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## 4 - Respiratory Physiology

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**Updated Catherine Sheehan, Sanjiv Sharma, July 2012**

**Associated clinical guidelines/protocols:**

**Fundamental Knowledge:**

*List of topics relevant to PIC that will have been covered in membership examinations.*

***They will not be repeated here.***

**Anatomy:**

- Anatomy of upper and lower respiratory tract, mediastinum, rib cage, muscles of respiration and diaphragm.
- Innervation (including cranial nerves to oropharynx), blood supply, and lymphatic drainage of respiratory tract
- Microstructure of the lung: alveolar-capillary unit.
- Differences in the child's versus adult's anatomy
- Processes involved in maturation and ongoing growth of the lungs.

**Physiology:**

- Basic physics governing the behaviour of gases; the gas laws, vapour pressure, saturated vapour pressure, hyper- and hypobaric pressures, density and viscosity of gases, measurement of volume and flow in gases and liquids, Poiseuille's equation, the Bernoulli principle; laminar and turbulent flow
- Principles of surface tension, surfactant
- Measurement of vapour concentrations.
- Measurement of pH, pCO<sub>2</sub>, pO<sub>2</sub>
- Control of breathing; chemo receptors, mechanoreceptor, nerves

## Information for Year 1 ITU Training (basic):

### **Physiology:**

- Mechanics of breathing: pressure, volume, compliance, resistance.
- Principles governing gas exchange: O<sub>2</sub> and CO<sub>2</sub> transport. Effects of ventilation perfusion mismatch and shunting.
- Principles of oxygen supply, delivery to the tissues and consumption.
- Functions of haemoglobin in oxygen carriage
- Acid-base equilibrium

### **Pathophysiology:**

- Definition of acute and chronic respiratory failure and assessment of severity.
- Causes of respiratory failure, prevention and management.
- Effect of oxygen therapy
- Use of Nitric Oxide

### **Investigations:**

- Interpretation of blood gas.

## PHYSIOLOGY

### RESPIRATORY MECHANICS

#### Respiratory muscles

##### *Inspiratory muscles*

- Diaphragm – very powerful
- External intercostals – pull the ribs up and forwards
- Accessory inspiratory muscles – scalene muscles (elevate first 2 ribs) and sternomastoids (raise the sternum)
- Muscles of neck and head (seen in small babies in respiratory distress)

##### *Expiratory muscles*

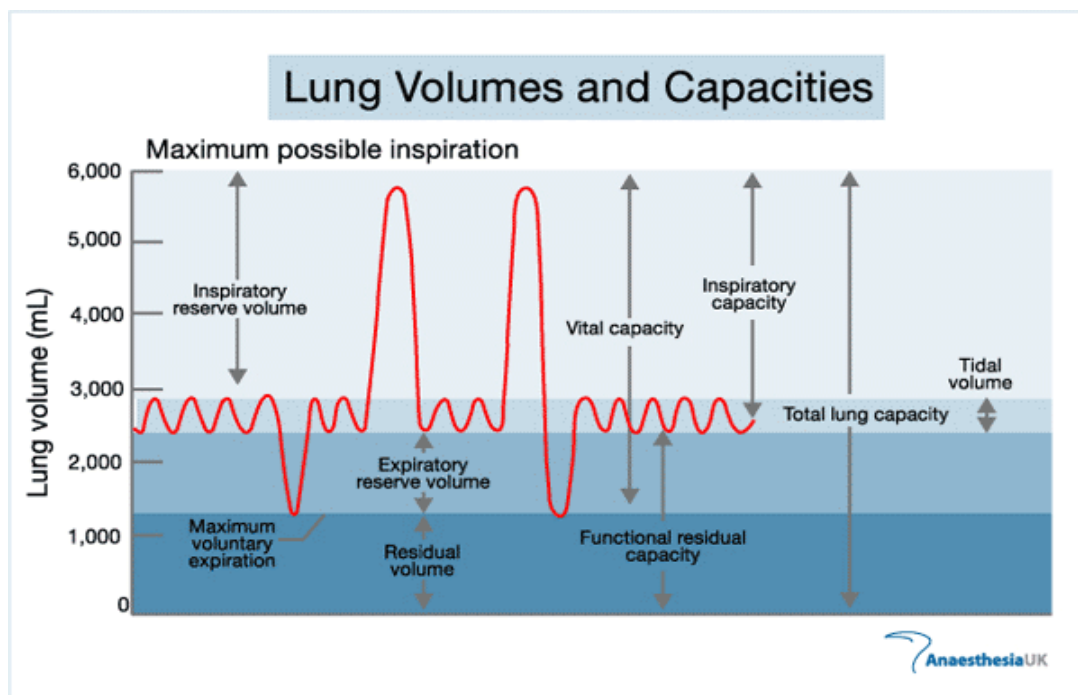
Expiration is usually passive and relies on the elastic recoil of the lungs and the chest wall. Under anaesthesia or extreme exercise expiration may become active due to the activation of abdominal muscles. Muscles have their use in forced expiration.

- Abdominal wall muscles – rectus abdominus, internal and external oblique
- Internal intercostal muscles – pull ribs down and inwards

#### Assessment of lung volumes

Spirometry with flow volume loops assesses the mechanical properties of the respiratory system by measuring expiratory volumes and flow rates.

#### *Definitions and terms*



**Figure 1:** Lung Volumes and Capacities

- Tidal volume (TV) is the volume of air moved in and out of the respiratory tract (breathed) during each ventilatory cycle
- Inspiratory reserve volume (IRV) is the additional volume of air that can be forcibly inhaled following a normal inspiration. It can be accessed simply by inspiring maximally, to the maximal inspiratory level
- Expiratory reserve volume (ERV) is the additional volume of air that can be forcibly exhaled following a normal expiration. It can be accessed simply by expiring maximally to the maximal expiratory level
- Vital capacity (VC) is the maximal volume of air that can be forcibly exhaled after a maximal inspiration.  $VC = TV + IRV + ERV$
- Residual volume (RV) is that volume of air remaining in the lungs after a maximal expiration. It cannot be expired no matter how vigorous or long the effort.  $RV = FRC - ERV$
- Functional residual capacity (FRC) is the volume of air remaining in the lungs at the end of a normal expiration.  $FRC = RV + ERV$
- Total lung capacity (TLC) is the volume of air in the lungs at the end of a maximal inspiration.  $TLC = FRC + TV + IRV = VC + RV$
- Forced expiratory volume 1 (FEV1) – the volume of air that is forcefully exhaled in one second
- Forced vital capacity (FVC) – the volume of air that can be maximally forcefully exhaled
- Ratio of FEV1 to FVC (FEV1/FVC) – expressed as a percentage
- Peak expiratory flow rate (PEFR) – the peak flow rate during expiration

Spirometry is typically reported in both absolute values and as a predicted percentage of normal. Normal values vary, depending on gender, race, age and height. It is therefore not possible to interpret pulmonary function tests (PFTs) without such information.

## Lung compliance

Compliance is defined as the volume change per unit pressure change and is usually expressed in mls/cmH<sub>2</sub>O

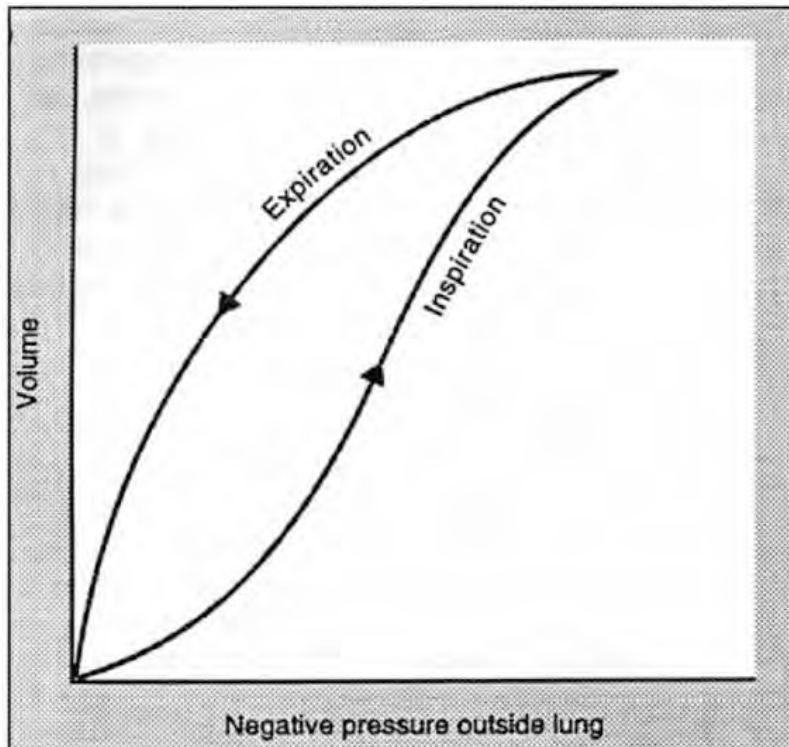
$$\text{Compliance} = \Delta V / \Delta P$$

It is classified into chest wall, lung or total lung compliance (distensibility).

Compliance can be measured by inserting an oesophageal probe into a co-operative patient, the patient inhales and exhales to a set volume. At each volume the intrapleural pressure is estimated using the oesophageal probe.

A pressure volume curve can then be plotted. If during the measurement process no gas flow occurs at each set volume then this is static compliance. (Gas flow ceases and equilibration occurs) If gas flow continues throughout measurement then this is dynamic compliance.

Using a spirometer certain fixed volumes can easily be measured e.g. TLC, RV and FRC. The pressure along the x axis is often plotted as the transpulmonary pressure (Alveolar pressure – Intrapleural pressure).



*Critical Care*

**Figure 2:** This graph illustrates lung compliance.

Initially as can be seen from the above curve at lower lung volumes the compliance of the lung is poor and greater pressure change is required to cause a change in volume. This occurs if the lungs become collapsed for a period of time.

At FRC compliance is optimal since the elastic recoil of the lung towards collapse is balanced by the tendency of the chest wall to spring outwards. At higher lung volumes the compliance of the lung again becomes less as the lung becomes stiffer.

Expiration is deemed a passive process due to the elastic recoil of the lung; because of this the inspiratory curve is not identical to the expiratory curve on a correctly drawn compliance curve. This is known as ***hysteresis***.

Compliance increases in old age and emphysema as elastic lung tissue is destroyed. It is decreased in pulmonary fibrosis, pulmonary oedema, atelectasis and in the extremes of lung volume.

### **Airway resistance**

Resistance is the pressure difference between the beginning and end of a tube divided by the flow of gas volume per unit time. In the lung, it is the difference between atmospheric pressure and alveolar pressure. The tracheobronchial tree is a dynamic system of cartilaginous structures that can distend or narrow, depending on the forces exerted on them. The smaller more distal airways are kept open by the balance of the intrapleural pressures and the elastic recoil of the lung.

During inspiration, elongation of the elastic pulmonary fibres increases the elastic retraction pressure and as the bronchioles are stretched by the stronger radial pull

the bronchial resistance decreases. With expiration, the elastic recoil of the lung increases, the bronchioles become narrower and the flow resistance increases.

These changes in the flow characteristics during the respiratory phases explain why the expiratory phase is slightly longer than the inspiratory phase. Dynamic compression of the small airways occurs when the intrapleural pressures increase to about 40 cmH<sub>2</sub>O during forced expiration. When the intrapleural pressures are considerably greater than the intraluminal pressures, narrowing or closure of the bronchioles occurs. If airway closure is premature, the closing volume encroaches on the functional residual capacity (FRC).

### ***Key Points***

- Expiration is normally a passive process
- Compliance is the change in volume per unit change in pressure
- Compliance can be dynamic or static depending on whether the gas flow is continuing or allowed to equilibrate during pressure measurements
- A spirometer cannot measure TLC, FRC or RV
- Compliance of the lungs is poor at very low or very high lung volumes
- Compliance is optimal at or just above FRC

### ***Clinical points***

- Patients using their accessory muscles may indicate increased work of breathing
- PEEP can help to maintain the lungs at FRC
- If used correctly CPAP can reduce the work of breathing by increasing FRC

## PRINCIPLES GOVERNING GAS EXCHANGE

The partial pressure of oxygen that is inhaled from our natural environment through normal inhalation is not maintained at the same partial pressure by the time it reaches the alveoli and indeed the mitochondria. The process by which this decrease in partial pressure occurs is called the oxygen cascade.

The air surrounding us – how much oxygen does it contain?

Dry atmospheric air gas – 21% of 100KPa

Therefore, 21 KPa or 160mmHg

However as gas is inspired it is diluted by water vapour which reduces the partial pressure of oxygen:

Water vapour – 6.3 KPa/ 47mmHg

$PO_2 = 0.21 \times (760-47) = 149\text{mmHg}$

$PO_2 = 0.21 \times (100-6.3) = 19.8\text{KPa}$

When the gas reaches the alveoli the partial pressure of oxygen will again decrease as some oxygen is absorbed and  $CO_2$  is excreted. The partial pressure at this point in the oxygen cascade can be determined by using the alveolar gas equation.

$$PAO_2 = PIO_2 - PACO_2/RQ$$

The RQ stands for respiratory quotient and is normally 0.8. It is determined by the amount of  $CO_2$  produced/ oxygen consumed.

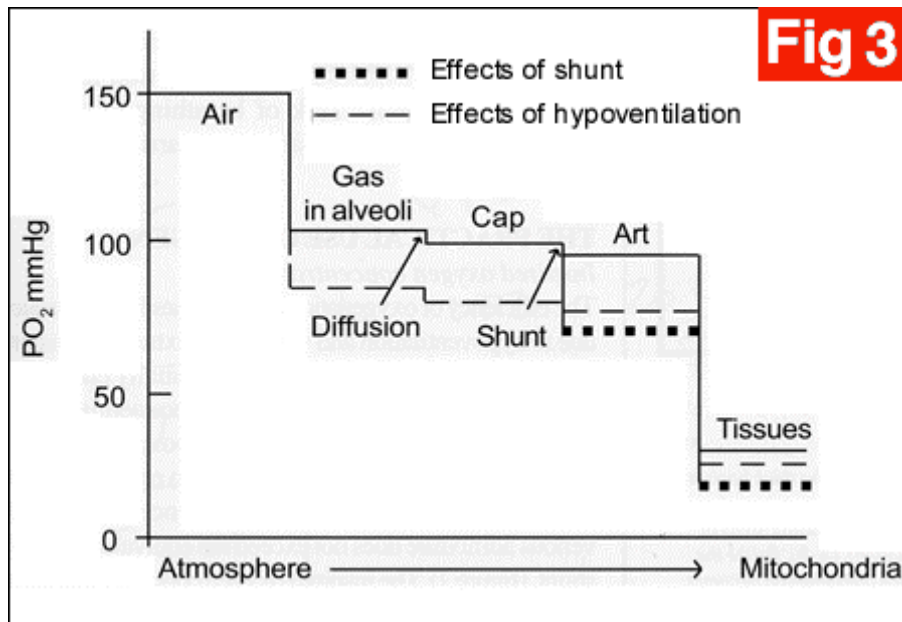
$$PAO_2 = 0.21 - 5/0.8 = 14\text{KPa} (106\text{mmHg})$$

Again when the gas reaches the arterial blood a further small drop in partial pressure will have occurred as blood known as venous admixture with a lower oxygen content mixes with the oxygenated alveolar blood.

Venous admixture is made up of blood that has passed through poorly ventilated regions of lung and thus has a lower  $O_2$  partial pressure. Venous admixture is also composed of venous blood which has drained the lungs and left side of the heart. This blood is known as true shunt and drains directly into the left side of the heart. Extraction of oxygen from this blood then causes the end capillary oxygen partial pressure to be 6-7KPa (40 - 50mmHg)

In the mitochondria the  $PO_2$  varies hugely from 1-5KPa (7.5-40mmHg)

This provides us with an explanation for the following graph, the oxygen cascade.



**Figure 3:** Diffusion of gases from alveoli to blood – the oxygen cascade

### Diffusion of Gases Across the Alveolar Membrane

The speed and ease of diffusion are controlled by the laws of diffusion.

*Fick's law* of diffusion states that gas transfer across a membrane is directly proportional to the concentration gradient.

*Graham's law* states that diffusion of a gas is inversely proportional to the square root of the molecular weight of the molecule.

Other factors which increase diffusion:

- Large surface area
- Thin membrane
- High solubility

The following equation incorporates the important factors:

Diffusion is proportional to  $A/T \cdot D \cdot (P_1 - P_2)$

A = Area

T = Thickness

D = Diffusion constant

$P_1 - P_2$  = Concentration gradient

Diffusion in the lungs can be limited in the presence of disease states e.g pulmonary oedema and thickening of the alveolar membrane in pulmonary fibrosis.

### Oxygen transport

Oxygen is carried in 2 forms in the blood:

- Oxygen combined to haemoglobin (97%)  
Haemoglobin molecule consists of 2 alpha and 2 beta chains; each chain is formed from an iron-porphyrin molecule - haem. Each haemoglobin molecule can bind 4 oxygen molecules (20ml oxygen per 100ml blood) or 15ml oxygen per 100ml in venous blood.



- Oxygen dissolved in the blood – this accounts for a minimal amount (0.3ml per dl)  
The amount dissolved obeys Henry's law – amount is proportional to the partial pressure. 0.023ml per kPa per 100ml blood.

### Oxygen content of blood

The theoretical maximum oxygen carrying capacity is 1.39 ml O<sub>2</sub>/g Hb, but direct measurement gives a capacity of 1.34 ml O<sub>2</sub>/g Hb.

1.34 is also known as **Hüfner's constant**.

The oxygen content of blood is the volume of oxygen carried in each 100 ml blood. It is calculated by:

$$(\text{O}_2 \text{ carried by Hb}) + (\text{O}_2 \text{ in solution}) = (1.34 \times \text{Hb} \times \text{SpO}_2 \times 0.01) + (0.023 \times \text{PaO}_2)$$

Where:

SO<sub>2</sub> = percentage saturation of Hb with oxygen

Hb = haemoglobin concentration in grams per 100 ml blood

PO<sub>2</sub> = partial pressure of oxygen (0.0225 = ml of O<sub>2</sub> dissolved per 100 ml plasma per kPa, or 0.003 ml per mmHg)

For a normal adult male the oxygen content of arterial blood can be calculated. Given arterial oxygen saturation (SpO<sub>2</sub>) = 100%, Hb = 15 g/100 ml and arterial partial pressure of oxygen (PaO<sub>2</sub>) = 13.3 kPa, then the oxygen content of arterial blood (CaO<sub>2</sub>) is:

$$\text{CaO}_2 = 20.1 + 0.3 = 20.4 \text{ ml/100 ml}$$

Similarly the oxygen content of mixed venous blood can be calculated. Given normal values of mixed venous oxygen saturation (SvO<sub>2</sub>) = 75% and venous partial pressure of oxygen (PvO<sub>2</sub>) = 6 kPa, so:

$$\text{CvO}_2 = 15.2 + 0.1 = 15.3 \text{ ml/100 ml}$$

### Oxygen delivery (DO<sub>2</sub>) and oxygen uptake (VO<sub>2</sub>)

Oxygen delivery is the amount of oxygen delivered to the peripheral tissue, and is obtained by multiplying the arterial oxygen content (CaO<sub>2</sub>) by the cardiac output (Q). For CaO<sub>2</sub> = 20.1 ml/100 ml and Q = 5 l/min:

$$\text{Oxygen delivery (DO}_2\text{)} = 1005 \text{ ml/min}$$

The oxygen returned is given by the product of the mixed venous oxygen content (CvO<sub>2</sub>) and the cardiac output. For CvO<sub>2</sub> = 15.2 ml/100 ml and Q = 5.0 l/min:

$$\text{Oxygen return} = 760 \text{ ml/min}$$

Oxygen uptake is the amount of oxygen taken up by the tissues that can be calculated from the difference between oxygen delivery and the oxygen returned to the lungs in the mixed venous blood. Thus:

$$\begin{aligned}\text{Oxygen uptake (VO}_2\text{)} &= (\text{oxygen delivery}) - (\text{oxygen return}) \\ &= 1005 - 760 \\ &= 245 \text{ ml/min}\end{aligned}$$

***To summarise:***

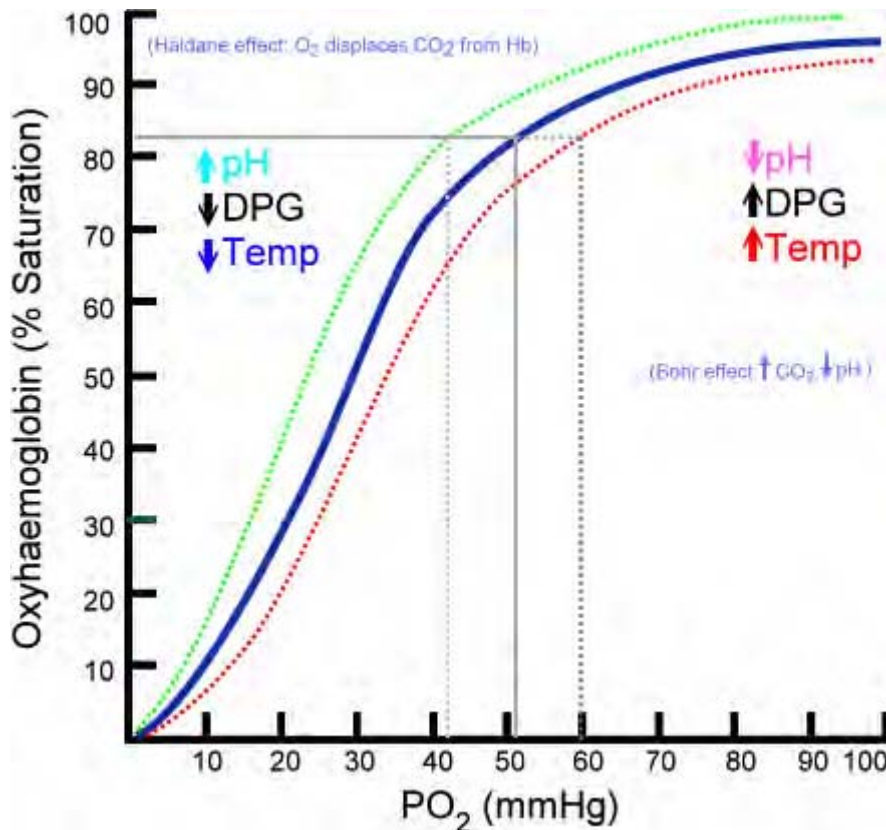
The primary goal of the cardio respiratory system is to deliver adequate oxygen to the tissues to meet their metabolic requirements, a balance between VO<sub>2</sub> and DO<sub>2</sub>. The balance between oxygen uptake by the body tissues and oxygen delivery to them is assessed by:

- The oxygen content of mixed venous blood CvO<sub>2</sub>, which is normally about 15 ml/100 ml
- The extraction ratio, which is the ratio of VO<sub>2</sub> to DO<sub>2</sub> expressed as a percentage. Normally the extraction ratio is about 25% but can double to 50% if tissue demand increases

Both of the above indices are dependent on mixed venous saturation (SvO<sub>2</sub>), and cardiac output.

**Oxygen dissociation curve**

- Sigmoid shaped curve relating the fact that binding of oxygen to the haemoglobin molecule is a cooperative process
- Describes the relationship of saturation of haemoglobin with oxygen at varying partial pressures
- Be aware of the P50 –(point at which Hb is 50% saturated)
- Decreasing pH, increasing temperature, 2,3-DPG and CO<sub>2</sub> tension will cause a right shift of the curve
- Increased pH, and reduction in CO<sub>2</sub> tension, temperature and 2,3-DPG produce a left shift of the curve
- If a right shift occurs the Hb molecule is more likely to offload oxygen to the tissues
- In a left shifted situation the Hb is less likely to release oxygen to the tissues



**Figure 4:** The Oxyhaemoglobin dissociation curve

The sigmoid shape of the oxygen dissociation curve is a result of the cooperative binding of oxygen to the four polypeptide chains. Cooperative binding is the characteristic of a haemoglobin to have a greater ability to bind oxygen after a subunit has bound oxygen. Thus, haemoglobin is most attracted to oxygen when three of the four polypeptide chains are bound to oxygen.

The oxygen dissociation curve is a graph that shows the percent saturation of haemoglobin at various partial pressures of oxygen. Commonly a curve may be expressed with the P50 value. This is a value which tells the pressure at which the red blood cells are fifty percent saturated with oxygen. The purpose of an oxygen dissociation curve is to show the equilibrium of oxyhaemoglobin and nonbonded haemoglobin at various partial pressures. At high partial pressures of oxygen, haemoglobin binds to oxygen to form oxyhaemoglobin. When the blood is fully saturated all the red blood cells are in the form of oxyhaemoglobin. As the red blood cells travel to tissues deprived of oxygen the partial pressure of oxygen will decrease. Consequently, the oxyhaemoglobin releases the oxygen to form haemoglobin.

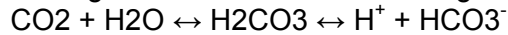
#### Factors that Influence Oxygen Binding

- Temperature- Increasing the temperature denatures the bond between oxygen and haemoglobin, which increases the amount of oxygen and haemoglobin and decreases the concentration of oxyhaemoglobin (Schmidt-Nielsen, 1997). The ODC shifts to the right.

- pH- A decrease in pH by addition of carbon dioxide or other acids causes a Bohr Shift. A Bohr shift is characterized by causing more oxygen to be given up as oxygen pressure increases. The ODC shifts to the right.

#### *The Bohr Effect*

This describes the affect that CO<sub>2</sub> has on influencing the release of oxygen to the tissues. On entering red blood cells the following reaction occurs:



An increase in H<sup>+</sup> will cause an acidosis and therefore encourage the release of oxygen from Hb. In the lungs where the CO<sub>2</sub> is being removed, the alkalosis will encourage the uptake of oxygen.

- Organic Phosphates: 2,3-diphosphoglycerate (2,3-DPG) is a substance made in the red blood cells. It controls the movement of oxygen from red blood cells to body tissues. Haemoglobin uses 2,3-DPG to control how much oxygen is released once the blood gets out into the tissues. The more 2,3-DPG in the cell, the more oxygen is delivered to body tissues. 2,3 DPG binds to haemoglobin which rearranges the haemoglobin into the T-state, thus decreasing the affinity of oxygen for haemoglobin (T and R State). The ODC shifts to the right.
- Carbon monoxide (CO) interferes with the O<sub>2</sub> transport function of blood by combining with Hb to form carboxyhaemoglobin (COHb). CO has about 240 times the affinity of O<sub>2</sub> for Hb. For this reason, small amounts of CO can tie up a large proportion of the Hb in the blood, thus making it unavailable for O<sub>2</sub> carriage. If this happens, the Hb concentration and PO<sub>2</sub> of blood may be normal, but its O<sub>2</sub> concentration is grossly reduced. The presence of COHb also shifts the O<sub>2</sub> dissociation curve to the left, thus interfering with the unloading of O<sub>2</sub>. This is an additional feature of the toxicity of CO.

### **Hyperbaric oxygen therapy (HBOT)**

This is oxygen therapy at greater than atmospheric pressure, usually 2-3 atmospheres, HBOT increases the amount of dissolved O<sub>2</sub> in the blood according to *Henry's law*. In 100 ml blood, 0.3 ml O<sub>2</sub> dissolves at PO<sub>2</sub> of 13.3 kPa (100mmHg). Thus for 100% O<sub>2</sub> at 3 atmospheres, dissolved O<sub>2</sub> = 5.7 ml. HBOT may be used in the treatment of carbon monoxide poisoning.

### **Carbon dioxide transport**

Carbon dioxide is carried in the blood in 3 ways:

- As bicarbonate – 90%
- As dissolved CO<sub>2</sub> – 5%
- As carbamino compounds – 5%

Carbamino compounds are formed by the reaction of the CO<sub>2</sub> with terminal amino groups of proteins and side chains of arginine and lysine. Haemoglobin is essential for this process to occur since it has 4 amino groups per molecule. Albumin also provides amino groups but only 1 per molecule.

### The Haldane effect

This phenomenon refers to the increased ability of blood to carry CO<sub>2</sub> when haemoglobin is deoxygenated. Deoxyhaemoglobin is 3.5 times more effective than oxyhaemoglobin in forming carbamino compounds.

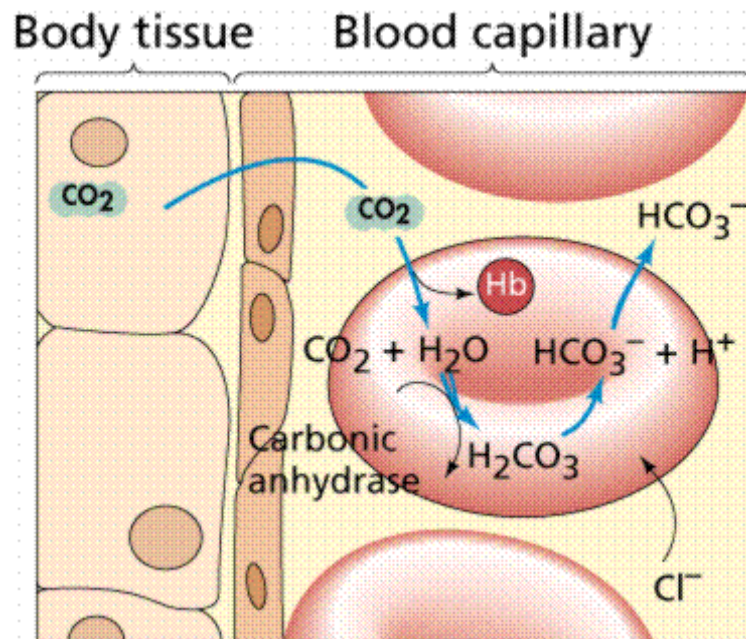


Figure 5: Carbon dioxide transport in blood

### Ventilation perfusion Relationships

As mentioned earlier any discrepancy between ventilation and blood flow in the lung will result in V/Q mismatch and potentially dangerous irregularities in gas exchange. If flow of blood to the lung units is to match that of ventilation to the same unit then the ratio of ventilation to perfusion should be in a ratio of 1:1. If the lung is being underventilated but perfused as normal then we say that the V/Q ratio is <1. If the lung is underperfused then the V/Q is >1.

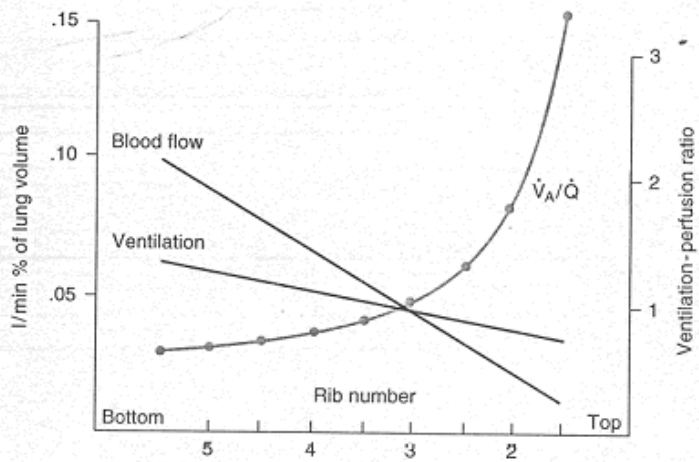
Even in a normal lung the V/Q ratio is not uniformly 1 throughout the lung as perfusion and ventilation both have favoured parts of the lung.

#### *Differences between the apices and bases of the lungs:*

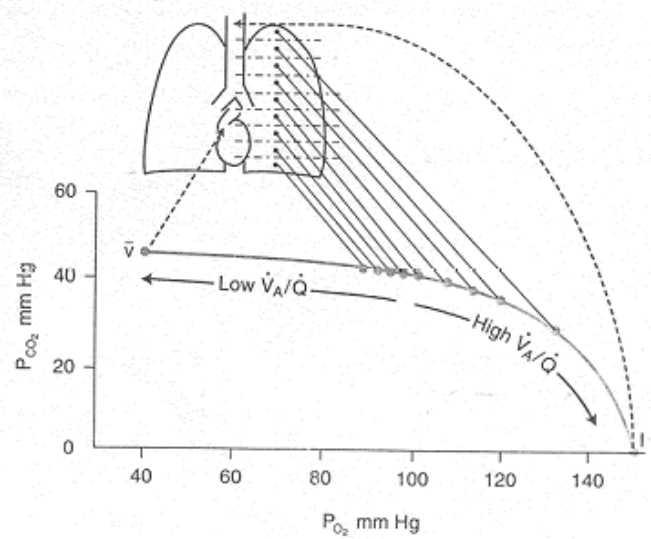
At the apices there is less ventilation than the bases as alveoli are already very stretched however there is proportionally less perfusion therefore the overall V/Q ratio is higher compared to the base of the lung.

Blood flow is directly affected by gravity and naturally has a tendency to flow to the bases of the lungs thus V/Q ratios towards the lower segments of the lung are usually greater than 1.

The vertical change in V/Q ratios in the lung is because although both ventilation and perfusion increase from top to bottom of the lung, perfusion increases much quicker than ventilation. Thus the V/Q ratio at the top of the lung is 3.3 whereas at the bases it is around 0.6. See the following illustration (figure 6).



**Figure 5-8.** Distribution of ventilation and blood flow down the upright lung (compare Figures 2-7 and 4-7). Note that the ventilation-perfusion ratio decreases down the lung.



**Figure 5-9.** Result of combining the pattern of ventilation-perfusion ratio inequality shown in Figure 5-8 with the effects of this on gas exchange as shown in Figure 5-7. Note that the high ventilation-perfusion ratio at the apex results in a high  $P_{O_2}$  and low  $P_{CO_2}$  there. The opposite is seen at the base.

**Figure 6: Ventilation perfusion relationships in the lungs**

**Alveolar –Arterial P<sub>O2</sub> gradient**

The value for the A-a gradient gives the clinician some idea about the amount of VQ mismatch and shunt that is present in the lungs. A typical normal value would be around 0.5-1 KPa (5mmHg) though values up to around 15mmHg may be accepted. It is calculated as  $PAO_2 - PaO_2$ . The  $PAO_2$  is calculated using the alveolar gas equation.

## Shunt

True shunt refers to a  $VQ = 0$ . That is to say that blood has passed through areas of the lung where no ventilation is occurring. As discussed earlier  $VQ$  mismatch is also referred to as shunt. Blood passes through areas of the lung which are poorly ventilated ie  $VQ < 1$ .

Physiological shunt refers to the amount of venous admixture which is directly added to main circulatory blood without having passed through the oxygenating mechanism of the lung. Blood from the bronchial veins draining the lung parenchyma and the thebesian veins draining the cardiac muscle represent the physiological shunt (around 5% of cardiac output.)

The shunt equation allows calculation of the amount of shunt present in an individual subject.

### The Shunt Equation:

$Q_s$  = Shunted blood flow

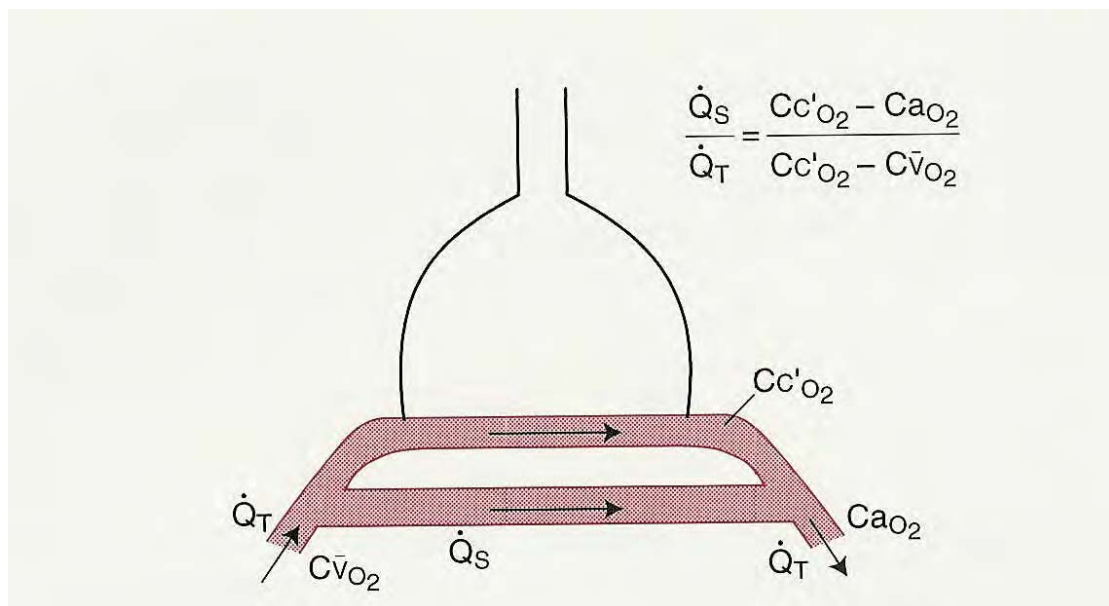
$Q_t$  = Cardiac output

$Q_t - Q_s$  = Blood flow through the lungs minus the shunted blood

$CcO_2$  = Oxygen content of end pulmonary capillary blood

$CaO_2$  = Oxygen content of arterial blood

$CvO_2$  = Oxygen content of mixed venous blood



**Figure 7:** A visualization of the shunt equation

The amount of oxygen leaving the lungs is  $Q_t \times CaO_2$ . This is equal to the shunted blood flow plus the oxygen content from the lung which would be:

$$(Q_s \times CvO_2) + (Q_t - Q_s) \times CcO_2$$

(shunt flow  $\times$  mixed venous  $O_2$  content + pulmonary capillary flow  $\times$  pulmonary capillary  $O_2$  content).

When these equations are rearranged it provides the classic shunt equation:

$$Q_s/Q_t = CcO_2 - CaO_2 / CcO_2 - CvO_2$$

### **Key points**

- The amount of oxygen inhaled is greatly different from the amount reaching the mitochondria
- The oxygen cascade describes the fall in oxygen as it passes from the air to the mitochondria
- Diffusion of gas is affected by molecular size, surface area and thickness of diffusion barrier and concentration gradient of the gas
- Oxygen content in the blood can be calculated by the flux equation
- CO<sub>2</sub> is mainly carried as bicarbonate in the blood
- Deoxygenated haemoglobin is more effective at carrying CO<sub>2</sub> than oxygenated haemoglobin

### **Clinical points**

- CO, Hb saturation and haemoglobin concentration are the prime factors affecting oxygen delivery
- These factors can be manipulated to optimise a patient
- Insertion of haemodynamic monitoring, fluid therapy, transfusion, supplemental oxygen therapy and the correct use of inotropes are the key components in optimisation strategies to improve oxygen delivery

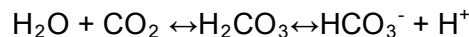
### **ACID-BASE EQUILIBRIUM**

Maintenance of stable pH in body fluids is necessary for normal enzyme activity, ion distribution and protein structure. Normally, blood pH is maintained at 7.35-7.45 (hydrogen ion (H<sup>+</sup>) concentration 35-45 nmol/l); intracellular pH changes with extracellular pH. During normal metabolism of neutral substances, organic acids are produced which generate hydrogen ions.

Maintenance of pH depends on:

- Buffers in tissues and blood, which minimise the increase in H<sup>+</sup> concentration.
- Regulation by kidneys and lungs; the kidneys excrete about 60-80mmol and the lungs about 15-20 000 mmol H<sup>+</sup> per day.

Because of the relationship between CO<sub>2</sub>, carbonic acid, bicarbonate (HCO<sub>3</sub><sup>-</sup>) and H<sup>+</sup>, and the ability to excrete CO<sub>2</sub> rapidly from the lungs, respiratory function is important in acid-base balance.



Thus hyper- and hypoventilation cause alkalosis and acidosis respectively. Similarly, hyper- or hypoventilation may compensate for non-respiratory acidosis or alkalosis respectively, by returning pH towards normal.



## PATHOPHYSIOLOGY

### Definition of acute and chronic respiratory failure and assessment of severity

Respiratory failure develops when the rate of gas exchange between the atmosphere and blood is unable to match the body's metabolic demands. It is diagnosed when the patient loses the ability to provide sufficient oxygen to the blood and develops hypoxemia or when the patient is unable to adequately ventilate and develops hypercarbia and hypoxemia.

Hypoxemia is caused by one of the following abnormalities:

- Alveolar ventilation (V) and pulmonary perfusion (Q) mismatch
- Intrapulmonary shunt
- Hypoventilation
- Abnormal diffusion of gases at the alveolar-capillary interface
- Reduction in inspired oxygen concentration
- Increased venous desaturation with cardiac dysfunction plus one or more of the above 5 factors

It is defined as a  $P_aO_2 < 8$  kPa (60 mmHg) and subdivided into two types according to the  $P_aCO_2$  level.

It can be divided into two main categories:

**Type I or "acute hypoxaemic" respiratory failure**, in which the  $P_aO_2$  is  $< 8$  kPa and the  $P_aCO_2$  is normal or low. Occurs with diseases that damage lung tissue, with hypoxaemia due to right-left shunts or V/Q mismatch.

**Type II or "ventilatory failure"**, with hypoxia ( $P_aO_2 < 8$  kPa) and a  $P_aCO_2$  of  $> 6$  kPa. Occurs when alveolar ventilation is insufficient to excrete the volume of  $CO_2$  being produced by tissue metabolism.

Inadequate alveolar ventilation due to reduced respiratory effort, inability to overcome an increased resistance to ventilation, failure to compensate for an increase in dead space and/or  $CO_2$  production.

The frequency of acute respiratory failure is higher in infants and young children than in adults for several reasons. This difference can be explained by defining anatomic compartments and their developmental differences in paediatric patients that influence susceptibility to acute respiratory failure.

These include the extrathoracic airway, the intrathoracic airways and lung, and the respiratory pump including the nervous system with central control (ie, cerebrum, brainstem, spinal cord, peripheral nerves), respiratory muscles, and chest wall (differences not further covered here).

## Assessment of severity

### History

- Any risk factors for respiratory failure? Young age; history of prematurity; immunodeficiency; and chronic pulmonary, cardiac, or neuromuscular disease (eg, cystic fibrosis, bronchopulmonary dysplasia, unrepaired congenital heart disease, or spinal muscular atrophy [SMA]).
- Does the patient have a cough, rhinorrhea, or other symptoms of an upper respiratory tract infection to define an etiology?
- Does the patient have a fever or signs of sepsis? Several infections can lead to respiratory failure because of a systemic inflammatory response, pulmonary edema, or acute respiratory distress syndrome (ARDS)..
- How long have the symptoms been present? The natural course of a respiratory illness must be considered. Respiratory syncytial virus (RSV) infections frequently worsen over the initial 3-5 days before improvement occurs.
- Does the patient have any pain? Pain can suggest pleuritis or foreign-body aspiration.
- Does the patient have a possible or known exposure to sedatives (eg, benzodiazepines, tricyclic antidepressants, narcotics) or has he or she recently undergone a procedure that used general anesthesia? This could suggest hypoventilation.
- Does the patient have symptoms of neuromuscular weakness or paralysis? What is the distribution of weakness and duration of symptoms to narrow the differential diagnosis?
  - Bulbar dysfunction suggests myasthenia gravis.
  - Distal weakness that progresses upward suggests Guillain-Barré syndrome.
  - Apnea associated with a traumatic injury suggests a cervical spinal cord injury.
- Does the patient have a history suggestive of a stroke or seizure?
- Does the patient have a history of headaches? With chronic hypercapnia, headaches typically occur at night time or upon the patient's awakening in the morning.

### Physical

During physical examination, clinicians should avoid interfering with the patient's mechanisms for compensation. Children often find the most advantageous position for breathing. Children with respiratory distress commonly sit up and lean forward to improve leverage for the accessory muscles and to allow for easy diaphragmatic movement. Children with epiglottitis sit upright with their necks extended and heads forward while drooling and breathing through their mouths. Making a child lie down or making him or her cry during an otoscopic examination can precipitate acute respiratory failure.

- General appearance
  - Does the patient appear well or sick?
  - Is the patient cyanotic?
- Respiratory rate, quality, and effort

- Bradypnoea is most often observed in central control abnormalities. Slow and large tidal volume breaths also minimize turbulence and resistance in significant extrathoracic airway obstruction (eg, epiglottitis).
- The fast and shallow breathing of tachypnea is most efficient in intrathoracic airway obstruction. It decreases dynamic compliance of the lung.
- Auscultation provides information about the symmetry and quality of air movement. Evaluate the patient for stridor, wheezing, crackles, and decreased breath sounds (eg, alveolar consolidation, pleural effusion).
- Grunting is an expiratory sound made by infants as they exhale against a closed glottis. It is an attempt to increase functional residual capacity and lung volume. This attempt is made in order to raise functional residual capacity above the critical closing volume and to avoid alveolar collapse. This is a concerning physical finding.
- Assess for accessory muscle use and nasal flaring. Suprasternal and intercostal retractions are present when highly negative pleural pressures are required to overcome airway obstruction or stiff lungs.
- Chest wall findings: Evaluate for paradoxical movement of the chest wall. In the presence of abnormalities of the pulmonary pump, paradoxical chest-wall movement occurs because of instability of the chest wall associated with absent intercostal muscle use. As the diaphragm contracts and pushes abdominal contents out, the chest wall retracts inward instead of expanding normally.
- Cardiovascular findings
  - Tachycardia and hypertension may occur secondary to increased circulatory catecholamine levels.
  - A gallop is suggestive of myocardial dysfunction leading to respiratory failure.
  - Peripheral vasoconstriction may develop secondary to respiratory acidosis.
- Neurologic findings
  - Patients may be lethargic, irritable, anxious, or unable to concentrate.
  - The inability to breathe comfortably creates anxiety, and superimposed hypoxemia and hypercapnia accentuates any restlessness and agitation. Increased agitation may indicate a general worsening of the patient's condition.

The most sensitive indicator of increasing respiratory difficulty is a rising respiratory rate. Tidal volume is a less sensitive indicator.

Minute ventilation rises initially in acute respiratory failure and then falls precipitously only at a late stage, when the patient is exhausted. Vital capacity is often a better guide to deterioration and is particularly useful in patients with respiratory inadequacy due to neuromuscular problems such as Guillain-Barre syndrome, where the vital capacity decreases as weakness increases

## Causes of respiratory failure, prevention and management

The most common reasons for respiratory failure in the pediatric population are divided into anatomic compartments, as follows:

- Extrathoracic airway
  - Acquired lesions
    - Infections (eg, retropharyngeal abscess, Ludwig angina, laryngotracheobronchitis, bacterial tracheitis, peritonsillar abscess)
    - Traumatic causes (eg, postextubation croup, thermal burns, foreign-body aspiration)
    - Other (eg, hypertrophic tonsils and adenoid)
  - Congenital lesions
    - Subglottic stenosis
    - Subglottic web or cyst
    - Laryngomalacia
    - Tracheomalacia
    - Vascular ring
    - Cystic hygroma
    - Craniofacial anomalies
- Intrathoracic airway and lung
  - Acute respiratory distress syndrome (ARDS)
  - Asthma
  - Aspiration
  - Bronchiolitis
  - Bronchomalacia
  - Left-sided valvular abnormalities
  - Pulmonary contusion
  - Near drowning
  - Pneumonia
  - Pulmonary edema
  - Pulmonary embolus
  - Sepsis
- Respiratory pump
  - Chest wall
    - Diaphragm eventration
    - Diaphragmatic hernia
    - Flail chest
    - Kyphoscoliosis
  - Respiratory muscles
    - Duchenne muscular dystrophy
    - Guillain-Barré syndrome
    - Infant botulism
    - Myasthenia gravis
    - Spinal cord trauma

- SMA
- Central control
  - CNS infection
  - Drug overdose
  - Sleep apnea
  - Stroke
  - Traumatic brain injury

## Management

Management of acute respiratory failure begins with a determination of the underlying etiology. While supporting the respiratory system and ensuring adequate oxygen delivery to the tissues, **initiate an intervention specifically defined to correct the underlying condition**. For example, a patient with status asthmaticus is given supplemental oxygen to treat hypoxemia, but corticosteroids and beta-agonist drugs are also given to treat the underlying pathology.

While treating the underlying cause, consider:

- Extra-thoracic airway support (nasopharyngeal/ oropharyngeal airway)
- Endotracheal intubation
- Oxygen therapy
- Lung and respiratory pump support
- Adjunctive therapies
  - Prone position
  - iNO
  - exogenous surfactant
  - ECMO

## Effect of oxygen therapy

Used to:

- Correct hypoxaemia due to V/Q mismatch, hypoventilation or impaired alveolar gas diffusion. Only partially corrects hypoxaemia due to shunt.
- Increase pulmonary O<sub>2</sub> reserves eg in case of apnoea, hypoventilation etc
- Increase the amount of dissolved oxygen eg in anaemia, cyanide poisoning and CO poisoning.  
Other uses include reduction of pulmonary hypertension

Methods of administration:

- High-flow (>15 L/min) oxygen delivery systems include a Venturi-type device that places an adjustable aperture lateral to the stream of oxygen. Oxygen is mixed with entrained room air, and the amount of air is adjusted by varying the aperture size. The oxygen hoods and tents also supply high gas flows.
- Low-flow (<6 L/min) oxygen delivery systems include the nasal cannula and simple face mask.
  - Humidified high-flow nasal cannula (HHFNC)

- Although no single universally accepted definition is available for what constitutes HHFNC therapy in neonates, a widely used and reasonable definition is optimally warmed (body temperature) and humidified respiratory gases delivered by nasal cannula at flow rates of 2-8 L/min.<sup>2</sup>
- Continuous positive airway pressure (CPAP)
  - CPAP may be indicated if lung disease results in severe oxygenation abnormalities such that an FiO<sub>2</sub> greater than 0.6 is needed to maintain a PaO<sub>2</sub> greater than 60 mm Hg.
  - CPAP in pressures from 3-10 cm H<sub>2</sub>O is applied to increase lung volume and may redistribute pulmonary edema fluid from the alveoli to the interstitium.
  - CPAP enhances ventilation to areas with low V/Q ratios and improves respiratory mechanics.
  - If a high concentration of FiO<sub>2</sub> is needed and if the patient does not tolerate even short periods of discontinued airway pressure, positive-pressure ventilation should be administered.
- Noninvasive positive-pressure ventilation (NPPV)
  - Noninvasive mechanical ventilation refers to assisted ventilation provided with nasal prongs or a face mask instead of an endotracheal or tracheostomy tube.
  - This therapy can be administered to decrease the work of breathing and to provide adequate gas exchange.
  - NPPV can be given by using a volume ventilator, a pressure-controlled ventilator, or a device for bilevel positive airway pressure (BIPAP or bilevel ventilator).
- Conventional mechanical ventilation
  - Mechanical ventilation increases minute ventilation and decreases dead space. This approach is the mainstay of treatment for acute hypercapnia and severe hypoxemia.
  - A primary strategy for mechanical ventilation should be the avoidance of high peak inspiratory pressures and the optimization of lung recruitment.
  - In adults with acute respiratory distress syndrome (ARDS), a strategy to provide low tidal volume (6 mL/kg) with optimized positive end-expiratory pressure (PEEP) offers a substantial survival benefit compared with a strategy for high tidal volume (12 mL/kg).
  - According to the permissive hypercapnia strategy in ARDS, arterial CO<sub>2</sub> is allowed to rise to levels as high as 100 mm Hg while the blood pH is maintained at greater than 7.2 by means of the intravenous administration of buffer solutions. This is done to limit inspiratory airway pressure to values less than 35 cm H<sub>2</sub>O.
  - PEEP should be applied to a point above the inflection pressure such that alveolar distention is maintained throughout the ventilatory cycle.
  - Conventional mechanical ventilation optimizes lung recruitment, increases mean airway pressure and functional residual capacity, and reduces atelectasis between breaths.
- Nonconventional modes of ventilation
  - High-frequency oscillatory ventilation (HFOV)
  - HFOV combines small tidal volumes (smaller than the calculated airway dead space) with frequencies of more than 1 Hz to minimize the effects of elevated peak and mean airway pressures.

- HFOV has proven benefit in improving the occurrence and treatment of air-leak syndromes associated with neonatal and pediatric acute lung injury.

## **Use of Nitric Oxide**

### *Inhaled nitric oxide (iNO)*

- Produced endogenously from action of enzyme NO synthetase on arginine. Relaxes vascular smooth muscle by binding to heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine monophosphate (cGMP), which then leads to vasodilation. When inhaled, decreases pulmonary vascular resistance and improves lung blood flow.
- This therapy is relatively safe because hemoglobin inactivates it quickly and because does not cause systemic vasodilation leading to hypotension.
- Methemoglobin and nitrogen dioxide (NO<sub>2</sub>) levels should be monitored.
- Inhaled NO is being studied for use in type I respiratory failure; in 1999, the FDA approved its use in neonates with hypoxic respiratory failure and evidence of pulmonary hypertension.

### **Paediatric Use**

- 20 ppm by ventilator initially; not to exceed 80 ppm; most children respond at 20 ppm and can be weaned to low doses; effect of pulmonary vasodilatation may be observed at 5 ppm
- Administer by using system that does not cause generation of excessive inhaled NO<sub>2</sub> and that measures concentrations of NO in breathing gas, with constant concentration throughout respiratory cycle

### **Interactions**

- Concomitant administration with NO-donor compounds (eg, nitroprusside, nitroglycerin) may have additive effects and increase risk of methemoglobinemia.

### **Precautions**

- Abrupt discontinuation may lead to worsening oxygenation and increasing pulmonary artery pressure (PAP); toxic effects include methemoglobinemia and pulmonary inflammation from reactive nitrogen intermediates; caution in thrombocytopenia, anemia, leukopenia, or bleeding disorders; monitor for PaO<sub>2</sub>, methemoglobin, and NO<sub>2</sub>; abrupt withdrawal causes rebound pulmonary hypertension.

## INVESTIGATIONS

### Interpretation of blood gas

#### *Introduction*

Acid base disturbances are indicators of serious underlying pathology, rather than being the pathology themselves. Arterial blood gas examination is a useful investigation in patients with suspected respiratory or metabolic disease and serial blood gas investigation can monitor the progress or treatment of the underlying disease. The blood gas should be considered in conjunction with the patient's clinical condition. It does have a limitation because we only measure the extracellular fluid and do not know what the intracellular pH and gas tensions are.

#### *Clinical significance*

The bicarbonate buffer system is the most important buffer system in the body and is the one measured with the blood gas. The lungs can adjust CO<sub>2</sub> exhalation, and the kidneys can adjust HCO<sub>3</sub><sup>-</sup> excretion or retention, so the precise ratio of acid to base can be maintained and adjusted.

The respiratory system (CO<sub>2</sub>) can make rapid adjustments within minutes. The metabolic component (renal, bicarbonate) takes hours or even days to adjust.

These two systems work together to maintain a fine balance. They aim to keep the extracellular pH 7.4 as this is the optimal environment for most metabolic activity such as chemical reactions catalysed by enzymes and transport of substances across cell membranes.

Pathological processes such as tissue hypoxia, renal failure, hypoventilation will all disrupt the normal acid base balance. If there is an abnormality in one part of the system, the other part will attempt to compensate and correct the pH.

Acid base disturbances and some examples of how they may occur:

<i>Acid base disturbances</i>		
Respiratory acidosis	PaCO <sub>2</sub> increased	This occurs when there is inadequate ventilation and CO <sub>2</sub> production is greater than CO <sub>2</sub> elimination. It may occur with airway obstruction, respiratory depression due to drugs or head injury, lung diseases, etc
Respiratory alkalosis	PaCO <sub>2</sub> decreased	This occurs with hyperventilation. The hyperventilation may be in response to hypoxaemia and hypoxic respiratory drive. The lungs are more efficient at eliminating CO <sub>2</sub> than at absorbing O <sub>2</sub> so patients with diseased lungs frequently have hypoxaemia with a normal or low CO <sub>2</sub> . Mechanical ventilation with a large minute volume also leads to respiratory alkalosis



Metabolic acidosis	$\text{HCO}_3^-$ decreased (base deficit)	<p>Multiple aetiologies</p> <ul style="list-style-type: none"> <li>Loss of bicarbonate due to GIT losses or chronic renal disease (Normal anion gap)</li> <li>Addition of inorganic acids such as diabetic ketoacidosis, lactic acidosis associated with tissue hypoxia, salicylate, ethylene glycol and other toxins, decreased acid excretion in renal failure (increased anion gap)</li> </ul>
Metabolic alkalosis	$\text{HCO}_3^-$ increased (base excess)	Occurs with loss of gastric acid (e.g. pyloric stenosis) and diuretic therapy. Metabolic alkalosis is commonly associated with low serum chloride
Mixed and respiratory acidosis	$\text{PaCO}_2$ increased metabolic and $\text{HCO}_3^-$ decreased	This is very dangerous and may occur in severe diseases such as septic shock, multiple organ dysfunction, cardiac arrest

Compensatory mechanisms will tend to restore the pH towards normal even though the  $[\text{HCO}_3^-]$  and the  $\text{PCO}_2$  are not restored until the primary disturbance is corrected. The compensatory mechanisms should not overshoot. For example a metabolic acidosis will drop the pH to  $<7.4$ . If there is respiratory compensation the pH will return towards normal but will not overshoot to become  $>7.4$ .

The primary defect (metabolic or respiratory) will go in the same direction as the pH. That is towards an acidosis if the pH is low or towards an alkalosis if the pH is high.

The compensatory effect (respiratory or metabolic) will go in the opposite direction. The compensation will bring the pH back towards normal but it will never overshoot and will seldom actually reach normal.

For example: if there seems to be a metabolic acidosis and a respiratory alkalosis, the pH tells you which one is primary and which one is compensatory. If the pH is low, the primary defect is metabolic acidosis with respiratory compensation. If the pH is high, the primary defect is respiratory alkalosis with metabolic compensation.

<i>Stepwise interpretation of the blood gas</i>		
1	Is the overall picture normal, acidaemia, alkalaemia?	<p>pH <math>&lt; 7.35</math> = acidaemia [...go to step 2]</p> <p>pH <math>&gt; 7.45</math> = alkalaemia [... go to step 5]</p>
2	If there is an acidaemia: is the primary defect metabolic or respiratory or mixed?	<p><math>\text{CO}_2</math> high = respiratory acidosis [...3]</p> <p>Bicarbonate low or BE negative = metabolic acidosis. [...4]</p> <p>Both of the above = mixed metabolic and respiratory acidosis.</p>
3	If there is respiratory acidosis: is there metabolic compensation?	The $\text{CO}_2$ is high (resp acidosis) but the metabolic component is going in the opposite direction (BE or SB high, towards metabolic alkalosis) then there is metabolic compensation.

4	If there is metabolic acidosis: is there respiratory compensation?	BE is negative (metabolic acidosis) but the respiratory component is going in the opposite direction (CO <sub>2</sub> low, towards resp alkalosis), then there is respiratory compensation.
5	If there is an alkalaemia, is the primary defect respiratory or metabolic?	The primary defect will go in the same direction as the pH (towards alkalosis): respiratory alkalosis will have low CO <sub>2</sub> metabolic alkalosis will have high SB and positive BE.
6	If metabolic or respiratory alkalosis, is there any compensation by the other one?	Same principles as above
7	Look at the oxygenation	Is the PO <sub>2</sub> consistent with the FiO <sub>2</sub> ? If it is lower than expected, it either indicates lung disease, right to left shunt, or venous sample. (A venous sample usually has PO <sub>2</sub> < 40mmHg, saturation < 75%). The lung is much more efficient at eliminating CO <sub>2</sub> than absorbing oxygen so lung disease will show in the low PO <sub>2</sub> but the PCO <sub>2</sub> is often normal or even low. If the CO <sub>2</sub> is very high, the O <sub>2</sub> will also be low.
8	Summarise the interpretation	eg. There is a metabolic acidosis (because the pH is low and BE is negative) with respiratory compensation (because the PCO <sub>2</sub> is low).
9	Try to establish the cause	

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