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# The Physiology of Oxygen Delivery

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**Summary**

In order to survive, humans have to be able to extract oxygen from the atmosphere and transport it to their cells where it is utilised for essential metabolic processes. Some cells can produce energy without oxygen (anaerobic metabolism) for a short time, although it is inefficient. Other organs, for example the brain, are made up of cells that can only produce the energy necessary for survival in the presence of a continual supply of oxygen (aerobic metabolism). Tissues differ in their ability to withstand anoxia (lack of oxygen) - the brain and the heart are the most sensitive.

## OXYGEN TRANSPORT FROM THE AIR TO THE TISSUES

Oxygen is transported from the air that we breathe to each cell in the body. In general, gases move from an area of high concentration (or pressure) to areas of low concentration (or pressure). If there is a mixture of gases in a container, the pressure of each gas (the partial pressure, indicated by the symbol P) is equal to the pressure that each gas would produce if it occupied the container alone. The total pressure of the gas mixture is the sum of the partial pressures of all the individual gases.

### Oxygen cascade

Oxygen moves down the pressure or concentration gradient from a relatively high level in air, to the levels in the respiratory tract and then alveolar gas, the arterial blood, capillaries and finally the cell (see Figure 1). The $PO_2$ reaches the lowest level (1-1.5kPa) in the mitochondria, the structures in cells responsible for energy production. This decrease in $PO_2$ from air to the mitochondrion is known as the oxygen cascade. The successive steps down in $PO_2$ occur for physiological reasons, but they can be influenced by pathological states, for instance hypoventilation, ventilation/perfusion inequality, or diffusion abnormality, that will result in tissue hypoxia.

### Atmosphere to alveolus

The air (atmosphere) around us has a total pressure of 101kPa (1 atmosphere of pressure = 760mmHg = 101kPa). Air is made up of 21% oxygen, 78% nitrogen and small quantities of $CO_2$, argon and helium. The pressure exerted by oxygen and nitrogen, when added together, approximates to atmospheric pressure. The pressure of oxygen ($PO_2$) of dry air at sea level is therefore 21.2kPa (21/100 x 101 = 21.2kPa). However by the time the inspired air reaches the trachea it has been warmed and humidified by the upper respiratory tract. The humidity is formed by water vapour which

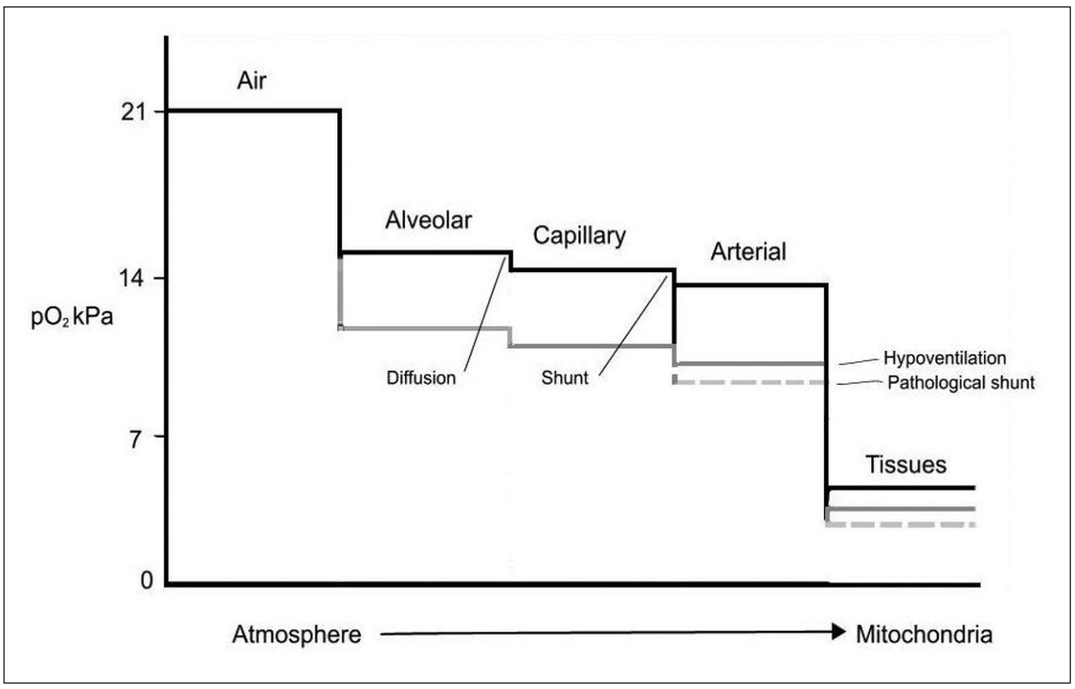


**Figure 1.** *The oxygen cascade. The effects of hypoventilation are shown as the grey line and the effects of a pathological shunt are shown as a dashed line*

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is a gas, so exerts a pressure. At 37°C the water vapour pressure in the trachea is 6.3kPa. Taking the water vapour pressure into account, the $PO_2$ in the trachea when breathing air is (101-6.3) x 21/100 = 19.9kPa. By the time the oxygen has reached the alveoli the $PO_2$ has fallen to about 13.4kPa. This is because the $PO_2$ of the gas in the alveoli ($PAO_2$) is further reduced by dilution with carbon dioxide entering the alveoli from the pulmonary capillaries. The $PAO_2$ can be calculated using the **alveolar gas equation**:

$$PAO_2 = FiO_2 - \frac{PaCO_2}{RQ}$$

Where RQ = the respiratory quotient, the ratio of $CO_2$ production to $O_2$ consumption, usually about 0.8

### Alveolus to blood

Blood returning to the heart from the tissues has a low $PO_2$ (4.3kPa) and travels to the lungs via the pulmonary arteries. The pulmonary arteries form pulmonary capillaries, which surround alveoli. Oxygen diffuses (moves through the membrane separating the air and the blood) from the high partial pressure in the alveoli (13kPa) to the area of lower partial pressure - the blood in the pulmonary capillaries (4.3kPa). After oxygenation, blood moves into the pulmonary veins and returns to the left side of the heart, to be pumped to the systemic tissues. In a 'perfect lung', the $PO_2$ of pulmonary venous blood would be equal to the $PO_2$ in the alveolus (the $PAO_2$). Two main factors cause the $PO_2$ of pulmonary venous blood to be less than the $PAO_2$, that is, to increase the **alveolar:arterial difference**. These are ventilation/perfusion mismatch (either increased deadspace or shunt) and slow diffusion across the alveolar-capillary membrane.

*Ventilation/perfusion (V/Q) mismatch*

In a 'perfect lung' all alveoli would receive an equal share of alveolar ventilation and the pulmonary capillaries that surround different alveoli would receive an equal share of cardiac output – i.e. alveolar minute ventilation and perfusion would be perfectly matched, V/Q = 1. Even in health this is not achieved and at almost all levels in a normal lung there is a relative imbalance of perfusion and ventilation (Figure 2). Perfusion is best at the base of the lung and gradually reduces towards the top of the lung, largely due to the effects of gravity. The alveoli at the base of a normal lung are at a lower resting volume in expiration (at functional residual capacity, FRC), but they are better ventilated (they increase their volume proportionately more) during inspiration. This concept is not intuitive and occurs because our major muscle of inspiration, the diaphragm, lies below

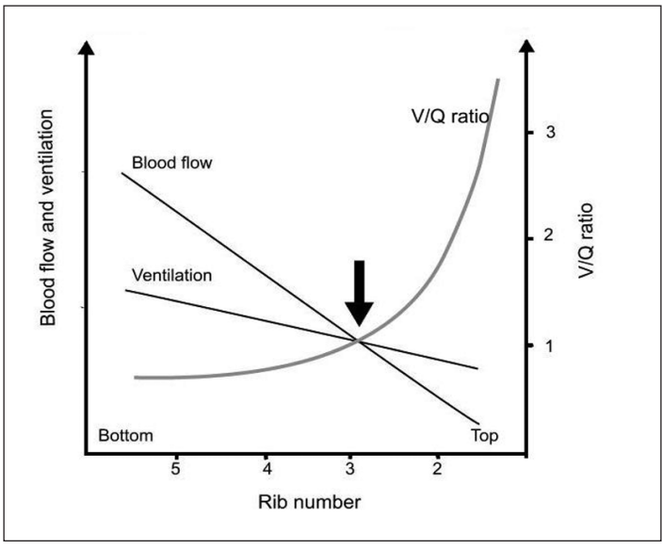


**Figure 2.** *Graph to show perfusion and ventilation in different segments moving up the lung. Arrow indicates area of lung with perfect matching of ventilation to perfusion*

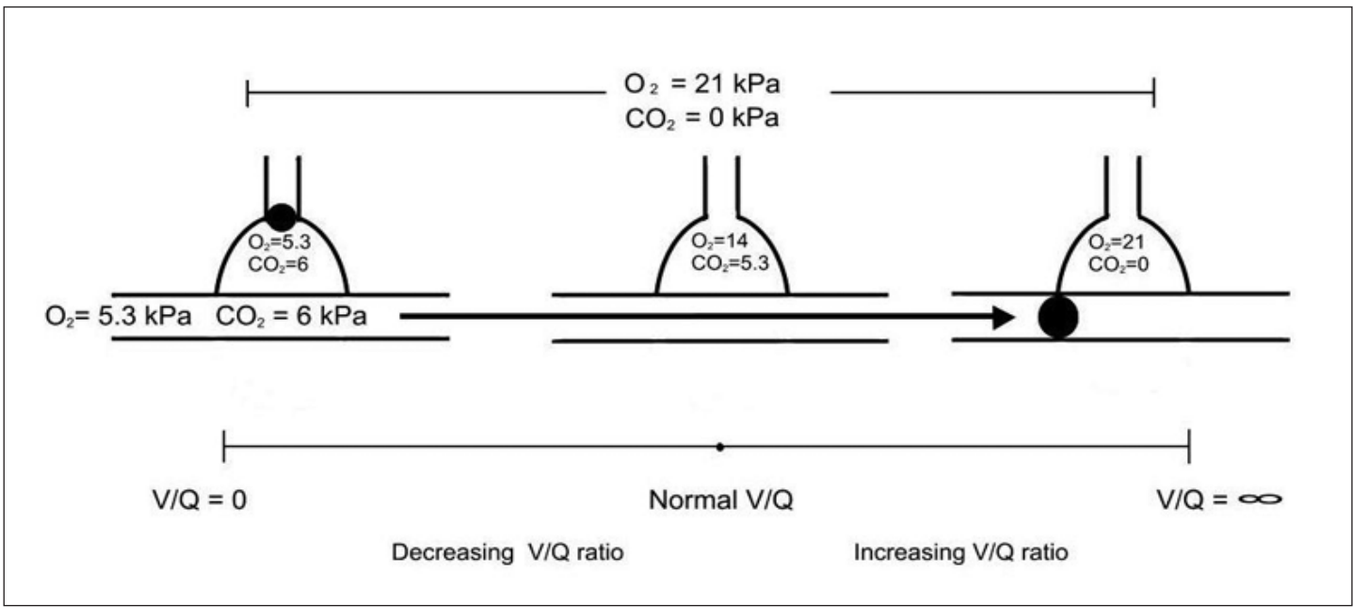


**Figure 3.** *Schematic diagram showing 3 lung units. The ideal situation and the two extremes of V/Q mismatch, i.e. shunt and dead space, are shown*

the lung contributing to better lung compliance towards the base of the lung. Both ventilation and perfusion improve as you move down the lung towards its base, but they are not perfectly matched. Areas at the top of the lung are relatively more ventilated than perfused (the extreme example of this is deadspace, where the lung volume is ventilated but there is insufficient perfusion for gas exchange to occur, V/Q >>1). Areas towards the base are perfused more than ventilated (the extreme example of this is a shunt, V/Q<<1). Both extreme examples of the spectrum of possible V/Q mismatches are illustrated in Figure 3.

Where blood flows past alveoli with no gas exchange taking place (shunt, see Figure 3), well ventilated alveoli (with high $PO_2$ in capillary blood) cannot compensate for the lack of oxygen transfer in the under-perfused alveoli with a low $PO_2$ in the capillary blood. This is because there is a maximum amount of oxygen that can combine with haemoglobin (this is shown by the oxygen-haemoglobin dissociation curve, later). Arterial oxygen, $PaO_2$ is therefore lower than the alveolar oxygen, $PaO_2$.

Lung pathology that exacerbates the physiological shunt includes atelectasis, consolidation of the lung, pulmonary oedema or small airway closure. Pulmonary embolism causes increased physiological deadspace.

*Diffusion*

Oxygen diffuses from the alveolus to the capillary until the $PcO_2$ is equal to that in the alveolus. This process is rapid (about 0.25seconds) and is normally complete by the time the blood has passed about one third of the way along the pulmonary capillary. The total transit time through the capillary is 0.75seconds (see Figure 4a).

In the normal lung, even if the cardiac output and blood flow past the alveoli is increased during exercise, there is enough time for equilibration (Figure 4b). Pulmonary disease may cause an abnormality of the alveolar-capillary membrane, thus impairing transfer of oxygen from the alveolus to the capillary (diffusion abnormality). At rest there may still be time for the $PaO_2$ to equilibrate with alveolar oxygen, but on exercise full oxygen transfer is impossible and hypoxaemia develops (Figure 4c). However, the ability of the lung to compensate is great and problems caused by poor gas diffusion are a rare cause for hypoxia, except with diseases such as alveolar fibrosis.

*Hypoxic pulmonary vasoconstriction*

In order to minimize the detrimental effect that shunt has on oxygenation, the blood vessels in the lung are adapted to vasoconstrict in response to low oxygen levels and therefore reduce blood flow to areas that are underventilated. This is termed hypoxic pulmonary vasoconstriction and reduces the effect of shunt.

## Oxygen carriage by the blood

Oxygen is carried in the blood in two forms. Most is carried combined with haemoglobin (Figure 5), and a small amount is dissolved in the plasma. Each gram of haemoglobin can carry 1.34ml of oxygen when fully saturated. Therefore every litre of blood with a Hb concentration of $15g.dl^{-1}$ can carry about 200ml of oxygen when fully saturated with oxygen (i.e. exposed to a $PO_2$ greater than 13kPa). At this $PO_2$ only 3ml of oxygen will dissolve in each litre of plasma.

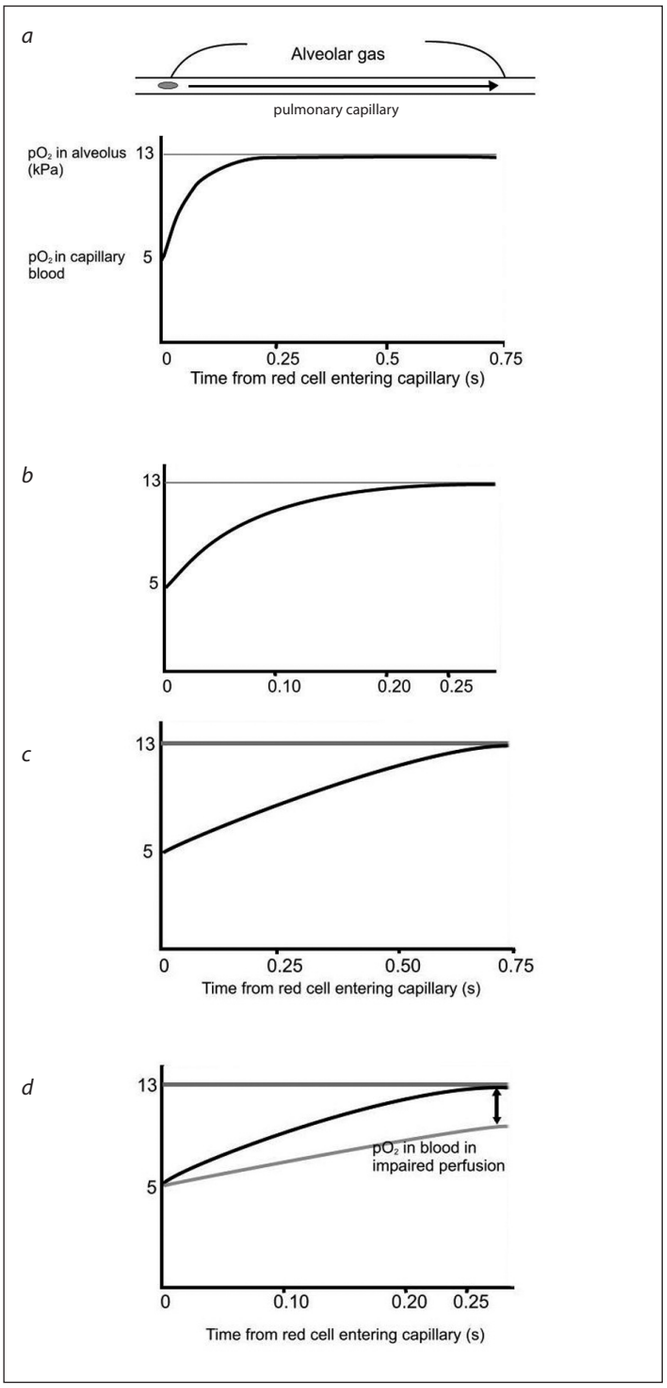


**Figure 4.** *(a) Normal diffusion from alveolus to capillary during passage of blood along the capillary. By 0.25s the red cell haemoglobin is completely saturated and the partial pressure of oxygen in the blood equilibrates with that in the alveolus and therefore diffusion stops. (b) Diffusion of oxygen with increased cardiac output (note the shorter time scale on the x-axis). The red cell may only be in contact with alveolar gas for 0.25s, however this will still allow sufficient time to achieve full saturation. (c) Impaired oxygen diffusion where there is an abnormal alveolar-capillary membrane. Saturation is just achieved at rest (solid line), but there is insufficient time for full saturation when the cardiac output is increased (d). This results in exertional desaturation (arrow)*

If the $PaO_2$ is increased significantly (by breathing 100% oxygen) then a small amount of extra oxygen will dissolve in the plasma (at a rate of 0.025ml $O_2$/100ml of blood/kPa $PO_2$) but there will normally be no significant increase in the amount carried by haemoglobin, as it is already >95% saturated with oxygen.

### Oxygen delivery

When considering the adequacy of oxygen delivery to the tissues, three factors need to be taken into account: haemoglobin concentration, cardiac output and oxygenation.

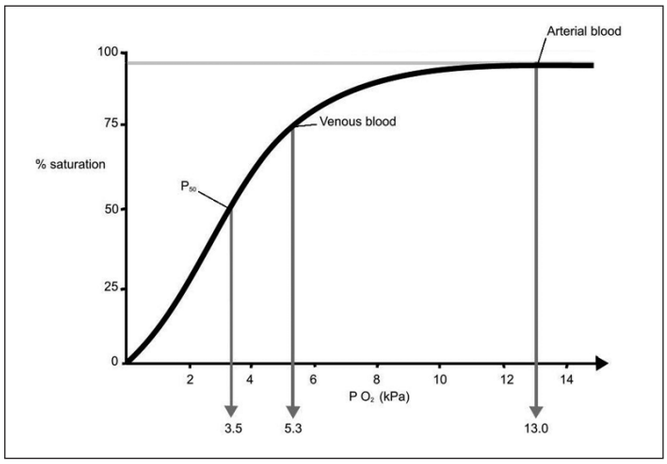


**Figure 5.** *The oxygen-haemoglobin dissociation curve. The sigmoid curve arises because of 'positive cooperativity' of the 4 haemoglobin subunit – when the first subunit binds to oxygen a conformation (shape) change makes it more likely that the second and third subunits will bind to oxygen*

The quantity of oxygen made available to the body in one minute is known as the oxygen delivery:

Oxygen delivery (ml $O_2.min^{-1}$) =

= Cardiac output ($l.min^{-1}$) x Hb concentration ($g.l^{-1}$) x 1.34 (ml $O_2.gHb^{-1}$) x % saturation

= 5000ml.$min^{-1}$ x 200ml $O_2$.1000ml $blood^{-1}$

= 1000ml $O_2.min^{-1}$

### Oxygen consumption

Approximately 250ml of oxygen are used every minute by a conscious resting person (resting oxygen consumption) and therefore about 25% of the arterial oxygen content is used every minute. The haemoglobin in mixed venous blood is about 73% saturated (98% minus 25%).

At rest, oxygen delivery to the cells of the body exceeds oxygen consumption. During exercise, oxygen consumption increases. The increased oxygen requirement is usually provided by an increased cardiac output (as shown in the formula above). A low cardiac output, low haemoglobin concentration (anaemia) or low oxygen saturation will result in reduced tissue oxygen delivery, unless there is a compensatory change in one of the other factors.

If oxygen delivery falls relative to oxygen consumption, the tissues extract more oxygen from the haemoglobin and the saturation of mixed venous blood falls below 70%. Below a certain point, decreased oxygen delivery cannot be compensated for by an increased oxygen extraction, and this results in anaerobic metabolism and lactic acidosis. This situation is known as supply-dependent oxygenation.

## OXYGEN STORES

In spite of our reliance on oxygen, the stores of oxygen in the body are small and would be unable to sustain life for more than a few minutes. If breathing ceases, oxygen stores are limited to the oxygen in the lung and oxygen in the blood. The amount of oxygen in the blood depends on the blood volume and haemoglobin concentration, as described above. The amount of oxygen in the lung is dependent on the lung volume at functional residual capacity (FRC) and the alveolar concentration of oxygen. The FRC is the volume of air (about 3 litres in an adult) that is present in the lungs at the end of a normal expiration; at this volume the elastic recoil of the lung (its tendency to collapse) is balanced by the tendency of the chest wall and diaphragm to resist lung collapse. When breathing air, the total oxygen stores (in blood and lung) are small. The major component of this store is the oxygen bound to haemoglobin (see Table 1); only a small part of these stores can be released without an unacceptable reduction in $PaO_2$ (when haemoglobin is 50% saturated, the $PaO_2$ will have fallen to 3.5kPa). Breathing 100% oxygen causes a large increase in the total oxygen stores as the FRC fills with oxygen. The major component of the store is now in the lung and 80% of this oxygen can be used without any reduction in haemoglobin saturation ($PaO_2$ is still about 14kPa). This is the reason why pre-oxygenation is so effective.

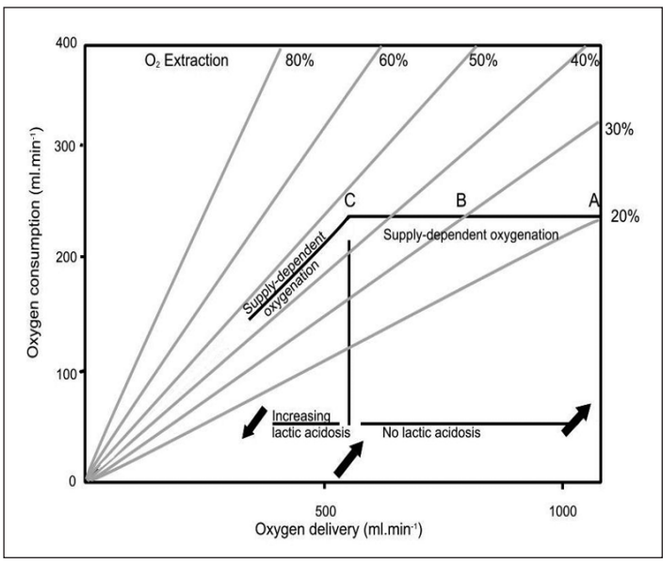


**Figure 6.** *Graph showing the balance between oxygen delivery and oxygen consumption. The horizontal solid line shows the extent to which oxygen delivery can be reduced and compensated by an increase in oxygen extraction (normally between 20-30%, between A and B). Point C shows the point beyond which compensation is insufficient and oxygen consumption is limited by delivery (supply-dependent), and anaerobic metabolism, producing lactic acid, results*

**Table 1.** *Principal stores of oxygen in the body*

| | Breathing AIR | Breathing 100% $O_2$ |
|---|---|---|
| $O_2$ store in the lungs at FRC | 450ml | 3000ml |
| $O_2$ store bound to haemoglobin | 850ml | 950ml |
| $O_2$ dissolved or bound in tissues | 250ml | 300ml |
| **Total** | **1550ml** | **4250ml** |

## OXYGEN TRANSPORT - THE EFFECTS OF ANAESTHESIA

Hypoventilation may occur during anaesthesia due to airway obstruction, the effects of volatile anaesthetic agents, opioids and other sedatives. Ketamine and ether (at less than 1 MAC) cause less respiratory depression than other anaesthetic agents. The $P_AO_2$ is a balance between the oxygen supplied by breathing and that used by metabolic processes in the body. Hypoventilation and a decreased inspired oxygen concentration will therefore cause a reduction in $P_AO_2$. The increased utilisation of oxygen when metabolic rate is raised (e.g. during postoperative shivering or pyrexia) also causes a reduction in $P_AO_2$.

If the $PaO_2$ falls to less than 8kPa the aortic and carotid body chemoreceptors respond by causing hyperventilation and increasing cardiac output through sympathetic nervous system stimulation. This normal protective response to hypoxia is reduced by anaesthetic drugs. This effect extends into the postoperative period.

Following induction of anaesthesia there is a rapid reduction in FRC, largely attributable to loss of tone in the respiratory muscles and chest wall. FRC drops below the closing volume in the lung – the expiratory volume at which airway closure first occurs. This primarily occurs in small airways in dependant parts of the lung; these areas may remain closed throughout the respiratory cycle to result in a shunt.

As described above, V/Q mismatch due to airway closure (shunt) will increase the alveolar-arterial difference. This 'venous admixture' increases from 1% to around 10% following induction of anaesthesia. With the possible exception of patients spontaneously breathing while anaesthetised with ketamine, this increase in venous admixture occurs irrespective of the anaesthetic agent used and whether muscle relaxants are used or not. It should be viewed as an unavoidable adverse effect of anaesthesia and explains the universal requirement for supplementary oxygen during surgery to achieve normal oxygenation. Furthermore, volatile anaesthetic agents suppress hypoxic pulmonary vasoconstriction, and blood flow to under-ventilated or collapsed alveoli is not reduced appropriately. In addition, many anaesthetic agents depress cardiac output and therefore decrease oxygen delivery.

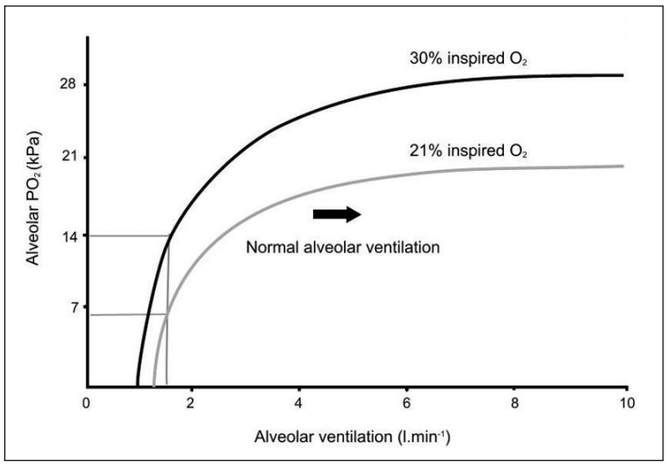


**Figure 7.** *The effect on $P_AO_2$ of increasing the $FiO_2$ from 21% (thin curve) to 30% (heavy curve) at a constant oxygen consumption of 200ml.min$^{-1}$. The effect on $P_AO_2$ of increasing the $FiO_2$ in a patient with an alveolar ventilation of 1.5l.min$^{-1}$ is shown*

Reduced tissue oxygen delivery during anaesthesia is partially compensated for by the fact that anaesthesia causes a 15% reduction in metabolic rate and therefore a reduction in oxygen requirements. Artificial ventilation causes a further 6% reduction in oxygen requirements as the work of breathing is removed. Anaesthetic agents do not affect the carriage of oxygen by haemoglobin.

## PRACTICAL USE OF OXYGEN

### Inspired oxygen concentration

The efficiency of oxygenation during anaesthesia is reduced due to hypoventilation and venous admixture. Inspired oxygen in the range of 25% to 30% is usually effective in restoring the $P_AO_2$ to normal when hypoxaemia is due to hypoventilation (Figure 7).

When hypoxaemia is due to venous admixture it is possible to restore the $P_AO_2$ by increasing the inspired oxygen concentration if the venous admixture does not exceed the equivalent of a 30% shunt (Figure 8).

The inspired oxygen concentration during maintenance of anaesthesia should routinely be increased to 30% whenever possible to compensate for hypoventilation and shunt which normally accompany anaesthesia. Additional oxygen may need to be administered to patients at risk of decreased oxygen delivery (anaemia or decreased cardiac output) or increased oxygen consumption (fever).

### Pre-oxygenation

The small volume of the oxygen stores of a patient breathing air means that there will be a rapid fall in oxygen saturation during apnoea (e.g. following induction of anaesthesia, during laryngospasm or during upper airway obstruction). Pre-oxygenation involves breathing 100% oxygen for three minutes through an anaesthetic circuit with a face mask firmly applied to the face. This is the time taken to replace the nitrogen in the FRC with oxygen using normal tidal ventilation ('denitrogenation'). Although FRC falls on induction of anaesthesia the extra oxygen contained within the FRC provides an essential store of oxygen for periods of apnoea, particularly during rapid sequence induction or difficult intubation. Patients with a small FRC

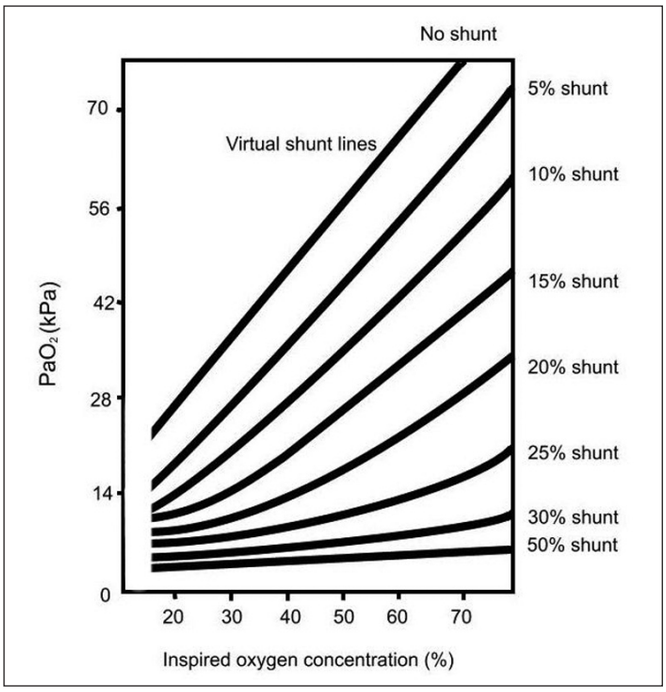


**Figure 8.** *The effect on $PaO_2$ (vertical axis) of an increasing $FiO_2$ (horizontal axis) in the presence of different sized shunts. It can be seen that increasing the $FiO_2$ when the shunt is very large (greater than 50% of cardiac output) is ineffective in increasing $PaO_2$*

(infants, pregnancy, the obese) or a low haemoglobin concentration, and therefore smaller oxygen stores, desaturate more rapidly and pre-oxygenation is especially indicated in these patients.

### Crisis management

When managing emergencies during anaesthesia, consideration should always be given to the immediate administration of 100% oxygen, while the cause is found and rectified. It is the most appropriate treatment for acute deterioration in cardiorespiratory function.

### Anoxic gas mixtures

If, during the course of an anaesthetic, 100% nitrous oxide is given to the patient in error, the fall in $PAO_2$ will be much more rapid than during apnoea. The $PAO_2$ can fall to dangerously low levels in as little as 10 seconds. This is because the oxygen in the patient's lungs and blood (oxygen stores) is being actively washed out with each breath that contains no oxygen. The fall in $PAO_2$ is therefore more rapid than would occur if it was only being used up by the metabolic needs of the body ($250 ml.min^{-1}$). Modern anaesthesia machines include a hypoxic link to prevent 100% nitrous oxide being administered in error.

### Diffusion hypoxia

Nitrous oxide is forty times more soluble in blood than nitrogen. When nitrous oxide is discontinued at the end of anaesthesia, nitrous oxide diffuses out of the blood into the alveoli in large volumes during the next 2 to 3 minutes. If the patient is allowed to breathe air at this time the combination of nitrous oxide and nitrogen in the alveoli reduces the $PAO_2$. This is called diffusion hypoxia and is avoided by increasing the alveolar concentration of oxygen by the administration of 100% oxygen for 2 to 3 minutes after discontinuing nitrous oxide.

### Postoperative oxygen

The causes of increased venous admixture (V/Q mismatch - shunt and airway closure) and the abnormal response to hypoxia continue into the postoperative period for up to three days following major surgery. Postoperative hypoventilation is common and may be due to the residual effect of anaesthesia, the use of opioid analgesia, pain or airway obstruction. Shivering in the immediate postoperative period causes an increase in oxygen consumption. Additional oxygen should therefore be given to all unconscious patients in recovery and to those awake patients who either shiver, hypoventilate, are desaturated or who are considered to be at increased risk (e.g. ischaemic heart disease).

On the ward during the postoperative period, episodes of airway obstruction during sleep are common and may aggravate borderline oxygenation due to the above factors. This is usually due to the use of opioid analgesia and a change in sleep pattern that occurs on the second and third postoperative nights. After major surgery, the risk of hypoxaemia extends well into the postoperative period. Small degrees of cyanosis are not easy to detect clinically, especially in anaemic patients, and therefore oxygen should be given to these patients wherever possible, especially overnight. Postoperative pain should be effectively treated, particularly following abdominal or thoracic surgery. If opioid analgesics are indicated, hypoventilation should be anticipated, and oxygen saturation monitored as a routine.

## PROBLEMS ASSOCIATED WITH OXYGEN ADMINISTRATION

It is has been suggested that high concentrations of oxygen (90-100%) administered to patients for a prolonged period (several days) may cause pulmonary damage. Whilst this is a concern, it should never prevent the use of oxygen to treat severe hypoxia. High concentrations of oxygen encourage collapse of alveoli with low ventilation/perfusion ratios. Oxygen is rapidly and completely absorbed from these alveoli and, when it is the only gas being given, these underventilated alveoli collapse (absorption atelectasis). When air and oxygen is used, the nitrogen present is absorbed more slowly and prevents the alveolus from collapsing. It is therefore sensible to administer the lowest $FiO_2$ that achieves adequate oxygenation (as guided by pulse oximetry).

Oxygen therapy may rarely depress ventilation in patients suffering from severe chronic obstructive airways disease. Patients who chronically retain $CO_2$ lose the hypercapnoeic stimulus to maintain ventilation and are therefore reliant on their hypoxic drive to self ventilate. Administration of oxygen may remove this drive and result in respiratory arrest. In practice this situation is rare, but again it is sensible to gradually titrate the $FiO_2$ to achieve a realistic oxygenation goal. It is often appropriate to tolerate moderate hypoxia in these patients (maximum $SaO_2$ 90-94%).

## FURTHER READING


- Nunn JF. Applied Respiratory Physiology (3rd Edition). Butterworths, 1987.
- West JB. Respiratory Physiology (4th Edition). Williams and Wilkins, 1990.