus, the fraction of atmosphere

The original version of this chapter was revised with correct equation at Figure 3.6. The correction to this chapter can be found at https://doi.org/10.1007/978-3-030-83738-9_14

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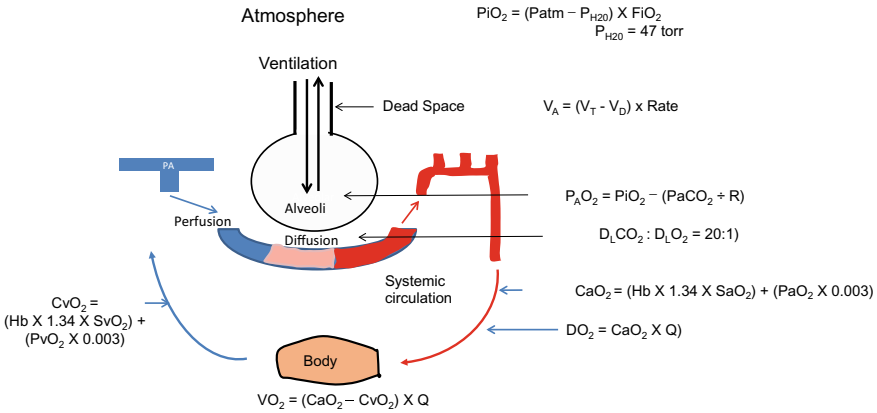



**Fig. 3.1** Various factors involved in respiration; Atmospheric composition, Ventilation, Diffusion, Perfusion, Oxygen delivery ($DO_2$), Oxygen consumption ($VO_2$), $CO_2$ production ($VCO_2$)

**Table.3.1** Relationship of barometric pressureand partial pressure of inspired air ($PiO_2$) when 100% humidified at different altitudes

| Altitudes (feet) | $P_{ATM}$(Torr) | ($P_{ATM}$-47[$P_{H2}$o])Torr | $O_2$% | $PiO_2$(Torr) |
|---|---|---|---|---|
| 0 | 760 | 713 | 20.93 | 149 |
| 600 | 747 | 700 | 20.93 | 147 |
| 5000 | 632 | 585 | 20.93 | 123 |
| 10,000 | 523 | 476 | 20.93 | 100 |
| 15,000 | 429 | 382 | 20.93 | 80 |
| 18,000[a] | 380 | 333 | 20.93 | 70 |
| 20,000 | 349 | 302 | 20.93 | 63 |
| 25,000 | 282 | 235 | 20.93 | 49 |
| 30,000 | 225 | 178 | 20.93 | 37 |

[a]Highest Village. Modified from Comroe JH. Physiology of Respiration, Year Book Medical Publishers, 2nd ED, Chicago, USA 1974

comprising of oxygen ($FiO_2$) is 0.21. Partial pressure of oxygen in inspired gas ($PiO_2$) is calculated as:

$$PiO_2 = (P_{atm} - 47) \times FiO_2$$

At sea level, $PiO_2$ = (760–47) × 0.21 = 149 torr. When breathing 40% $O_2$ at sea level, $PiO_2$ = (760 – 47) × 0.4 = 285 torr. At higher altitudes, breathing the same $FiO_2$ results in a lower $PiO_2$. In Denver (altitude 5,000 feet, $P_{ATM}$ = 632 mmHg) for example, breathing $FiO_2$ of 0.21 will result in $PiO_2$ = (632 – 47) × 0.21 = 123 torr and at $FiO_2$ of 0.4, it will be (632 – 47) × 0.4 = 234 torr.

## 3.2 Oxygenation and Ventilation

The amount of air moved in and out of the lungs every minute ($V_T$ x respiratory rate) is termed minute volume. Part of the inspired $V_T$ occupies conducting airways (anatomic dead space) which does not contribute to gas exchange. Still another part of $V_T$ enters alveoli that are not sufficiently perfused (alveolar dead space). Total dead space ($V_D$tot) is the sum of anatomic dead space ($V_D$anat) and alveolar dead space ($V_D$alv). Alveolar ventilation (VA) is calculated as:

$$\dot{V}_A = [V_T - (Vd_{anat} + Vd_{alv})] \times RR$$

where RR is the respiratory rate (Fig. 3.2).

Although dead space is often looked at as moving in bulk, in reality the gas moves at a higher velocity in the center compared to the periphery where frictional resistance slows it down. Thus, alveolar ventilation may be higher than expected because of asymmetric velocity of the inspired gas compared to uniform velocity in a bulk flow model. The relationship of $V_T$ and $V_D$tot is calculated as:

$$\frac{V_D}{V_T} = \frac{\left(P_{A_{CO2}} - P_{\overline{E}_{CO2}}\right)}{P_{A_{CO2}}}$$

where, $P_ECO_2$ is mixed expired $PCO_2$. $P_ACO_2$ is assumed to be same as $PaCO_2$ since there is no A-a $CO_2$ gradient. To calculate $V_D$alv, $P_{ET}CO_2$ is used to replace mixed $P_ECO_2$.

$V_D alv/V_T = (PaCO_2 - P_{ET}CO_2) \div PaCO_2$.

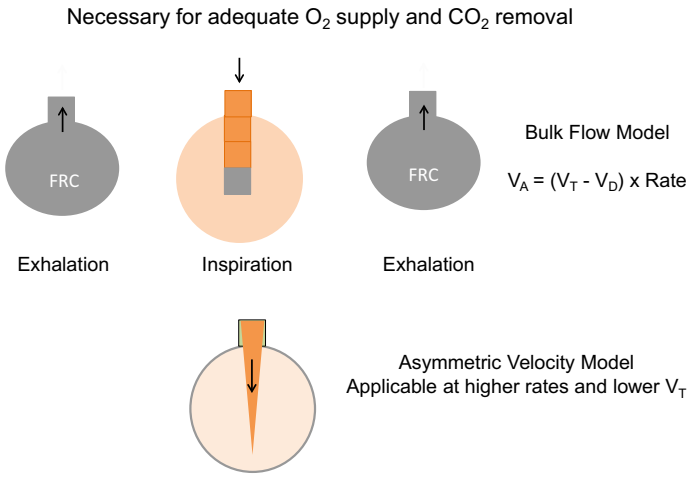



**Fig. 3.2** Alveolar ventilation with bulk flow model and asymmetric velocity model

In normal lungs, $P_{ET}CO_2$ should be close to $PaCO_2$ and thus $V_D$alv should be negligible. Increasing difference in $PaCO_2$ and $P_{ET}CO_2$ is indicative of increasing $V_D$alv. Increased $V_D$alv is encountered when pulmonary perfusion is insufficient to match ventilation such as in decreased cardiac output, pulmonary embolism, hypovolemia and excessive PEEP. $V_A$ is inversely proportional to $PaCO_2$. The relationship between $V_A$ and $PaCO_2$ is hyperbolic but at the bedside, in the ranges of $PaCO_2$ commonly seen, it can be assumed to be linear. Therefore, when $V_A$ is doubled, $PaCO_2$ is halved. Conversely when $V_A$ is halved, $PaCO_2$ is doubled. With minor changes during the respiratory cycle the total pressure of all gases in alveoli is very similar to the total pressure of inspired gas. Alveolar gas composition depends on partial pressure of gases in the inspired gas, $PaCO_2$ (assumed to be same as alveolar $PCO_2$) and respiratory quotient (R). The simplified alveolar air equation is used to calculate the alveolar $PO_2$ ($P_AO_2$) as follows:

$$P_AO_2 = PiO_2 - \left(\frac{P_aCO_2}{R}\right)$$

For practical purposes, R is assumed to be 0.8. According to the alveolar air equation, for a given $PiO_2$, a rise in $PaCO_2$ of 10 torr will result in a decrease in $P_AO_2$ by $10 \div 0.8 = 10 \times 1.25 = 12.5$ torr. Thus, pure hypoventilation will decrease $P_AO_2$ with increase in $PaCO_2$ by a factor of 1.25. In a normal person, $PiO_2$ is about 150 torr. With a $PaCO_2$ of 40 torr, the $P_AO_2$ will be $150 - (40 \times 1.25)$ torr or $150 - 50 = 100$ torr. An increase in $FiO_2$ and therefore the $PiO_2$ will raise $P_AO_2$ without affecting $PaCO_2$. Dangerous level of hypercarbia may coexist without hypoxia in hypoventilating patients who are breathing supplemental $O_2$.

The alveolar gas is is exchanged with the systemic venous (pulmonary arterial) blood through the process of diffusion which is influenced by the alveolar capillary barrier and the time available for equilibration. The "arterialized" blood is returned via pulmonary venous circulation to the heart to be pumped through the systemic arterial circulation. Diffusion in the gas phase (within the alveoli) is inversely proportional to the square root of the molecular weight of a gas molecule. Diffusion into the liquid phase (pulmonary capillary blood) is directly proportional to the solubility of a gas molecule. Considering the respective molecular weights and solubility, $CO_2$ is about 20 times more diffusible than $O_2$. In health, the diffusion for both $O_2$ and $CO_2$ is complete by the time pulmonary capillary blood is no longer in contact with the alveolar gas. Clinically significant diffusion barrier manifests as hypoxia without impairing $CO_2$ elimination. Increasing $FiO_2$ and increasing alveolar-capillary $O_2$ gradient will improve oxygenation to some extent. However, even 100% $O_2$ is only about 5 times more concentrated than room air (as far as $O_2$ is concerned) while $CO_2$ is 20 times more diffusible than $O_2$. In other words, before hypercarbia to develop solely because of a diffusion gradient, life will be incompatible in presence of severe hypoxemia even while breathing 100% oxygen. Presence of hypercarbia suggests additional factors such as alveolar hypoventilation and ventilation/perfusion mismatch. Alveolar-arterial oxygen ($A\text{-}aO_2$) gradient is often utilized to monitor for oxygenation defects in impairment of diffusion and V/Q mismatch.

## 3.3 Distribution of Ventilation

Alveoli are perfused with systemic venous (pulmonary arterial) blood which gets arterialized after diffusion is complete. Pulmonary venous (systemic arterial) blood should have the same $PO_2$ and $PCO_2$ as in the alveolar gas. However, the arterial blood gas composition is different from alveolar gases even in normal individuals because alveolar ventilation (V) and perfusion (Q) are not matched uniformly. Some alveoli receive more ventilation compared to perfusion (high V/Q ratio, dead space ventilation units) while some receive perfusion in excess of ventilation (low V/Q ratio, shunt perfusion units). Ventilation perfusion (V/Q) relationships in a normal lung are easily understood by consideration of West Zones (Fig. 3.5)

Because of the lung recoil and gravitational force, the intrapleural pressure is more negative in non-dependent parts (upper lobes in upright position) of the lung compared to the dependent parts (lower lobes in upright position). At FRC, the alveoli in non-dependent areas of the lung are therefore at a more horizontal part of the pressure volume curve (more distended or aerated but less compliant) whereas the alveoli in the dependent areas are at a more vertical portion of the lung (less distended or aerated but more compliant). For the same change in intrapleural

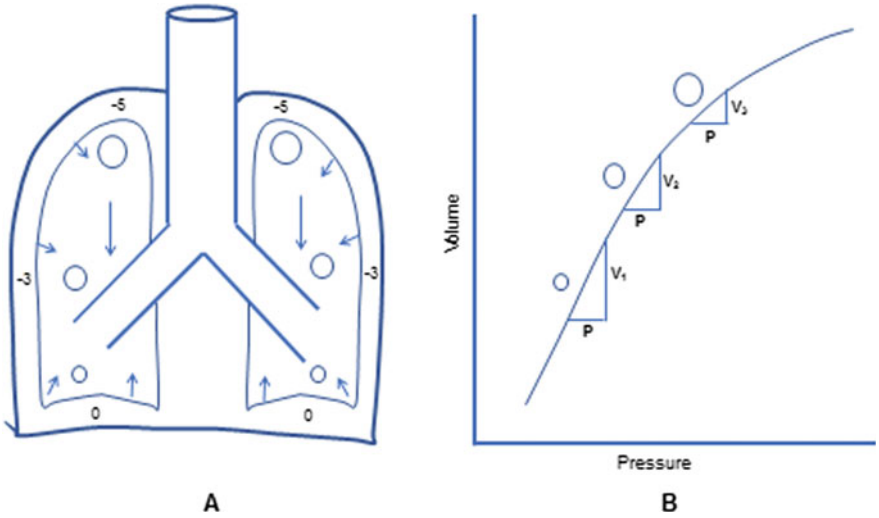



**Fig. 3.3** **a** Illustrative representation of intrapleural pressures at FRC. Because of the lung recoil pressure and gravitational force, the intrapleural pressure is more negative in the non-dependent (upper lobes in upright position) portions of the lung compared to the dependent (lower lobes in upright position) portions. **b** Alveoli subjected to greater intrapleural pressure are therefore more distended (aerated) but less compliant. Alveoli that are surrounded by less negative pressure are less aerated but more compliant. For an identical change in inflation pressure, the change in volume is greater in dependent regions of the lung compared to non-dependent regions

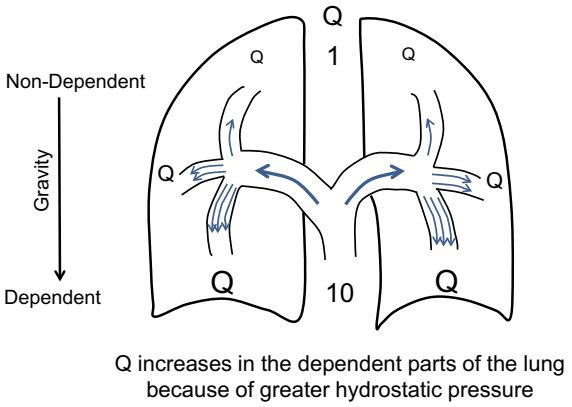



**Fig. 3.4** Distribution of pulmonary perfusion is gravity dependent with dependent areas of the lung getting a larger share of the blood flow

pressure during inspiration, the dependent alveoli will receive greater portion of ventilation. At FRC, ventilation increases from non-dependent to dependent areas of the lung (Fig. 3.3).

## 3.4 Distribution of Perfusion

The distribution of perfusion is very much position dependent. In an upright individual, perfusion is greatest in the lower lobes (Fig. 3.4). In a supine position in which most critically ill patients are cared for, greater proportion of perfusion as well as ventilation are distributed to posterior regions of the lung.

## 3.5 Distribution of Ventilation and Perfusion

Because of the higher hydrostatic force aided by gravity, perfusion also increases from non-dependent portions to dependent portions. However, the increase in perfusion is considerably greater than the increase in ventilation. V/Q ratios favor ventilation in the non-dependent areas and they favor perfusion in the dependent areas. Although both ventilation and perfusion increase from dependent to non-dependent areas of the lung, the increase in perfusion is considerably greater than the increase in ventilation. While ventilation increases a little over 3 folds, the increase in perfusion may be as much as tenfold. The V:Q ratio is about 3:1 in the non-dependent and about 0.6:1 in the dependent parts of the lung. Thus, the V/Q ratios favor dead space ventilation in non-dependent parts and venous admixture in the dependent parts (Fig. 3.5). In situations such as ARDS, the dependent areas are more affected with capillary leakage. These areas receive less ventilation while still receiving larger share of perfusion. This leads to marked V:Q mismatch and

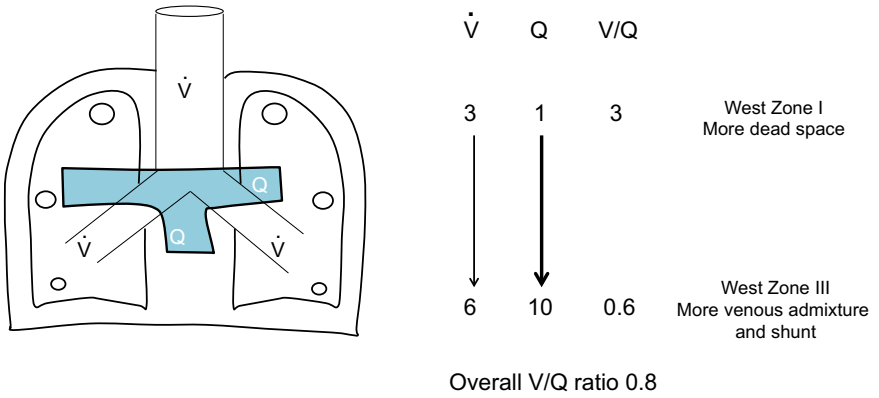
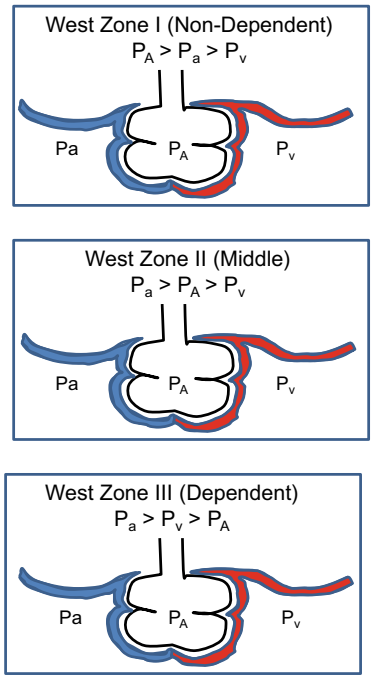



**Fig. 3.5** Regional ventilation, perfusion and V/Q Ratios: Both ventilation and perfusion increase from non-dependent to dependent parts of the lung. The increase in perfusion is disproportionately greater than increase in ventilation resulting in V:Q ratios approximately 3:1 in non-dependent areas and 0.6:1 in dependent areas

hypoxemia. Caring such patients in prone position, shifts the perfusion to anterior portions of the lung which are less affected and better ventilated.

## 3.6 Regional V:Q Relationships (West Zones)

Alveolar pressure ($P_A$) , pulmonary capillary arterial pressure (Pa) and pulmonary capillary venous pressure ($P_V$) determine the type of V:Q relationship and they form the basis of West zones described by John West. In West zone I, $P_A$ is > Pa which is > Pv. The alveolar pressure tamponades the pulmonary blood flow in Zone I. Ventilation is in excess of what is required to fully arterialize the pulmonary arterial blood amounting to wasted or dead space ventilation. Zone I is accentuated in hypovolemia, low cardiac output, pulmonary hypertension, excessive PEEP and pulmonary embolism. The overall VD/VT ratio is increased in Zone I. In West zone II, Pa is > $P_A$ which is > $P_V$. Ventilation and perfusion are better matched in the sense the pulmonary arterial blood is adequately arterialized with appropriate amount of ventilation. In West zone III, both Pa and Pv exceed $P_A$ resulting in a relationship of Pa > Pv > $P_A$. In these areas ventilation is insufficient to fully arterialize the pulmonary arterial blood thereby leading to venous admixture or right to left shunting. Zone III is increased in pulmonary edema, fluid overload and atelectasis. When using prone positioning in ARDS, the clinician attempts to improve V:Q matching by converting Zone III to Zone II type of V:Q relationship (Fig. 3.6).




V:Q ratio 3:1 Dead space ventilation
Accentuated with Hypovolemia, Low cardiac output, Excessive PEEP, Pulmonary HTN

$V_D/V_T = (PaCO_2 - PECO_2) \div PaCO_2$

V:Q more evenly matched
Aim of prone positioning in ARDS

V:Q ratio 6:10 (0.6) Venous admixture
Accentuated with High closing capacity, Atelectasis, ARDS, Pulmonary edema

$Q_S/Q_T = (C_CO_2 - C_aO_2) \div (C_CO_2 - C_{\bar{V}}O_2)$

**Fig. 3.6** Ventilation–Perfusion Relationship (West zones). Zone I is characterized by high V:Q ratios whereas Zone III has lower V:Q ratios

## 3.7 Ventilation (V) and Perfusion (Q) Mismatch

There are 3 prototypical V:Q relationships (Fig. 3.7). The first one is when ventilation is inadequate to fully arterialize the blood flowing past the hypoventilating alveolus. The end-result is a part (or all) of pulmonary capillary blood to remain variably deoxygenated and mix with the arterialized blood from other adequately ventilating lung segments. In this situation the arterial $PO_2$ ($PaO_2$) will be less than alveolar $PO_2$ ($P_AO_2$) as calculated by the alveolar air equation. The blood gas abnormality is referred to as venous admixture or intrapulmonary right to left shunt. The second V:Q relationship is when ventilation is appropriate for the given perfusion. In this situation, the pulmonary capillary blood is fully arterialized and $PaO_2$ and $P_AO_2$ are equal. The third V:Q relationship characterizes areas with decreased perfusion compared to ventilation. The part of the atmospheric air enters and leaves alveoli without contributing to the gas exchange. This type of V/Q mismatch is termed dead-space ventilation. In such situations $P_ACO_2$ is markedly less than $PaCO_2$.

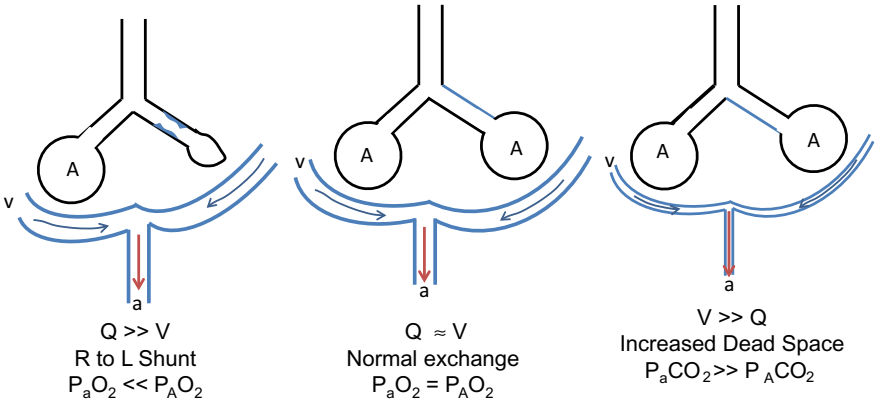



**Fig. 3.7** Three types of V:Q relationship may exists: Normal V/Q, Shunt units and Dead space units

## 3.8 $O_2$ Transport and Utilization

The amount of oxygen carried by the arterial blood is in two forms: (i) in a dissolved state and (ii) combined with hemoglobin. The amount of dissolved oxygen is linearly related to $PO_2$. For every 100 torr $PO_2$, there is 0.3 mL oxygen dissolved in 100 mL of solvent. Dissolved $O_2$ serves two important functions. In this form $O_2$ is immediately available for tissue uptake. Dissolved oxygen also determines the extent to which hemoglobin is saturated by $O_2$. However this amount in and of itself, is hardly sufficient to satisfy tissue $O_2$ demands (Fig. 3.8).

The $O_2$ consumption for a healthy adult is approximately 250 mL/min. At a normal $PaO_2$ of 100 torr, there is 3 mL/L of dissolved $O_2$ in blood. If all of $O_2$ in blood was in the state of dissolved oxygen, it would require 83 L/min of cardiac output even if all of it were to be utilized by the body. The way hemoglobin associates and dissociates with $O_2$ constitutes an efficient means of transporting and utilizing oxygen. Each gram of hemoglobin when 100% saturated with $O_2$, carries 1.34 ml of oxygen. Thus, 15 G of hemoglobin per 100 mL of blood can carry approximately 20 ml of $O_2$ when nearly fully saturated with oxygen. This amounts to 200 mL of $O_2$ in 1000 mL of blood. With cardiac output of 5L per minute, an adult delivers 200 X 5 or 1000 mL of oxygen to the tissues every minute. With a resting $O_2$ consumption of 250 mL/min, as much as 750 mL (75% $HbO_2$ saturation) can still be returned back to the heart in mixed venous blood. Normally, arterial blood $HbO_2$ saturation is nearly complete much before we attain a normal $PaO_2$ because of the dissociation curve. For example, at $PO_2$ of 100 torr; hemoglobin-oxygen saturation is 97.5%, an increase of only 3.5% compared to the saturation at $PO_2$ of 70 torr where it is 94%. Relatively little $O_2$ can be added at higher $PO_2$s (Fig. 3.9).

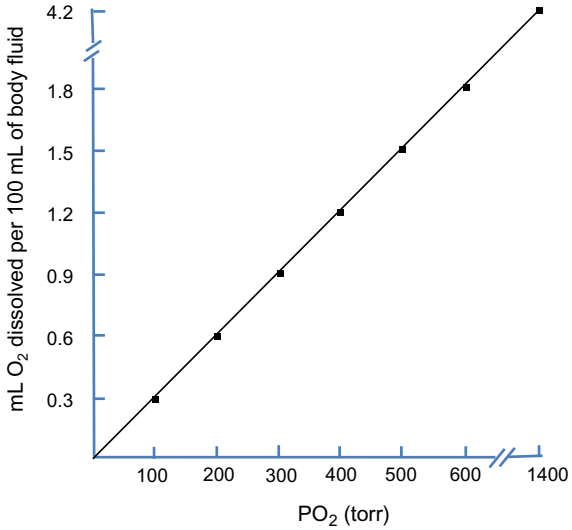



**Fig. 3.8** Relationship of dissolved $O_2$ and $PO_2$ is linear. For every 100 torr, 0.3 ml of $O_2$ is in a dissolved state in a solution. Dissolved $O_2$ = ($PO_2$ in torr × 0.003)/mL of body fluid

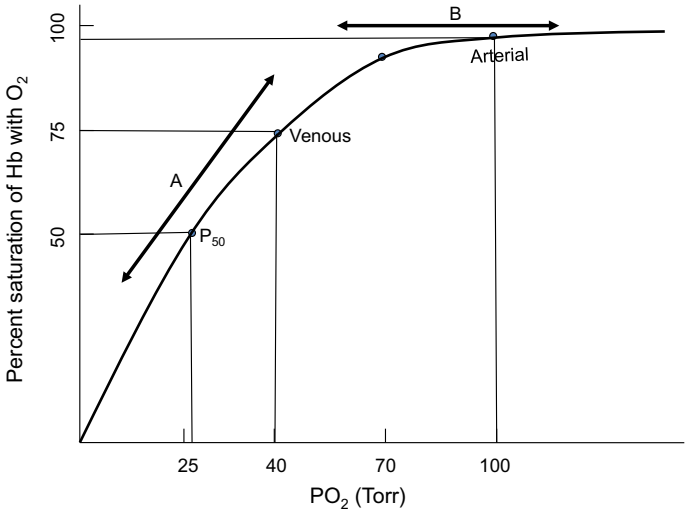



**Fig. 3.9** Relationship of Hb-$O_2$ saturation and $PO_2$. In part of the curve labeled A, the change in the amount of Hb-$O_2$ saturation is considerably greater for a given change in $PO_2$ compared to the part labeled B. $P_{50}$ refers to $PO_2$ at which Hb is 50% saturated

The hemoglobin molecule contains 4 heme chains each with an iron molecule in a reduced, ferrous (Fe++) state, and 4 globin chains. The spatial arrangement of the heme chains, Fe++ and globin chains is necessary for $O_2$ to bind reversibly with the heme part of the hemoglobin molecule. If the iron molecule is in an oxidized to a ferric state (Fe+ ++ ), methemoglobin is formed which is incapable of binding with $O_2$. Carbon monoxide (CO) reversibly binds with hemoglobin at the same sites as $O_2$ but with about 210 time greater affinity. Thus presence of mere 0.1% atmospheric CO will result in 50% carboxyhemoglobin (COHb) and 50% $HbO_2$ in arterial blood when breathing room air (21% $O_2$)! Both methemoglobinemia and CO poisoning can lead to life-threatening decline in blood $O_2$ content despite adequate $PaO_2$. 2,3-DPG, a product of RBC anaerobic glycolysis, plays an important part in association and dissociation of hemoglobin and oxygen. It binds with deoxyhemoglobin much more efficiently than with oxyhemoglobin. At lower $PO_2$ levels such as would occur in the tissues, 2,3-DPG facilitates $O_2$ to dissociate from the hemoglobin and make itself available for aerobic metabolism. At higher $PO_2$ levels such as would occur in the lung, oxygen binds more readily with hemoglobin not allowing 2,3-DPG to bind with hemoglobin. At high altitudes and in patients with anemia and other hypoxic conditions, 2,3-DPG concentration is increased allowing for greater release of $O_2$ to the tissues. Fetal hemoglobin has less affinity to 2,3-DPG and therefore it binds to $O_2$ more readily.

Several factors influence the shape of $HbO_2$ dissociation curve. A shift to the left or a decrease in $P_{50}$ ($PO_2$ at which $HbO_2$ saturation is 50%) is a characteristic of fetal hemoglobin, hypothermia, alkalosis and a decrease in 2,3-DPG. On the other hand, a shift to the right or an increase in $P_{50}$ is observed in hyperthermia, acidosis and an increase in 2,3-DPG. A shift to the right facilitates release of $O_2$ at the tissue level. (Fig. 3.10).

Following equations represent the relationship of arterial $O_2$ content ($CaO_2$), venous $O_2$ content ($CvO_2$), Cardiac output (CO), Oxygen delivery ($DO_2$), and Oxygen consumption ($VO_2$).

$$CaO_2 = [(Hb \times 1.34 \times SaO_2\%) + (PaO_2 \times 0.003)] \times 10$$

where $CaO_2$ is Oxygen content of blood in mL/L, Hb is Hemoglobin concentration in G/dL, $SaO_2$ is the Arterial Oxygen Saturation, $PaO_2$ is the Arterial Oxygen Tension in mmHg. Please note that the multiplication by 10 is to convert $O_2$ content/100 mL to $O_2$ content/1000 mL or 1 L.

Similarly, the oxygen content of mixed venous blood can be calculated as follows:

$$CvO_2 = [(Hgb \times 1.34 \times SvO_2\%) + (PvO_2 \times 0.003)] \times 10$$

Delivery of oxygen to the tissues by the circulatory system is estimated using the formula:

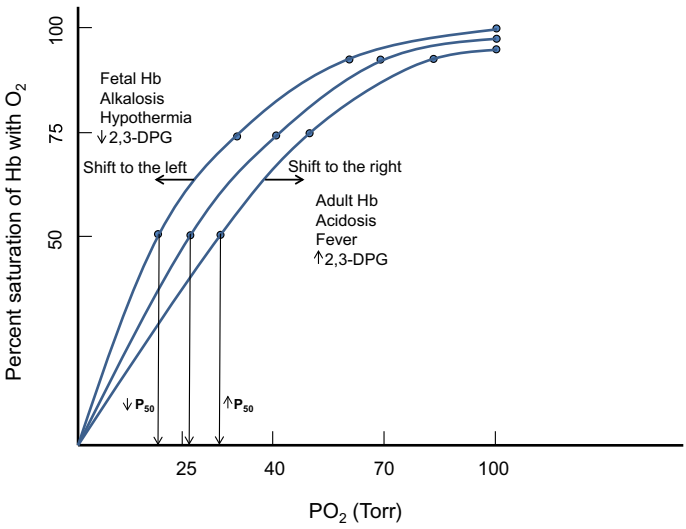



**Fig. 3.10** $HbO_2$ dissociation curves shift to the left (increased $O_2$ affinity) or to the right (decreased $O_2$ affinity) under certain clinically encountered situations

$$\dot{D}O_2 = CaO_2 \times C.O.$$

where $DO_2$ is the delivery of oxygen in mL/min, $CaO_2$ is the arterial oxygen content in mL/L, and C.O. is the cardiac output in L/min.

Oxygen consumption by the tissues is measured in mL of oxygen per minute and is expressed as:

$$\dot{V}O_2 = (CaO_2 - C\bar{v}O_2) \times C.O.$$

where $VO_2$ is oxygen consumption per minute, $CaO_2$ is the arterial oxygen content, $CvO_2$ is the mixed venous oxygen content, and C.O. is the cardiac output.

The ratio of oxygen consumption to oxygen deliver is called Oxygen Extraction. It is the fraction of the oxygen delivery that is consumed by the tissues. It is calculated as follows:

$$Oxygen\,Extraction(O_{2Extr}) = \frac{\dot{V}O_2}{\dot{D}O_2}$$

Since Cardiac Output is in both the numerator and the denominator, oxygen extraction can be simplified as follows (Fig. 3.11):

$$Oxygen\,Extraction(O_{2Extr}) = \frac{(CaO_2 - C\bar{v}O_2)}{CaO_2}$$

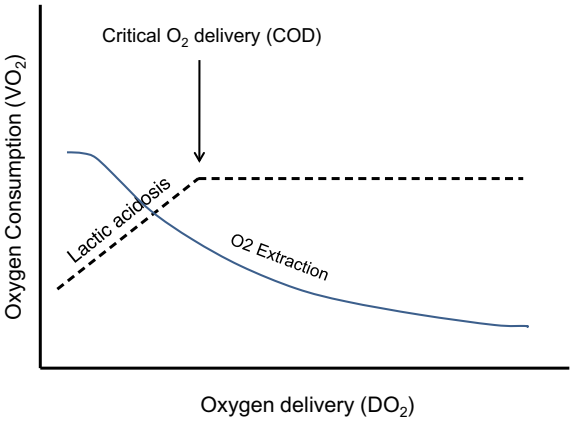



**Fig. 3.11** As $DO_2$ decreases, $VO_2$ remains constant over a wide range by increasing $O_2$ extraction to maintain aerobic metabolism. Fall in $DO_2$ beyond a certain point (critical $O_2$ delivery) results in anerobic metabolism and lactic acidosis despite continued increase in $O_2$ extraction

Normal resting adult has $DO_2$ of approximately 1 L/min and $VO_2$ of 250 mL/min. Thus 75% of delivered $O_2$ is returned back to heart in the mixed venous blood. $CvO_2$ is a reflection of the $DO_2$-$VO_2$ relationship. For sake of convenience, $SvO_2$ is substituted for $CvO_2$ since most of the oxygen content is accounted for by hemoglobin saturated with $O_2$. The relationship between $VO_2$, $DO_2$ and $O_2$ extraction is shown in Fig. 3.11. When $DO_2$ is decreased, $VO_2$ is initially kept constant to maintain aerobic metabolism by increasing $O_2$ extraction. A decrease in $DO_2$ below a certain level results in a decreased $VO_2$ despite increased $O_2$ extraction. $DO_2$ below which increased $O_2$ extraction does not satisfy aerobic metabolic demand of the tissues is termed critical $O_2$ delivery (COD). When $DO_2$ falls below COD, anaerobic metabolism begins with accumulation of lactic acid. Provided $VO_2$ and $CaO_2$ remain unchanged, $SvO_2$ is an indication of adequacy of CO to maintain aerobic metabolism. Declining $SVO_2$ is suggestive of decreasing cardiac output.

## 3.9 Abnormalities of Gas Exchange

As outlined in the preceding discussion, several factors determine gas exchange at the alveolar capillary junction. Analysis of arterial blood gases provides both diagnostic clues as well as therapeutic approach in management of respiratory disorders. The challenge to the clinician is that arterial sample is often not available and a capillary blood sample has to be relied on in many circumstances. Also, a precise $FiO_2$ is usually not available in many patients. The clinician has to rely on many assumptions and clinical experience.

There are four main types of abnormalities in gas exchange. These are (a) alveolar hypoventilation (b) ventilation-perfusion (V-Q) mismatch (c) diffusion defects and (d) absolute right to left shunt (Table 3.2). In many patients more than one disorder may be present. For example, a patient with alveolar hypoventilation may also have a component of V-Q mismatch and a patient with a diffusion defect

may become exhausted and develop hypoventilation. In such a situation, the clinician must determine the major component of gas exchange abnormality to plan a targeted intervention.

Alveolar hypoventilation results when sufficient air is not moved in and out of the alveoli. There are 3 major types of clinical situations which manifest as alveolar hypoventilation. These are: airway obstruction above the carina (choanal atresia,

**Table.3.2** Interpretation of arterial blood gas (ABG) values

| Lesion | Effect | Typical ABG |
|---|---|---|
| * Central (above the carina) airway obstruction<br>* Depressed respiratory center<br>* Ineffective neuromuscular function | Uniform alveolar hypoventilation | * Early increase in $PaCO_2$<br>* Proportionate decrease in $PO_2$ depending on alveolar air equation<br>* Response to supplemental oxygen: Excellent |
| Intrapulmonary airway obstruction | Venous admixture<br>V/Q mismatch | * Mild: ↓ $PCO_2$, ↓ $PO_2$<br>* Moderate: "Normal $PCO_2$ ↓↓$PO_2$<br>* Severe: ↑ ↑$PCO_2$ ↓↓↓ $PO_2$<br>* Response to supplemental oxygen: Good |
| Alveolar-Interstitial pathology | V/Q mismatch, venous admixture, R to L shunt<br>Diffusion defect | * Early decrease in $PO_2$ depending on severity<br>* Normal or low $PCO_2$<br>* ↑ $PCO_2$ if fatigue occurs<br>* Response to supplemental oxygen: Fair to poor |
| Extrapulmonary right to left shunt | Systemic venous blood bypasses alveoli, absolute R to L shunt | * Hypoxemia depending on magnitude of the shunt<br>* Response to supplemental oxygen: Very poor |

subglottic stenosis, vascular ring etc.), weakness of muscles of respiration (Guillain-Barré syndrome, myasthenia gravis, diaphragmatic paralysis etc.) and depressed respiratory center (CNS depressants, congenital central hypoventilation syndrome, brain stem dysfunction etc.). Airway obstruction below the carina may also manifest with predominant alveolar ventilation if the obstruction is relatively uniform such as in bronchiolitis obliterans. Alveolar ventilation is inversely proportional to $PaCO_2$; a certain percentage decline in alveolar ventilation [(Vt – Vd) x rate] will lead to an increase in $PaCO_2$ by a similar percentage. The hallmark of alveolar hypoventilation is elevated $PaCO_2$ and a proportionate decline in $PAO_2$ as determined by alveolar air equation;

For $FiO_2 < 1$, the equation can be simplified to:

$$PAO_2 = PiO_2 - \frac{PACO_2}{R}$$

For bedside calculations, $PACO_2$ is substituted for $PaCO_2$. Thus for a given $PiO_2$, $PAO_2$ will fall only by the rise in $PaCO_2 \div R$. Since R is assumed to be 0.8, the fall in $PAO_2$ will be approximately by rise in $PaCO_2 \times 1.25$. In the absence of significant parenchymal disease and intrapulmonary shunting, administration of supplemental $O_2$ will increase $PiO_2$ and readily reverse hypoxemia despite persistent hypercarbia.

In intrapulmonary airway obstruction (asthma, bronchiolitis, aspiration), the obstruction is not uniform in nature. Some areas are more obstructed than others while some still are relatively unaffected resulting in multiple areas having different extent of ventilation; some are hypoventilated while others are hyperventilated. Pulmonary capillary blood coming from hypoventilated areas has higher $PaCO_2$ and a lower $PaO_2$, whereas that coming from hyperventilated areas has lower $PaCO_2$ and higher $PaO_2$. A lower $PaCO_2$ can compensate for the higher $PaCO_2$ because the Hb-$CO_2$ dissociation curve is relatively linear. An equal amount of blood with $PaCO_2$ of 30 torr mixing with $PaCO_2$ of 50 torr will result in a $PaCO_2$ of 40 torr. A higher $PaO_2$ however cannot compensate for a lower $PaO_2$ in the presence of desaturated hemoglobin because of the shape of the $HBO_2$ dissociation curve. It is the % $HbO_2$ saturation that averages out since far more $O_2$ is responsible for combing with Hb than the dissolved $O_2$ reflecting the $PO_2$. For example, an equal amount of blood with $PaO_2$ of 25 torr and $HBO_2$ saturation of 50% mixing with $PaO_2$ of 110 torr and $HbO_2$ saturation of near 100% will result in $HbO_2$ saturation of 75% and $PaO_2$ of 40 torr. The blood gas abnormality in such situations is referred to as V-Q mismatch, venous admixture or partial right to left intrapulmonary shunting. In mild disease, the hyperventilated areas predominate outnumbering the hypoventilated ones. The end result is hypocarbia and respiratory alkalosis. An elevated $PaO_2$ in the hyperventilated areas however cannot compensate for the low $PaO_2$ in hyperventilated area resulting in mild hypoxemia. With increasing severity, more areas become hypoventilated resulting in normalization of $PaCO_2$ (crossover point) with a further progressive decline in $PaO_2$. A normal or slightly elevated $PaCO_2$ in intrapulmonary airway obstruction raises concern for

impending respiratory failure. As the disease severity increases, more and more lung units are hypoventilated, resulting in hypercarbia, respiratory acidosis and hypoxemia. Supplemental $O_2$ is effective if it is able to reach the hypoventilated alveoli.

In alveolar and interstitial pathology (ARDS, interstitial pneumonia, pulmonary edema), arterial blood gas values reflect intrapulmonary right to left shunting and diffusion barrier. Systemic venous blood flows across unventilated alveoli without getting oxygenated. The diffusion impediment is 20 times greater for $O_2$ than for $CO_2$. Hypoxemia developing early and getting progressively severe is a hall mark of such diseases. Most patients develop hyperventilation manifesting hypocarbia. An increase in $PaCO_2$ is observed only after muscle fatigue and exhaustion ensue. Response to supplemental $O_2$, while life-saving, may not be as robust as in other respiratory pathophysiologic alterations. In severe situations, hypoxemia may become resistant to $O_2$ therapy.

In conditions where systemic venous blood completely bypasses the alveolar-capillary bed (cyanotic heart disease, pulmonary arteriovenous fistula etc.), hypoxemia is the predominant feature as a fixed amount of deoxygenated blood mixes with oxygenated blood. Supplemental oxygen does not increase $PaO_2$ since the deoxygenated shunted blood has no chance of getting in contact with alveolar gas.

## 3.10 Regulation of Respiration

Blood gas homeostasis to suit the body's requirements is maintained by a complex interaction of controllers, sensors and effectors (Fig. 3.12). The central respiratory controller is represented by a group of neurons in the CNS that receives information from sensors and sends motor impulses to muscles of respiration which serve the function of the effectors. The most important effector is the diaphragm which is aided by the intercostal, abdominal and neck muscles as accessories when needed. The effectors target the lungs to adjust alveolar ventilation and control pH, $PaCO_2$ and $PaO_2$. The entire respiratory regulatory mechanism undergoes maturational changes from the neonatal to adult life. It is also subject to modifications by the sleep states, disease processes, pharmacologic agents and acclimatization to the environment.

### *3.10.1 Central Respiratory Controller*

Two functionally and anatomically distinct group of neurons located in the CNS control the process of respiration: voluntary and automatic.

*Voluntary control of respiration* resides in the cerebral cortex and limbic forebrain areas. Major sensory inputs consist of smell, vision, emotions, pain, touch

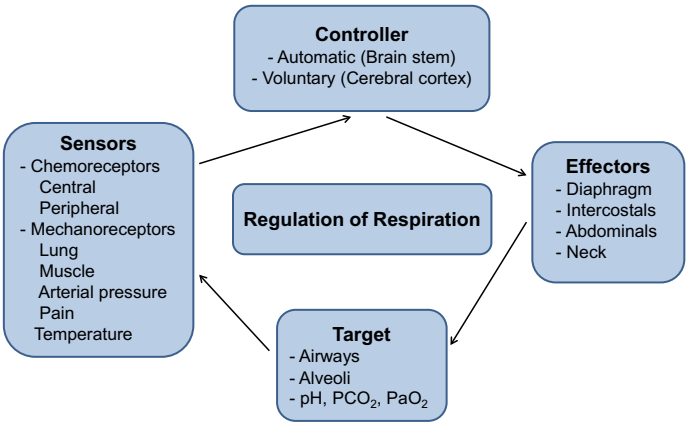



**Fig. 3.12** Control of respiration

etc., and motor impulses are sent to the effectors through corticobulbar and corticospinal tracts. Voluntary control of respiration requires a certain level of consciousness, and is important for protection against aspiration and inhalation of noxious gases. Patient with toxic/metabolic/infectious/traumatic encephalopathies and pharmacologic sedation may lose voluntary control of respiration depending on the extent of CNS dysfunction.

*Automatic control of respiration* is located in the brainstem. Neuronal circuits, referred to as central pattern generators (CPGs) spontaneously generate rhythmic motor output without requiring conscious input, and are responsible for breathing, swallowing and chewing. CPGs responsible for breathing are located in pons and medulla. A group of neurons located in lower pons constitutes the apneustic center which is responsible for pronged inspiratory effort interrupted by brief periods of expiratory activity. Another group of neurons in the upper pons termed pneumotaxic center, is involved in inhibiting the activity of CPGs. The role of apneustic and pneumotaxic centers is to fine-tune the rhythmic respiratory activity of CPGs. Global CNS depression from any cause can manifest as slow and shallow respirations, hypoventilation and respiratory acidosis. Similarly, localized CNS lesions are manifested by specific patterns of abnormal ventilation.

### *3.10.2 Sensors*

Multiple mechanisms exist that can sense abnormalities of gas exchange, acid–base imbalance and respiratory system dysfunction, and send that information to the central respiratory controller to modify the breathing pattern. These mechanisms exist in the form of sensory nerve endings termed chemoreceptors and mechanoreceptors depending on the type of stimulus that is being sensed.

Chemoreceptors are further classified as central or peripheral depending on their location.

Central chemoreceptors are located within the CNS. They reside over a wide area that includes posterior hypothalamus, cerebellum, locus ceruleus, raphe and brain stem. They sense a change in chemical composition of the body fluid they are exposed to. Central chemoreceptors respond to the chemical changes in the extracellular fluid (ECF) of the brain represented by cerebrospinal fluid (CSF). The ventilatory response is predominantly due to a change in the $H^+$ concentration (pH) of the brain ECF. The brain ECF and blood are separated by the blood brain barrier which is relatively impermeable to $H^+$ and $HCO_3^-$ but freely permeable to $PCO_2$. A rise in $PaCO_2$ is quickly reflected in a rapid rise in the CSF $PCO_2$. The consequent fall in CSF pH is sensed by the central chemoreceptors which then send excitatory impulses to the controller resulting in increased ventilation via the effectors. CSF pH in normal conditions is slightly acidic, around 7.32. With its lower protein level and absence of hemoglobin, CSF also has much less buffering capacity compared to that of the blood. Consequently, for an equivalent change in $PaCO_2$, the change in CSF pH is much more pronounced than that in the blood. In disease states characterized by chronically elevated $PaCO_2$, the CSF pH tends to normalize as $HCO_3^-$eventually equilibrates across the BBB. Patients with chronically elevated $PaCO_2$ therefore have a relatively normal CSF pH and they do not have the same ventilatory response that is observed with acute hypercarbia.

Peripheral chemoreceptors are clusters of cells referred to as carotid bodies just above the bifurcation of the common carotid and external carotid arteries, and aortic bodies above and below the aortic arch. Carotid bodies are far more powerful sensors than aortic bodies. The cells comprising carotid and aortic bodies have a very high metabolic rate as well as blood flow to meet their metabolic demands. The main stimulus for peripheral chemoreceptors is hypoxia. Decrease in $PaO_2$ ($SaO_2$), blood flow (low cardiac output), and impaired $O_2$ utilization (cyanide poisoning) classically described as hypoxemic hypoxia, stagnant hypoxia and histotoxic hypoxia respectively, are potent stimulators of peripheral chemoreceptors. Anemia and dyshemoglobinemias do not stimulate peripheral chemoreceptors as long as $PaO_2$ and cardiac output are adequate. This is because the dissolved oxygen in the blood in form of $PaO_2$ and high blood flow easily satisfy the exceptionally high $O_2$ requirement of the chemoreceptors. Relationship of $PaO_2$ and stimulation of peripheral chemoreceptors is non-linear. Chemoreceptor stimulation begins at $PaO_2$ below 500 torr and a small increase in ventilation occurs incrementally until $PaO_2$ reaches 100 torr. The response time for peripheral chemoreceptor is much faster than central chemoreceptor stimulation. Even during normal respiration, carotid bodies response rate is fast enough to alter their discharges sensing small cyclic changes in $PaO_2$ during inspiration and exhalation. At $PaO_2$ less than $\sim$ 50 torr, carotid body stimulation increases exponentially. Subjective feeling of dyspnea from pure hypoxia alone does not occur until $PaO_2$ falls below $\sim$50 torr ($SaO_2$ below $\sim$ 85%). Peripheral chemoreceptors account for almost all the hyperventilation response to hypoxia. They also respond to $PCO_2$ but the increase in alveolar ventilation per torr $PCO_2$ is much less than that from central

**Table.3.3** Characteristics of central and peripheral chemoreceptor stimulation

| | Central chemoreception | Peripheral chemoreception |
|---|---|---|
| Site | Central Nervous System | Carotid and Aortic bodies |
| Primary Stimulus | CSF pH ( $PaCO_2$) | Hypoxia |
| Response to hypoxia | None or depressed | Marked stimulation |
| Response to acutely $PaCO_2$ | + + + | + |
| Response time | Slow | Fast |
| Acclimatization | Readily occurs | Does not occur easily |
| Sedation/anesthesia | Easily depressed | Not easily depressed |

chemoreceptor stimulation. Adaptation to stimulus (Increased $PaCO_2$) occurs in days for central chemoreceptors but hypoxic stimulation of peripheral chemoreceptors persists for a long time, even for life, for people living at high altitudes as reflected by their lower $PaCO_2$ levels. The difference in central and peripheral chemoreception is presented in Table 3.3.

In certain disease states such as asthma a blunted response to hypoxia is well documented. In recent SARS-CoV-2 pandemic, similar observations of "happy hypoxia" have been reported describing patients with minimal respiratory distress in spite of considerable arterial $O_2$ desaturation. Pure peripheral chemoreceptor stimulation results in bradycardia. In most situations with acute hypoxia, tachycardia develops because of action of muscles of respirations causing lung inflation. Two situations where bradycardia is a pronounced effect of sole peripheral chemoreceptor stimulation are: hypoxic patients with neuromuscular blockade and neuromyopathy, and in intrauterine life. In chronic hypercarbic states, the central chemoreceptors have adapted to elevated $PaCO_2$ and the respirations are maintained mainly by the hypoxic drive from the peripheral chemoreceptors. Administration of high concentration of $O_2$ can potentially abolish the hypoxic peripheral chemoreception resulting in hypoventilation, respiratory acidosis and $CO_2$ narcosis. Care must be taken in delivering supplemental $O_2$ to such patients to avoid serious hypoventilation.

Mechanoreceptors

*Stretch receptors* located within the airway smooth muscles, are stimulated by lung inflation. They are important in adjusting the respiratory rate in health and disease and minimizing work of breathing. In diseases with decreased lung compliance, alveoli fill up quickly thus the transpulmonary pressure is transmitted quickly to the airways stretch receptors resulting in inhibition of inspiration. The breathing pattern is rapid and shallow. In diseases of increased resistance, alveoli take longer time to fill up thus delaying stimulation of the stretch receptors and thus resulting in deeper and slower respiration.

*Muscle receptors* are located in diaphragm and intercostal muscles. Stretching of these muscles is sensed by the muscle spindle to control the strength of contraction.

Excessive distortion of diaphragm and intercostal muscles inhibits inspiratory activity.

*J receptors* are located in the alveolar walls close to the pulmonary capillaries. Pulmonary capillary engorgement and interstitial and alveolar fluid collection activate J receptors resulting in rapid, shallow respiration and dyspnea.

*Irritant receptors* are located in between the epithelial cells in the airway mucous membrane throughout the respiratory tract. They are stimulated by particulate matter and noxious gases as well as cold air. Their stimulation results in bronchoconstriction and cough.

*Arterial baroreceptors* located in aortic arch and carotid sinus, respond to arterial blood pressure. Hypotension results in tachypnea and hyperpnea.

### *3.10.3 Effectors*

The most important effector of respiration is the diaphragm. Intercostals and abdominal muscles are recruited when additional increase in ventilation is necessary. Sternocleidomastoids and paraspinal muscles may be called upon to additional contribution to the respiratory effort. Developmental changes significantly influence the ability of the diaphragm to sustain large elastic work load and resist fatigue. As compared to the skeletal muscles which contain primarily fast twitch, fatigable type 2 × and 2b fibers, the predominant muscle fiber types in the diaphragm are the fatigue resistant slow twitch type 1 and intermediate fatigue resistant fast twitch type 2a fibers. The type 1 fibers have slower shortening velocities than fast type 2a fibers but are highly fatigue resistant due to their lower ATP consumption and their reliance almost exclusively on aerobic metabolism. Type 2a fibers on the other hand are fast-twitch, less oxidative and are more prone to fatigue. This combination of fiber types allows for good fatigue resistance and increased force generation when necessary. Diaphragms of newborns and infants have a lower muscle mass when indexed for body size. In addition, they have lower percentages of fatigue resistant type I fibers. The diaphragm of preterm infants contains only 10% type I fibers. This increases to 25% in term neonates and 55% in children greater than 2 years of age. These developmental differences predispose neonates and infants to respiratory muscle fatigue and respiratory failure.

## Suggested Readings

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