THE PHYSIOLOGY OF OXYGEN DELIVERY

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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 (e.g.brain) are made up of cells that can only make 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. Initially a lack of oxygen affects organ function but with time irreversible damage is done (within minutes in the case of the brain) and revival is impossible.

OXYGEN TRANSPORT FROM AIR TO 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 (pressure) to areas of low concentration (pressure). If there are a mixture of gases in a container, the pressure of each gas (partial pressure) is equal to the pressure that each gas would produce if it occupied the container alone.

Atmosphere to alveolus

The air (atmosphere) around us has a total pressure of 760 mmHg (1 atmosphere of pressure = 760mmHg = 101kPa = 15lbs/sq. in). Air is made up of 21% oxygen, 78% nitrogen and small quantities of CO_2, argon and helium. The pressure exerted by the main two gases individually, when added together, equals the total surrounding pressure or atmospheric pressure. The pressure of oxygen (PO_2) of dry air at sea level is therefore 159 mmHg (21/100 x 760=159). 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 as a gas exerts a pressure. At 37^oC the water vapour pressure in the trachea is 47 mmHg. Taking the water vapour pressure into account, the PO_2 in the trachea when breathing air is (760-47) x 21/100 = 150 mmHg. By the time the oxygen has reached the alveoli the PO_2 has fallen to about 100 mmHg. This is because the PO_2 of the gas in the alveoli (P_AO_2) is a balance between two processes: the removal of oxygen by the pulmonary capillaries and its continual supply by alveolar ventilation (breathing).

Alveolus to blood

Blood returning to the heart from the tissues has a low PO_2 (40 mmHg) 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 pressure in the alveoli (100 mmHg) to the area of lower pressure of the blood in the pulmonary capillaries (40 mmHg). After oxygenation blood moves into the pulmonary veins which return 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. Three factors may cause the PO_2 in the pulmonary veins to be less than the P_AO_2: ventilation/perfusion mismatch, shunt and slow diffusion.

Ventilation/perfusion 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 ie.ventilation and perfusion would be perfectly matched.

Diseased lungs may have marked mismatch between ventilation and perfusion. Some alveoli are relatively overventilated while others are relatively overperfused (the most extreme form of this is shunt where blood flows past alveoli with no gas exchange taking place (figure 1). Well ventilated alveoli (high PO_2 in capillary blood) cannot make up for the oxygen not transferred in the underventilated alveoli with a low PO_2 in the capillary blood. This is because there is a maximum amount of oxygen which can combine with haemoglobin (see haemoglobin-oxygen dissociation curve figure 2a). The pulmonary venous blood (mixture of pulmonary capillary blood from all alveoli) will therefore have a lower PO_2 than the PO_2 in the alveoli (P_AO_2). Even normal lungs have some degree of ventilation/perfusion mismatch; the upper zones are relatively overventilated while the lower zones are relatively overperfused and underventilated.

Shunt occurs when deoxygenated venous blood from the body passes unventilated alveoli to enter the pulmonary veins and the systemic arterial system with an unchanged PO_2 (40 mmHg). (Figure 1.) Atelectasis (collapsed alveoli), consolidation of the lung, pulmonary oedema or small airway closure (see later) will cause shunt.

Diffusion

Oxygen diffuses from the alveolus to the capillary until the PO_2 in the capillary is equal to that in the alveolus. This process is normally complete by the time the blood has passed about one third of the way along the pulmonary capillary.

In the normal lung, the diffusion of oxygen into the blood is vary rapid and is complete, even if the cardiac output is increased (exercise) and the blood spends less time in contact with the alveolus. This may not happen when the alveolar capillary network is abnormal (pulmonary disease). 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.

In order to decrease the detrimental effect that shunt and ventilation/perfusion mismatch have on oxygenation, the blood vessels in the lung are adapted to vasoconstrict and therefore reduce blood flow to areas which 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 2b) but there is a very small amount dissolved in the plasma. Each gram of haemoglobin can carry 1.31 ml of oxygen when it is fully saturated. Therefore every litre of blood with a Hb concentration of 15g/dl can carry about 200 mls of oxygen when fully saturated (occupied) with oxygen ($PO_2 >100$ mmHg). At this PO_2 only 3 ml of oxygen will dissolve in every litre of plasma.
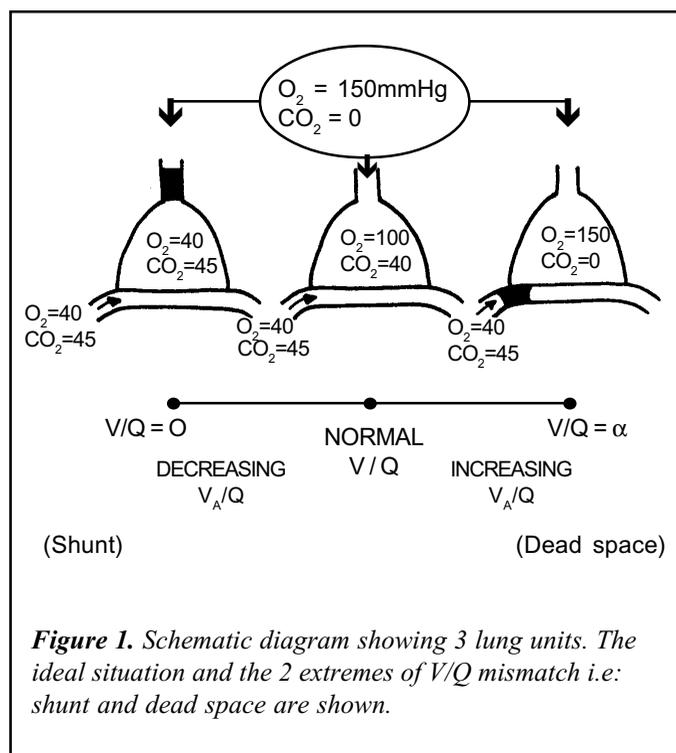
Figure 1. *Schematic diagram showing 3 lung units. The ideal situation and the 2 extremes of V/Q mismatch i.e: shunt and dead space are shown.*

If the PO2 of oxygen in arterial blood (PA02) is increased significantly (by breathing 100% oxygen) then a small amount of extra oxygen will dissolve in the plasma (at a rate of 0.003 ml O_2/100ml of blood /mmHg PO2) but there will normally be no significant increase in the amount carried by haemoglobin, which is already >95% saturated with oxygen. When considering the adequacy of oxygen delivery to the tissues, three factors need to be taken into account, haemoglobin concentration, cardiac output and oxygenation.

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. The PO2 reaches the lowest level (4-20 mmHg) in the mitochondria (structures in cells responsible for energy production). This decrease in PO2 from air to the mitochondrion is known as the oxygen cascade and the size of any one step in the cascade may be increased under pathological circumstances and may result in hypoxia (figure 3).
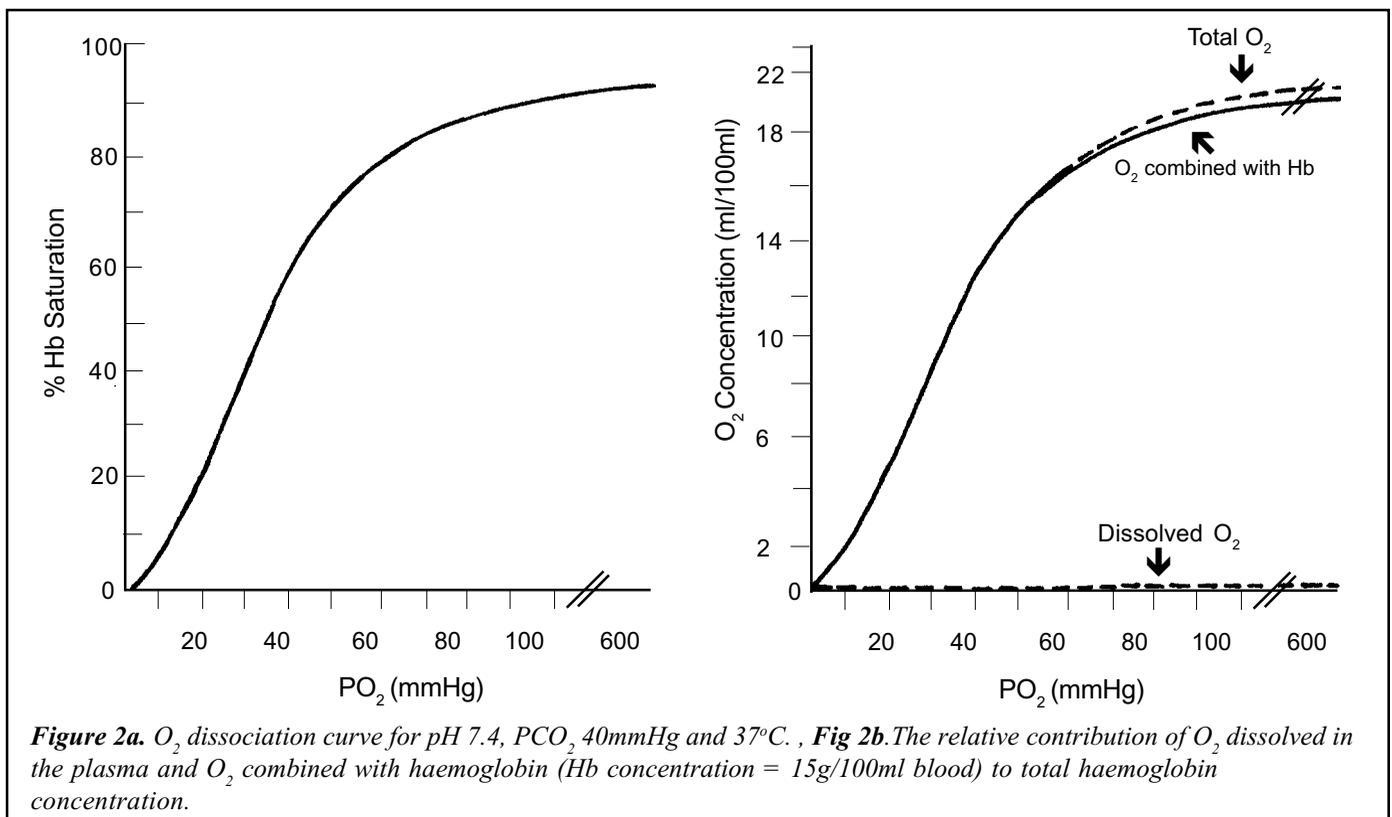
Oxygen delivery

The quantity of oxygen made available to the body in one minute is known as the oxygen delivery and is equal to the cardiac output x the arterial oxygen content (see previously) ie. 5000ml blood/min x 200 mlO2/1000 ml blood = 1000ml O2/min.
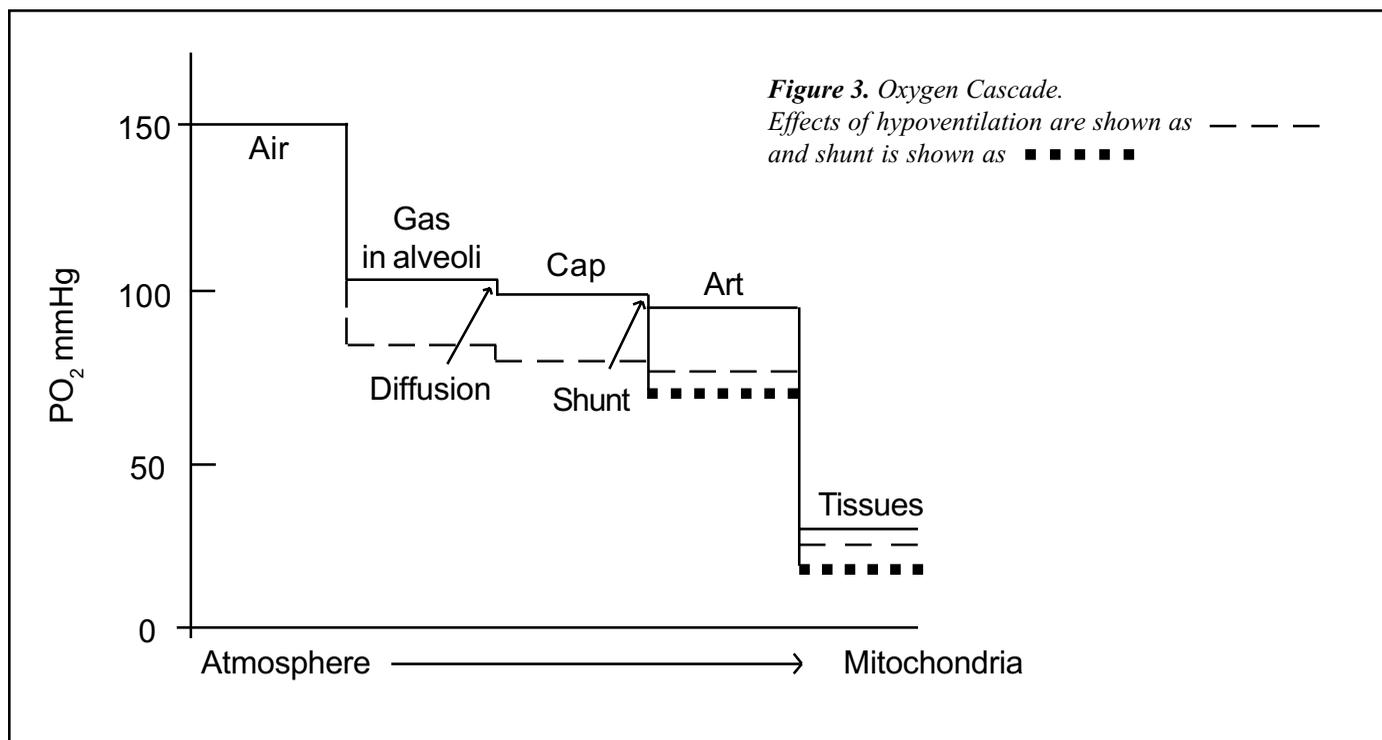
Oxygen delivery (mls O2/min) = Cardiac output (litres/min) x Hb concentration (g/litre) x 1.31 (mls O2/g Hb) x % saturation

Oxygen consumption

Approximately 250 ml of oxygen are used every minute by a conscious resting person (oxygen consumption) and therefore about 25% of the arterial oxygen is used every minute. The haemoglobin in mixed venous blood is about 70% saturated (95% less 25%).

In general there is more oxygen delivered to the cells of the body than they actually use. When oxygen consumption is high (eg. during exercise) the increased oxygen requirement is usually provided by an increased cardiac output – see formula above for how this works. However, a low cardiac output, a low haemoglobin concentration (anaemia) or a low haemoglobin O2 saturation will result in an inadequate delivery of oxygen, unless a compensatory change occurs in one of the other factors. Alternatively, if oxygen delivery falls relative to oxygen consumption the tissues extract more oxygen from the haemoglobin (the saturation of mixed venous blood falls below 70%)(a-b in figure 4). A reduction below point 'c' in figure 4 cannot be compensated for by an increased oxygen extraction and results in anaerobic metabolism and lactic acidosis.

Figure 2a. *O_2 dissociation curve for pH 7.4, PCO_2 40mmHg and 37°C. ,* ***Fig 2b.****The relative contribution of O_2 dissolved in the plasma and O_2 combined with haemoglobin (Hb concentration = 15g/100ml blood) to total haemoglobin concentration.*

Figure 3. *Oxygen Cascade.*
Effects of hypoventilation are shown as — — —
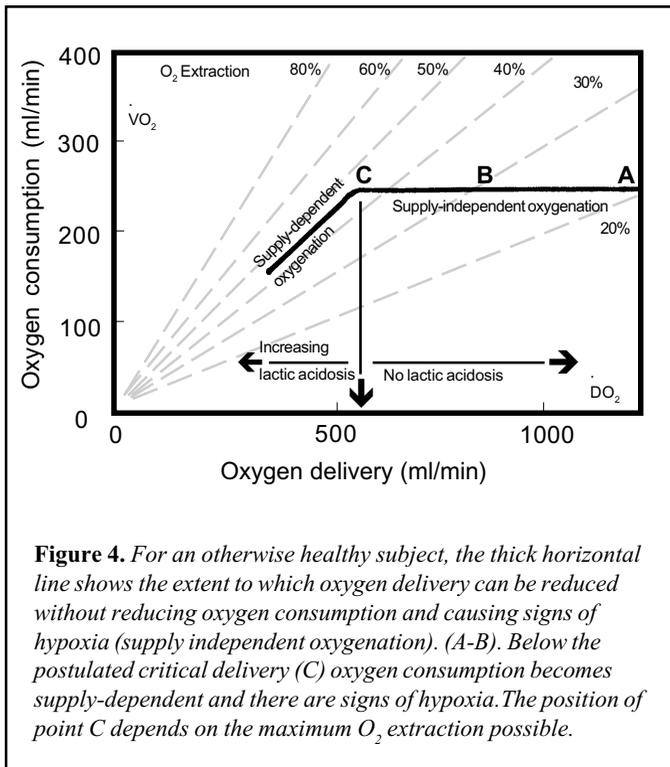*and shunt is shown as* ■ ■ ■ ■ ■

OXYGEN STORES

In spite of the great importance of 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 in the blood. The amount of oxygen in the blood depends on the blood volume and haemoglobin concentration. 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 ie when the elastic recoil of the lung is balanced by the relaxed chest wall and diaphragm. While breathing air the total stores (oxygen in blood and lung) are small and because the major component of this store is the oxygen bound to haemoglobin (see figure 5) only a small part of these stores can be released without an unacceptable reduction in PaO_2 (when haemoglobin is 50% saturated with oxygen the PaO_2 will have fallen to 26 mmHg). Breathing 100% oxygen causes a large increase in the total 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 still about 100mmHg). This is the reason why pre-oxygenation is so effective. (see later)

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. In contrast, ketamine and ether anaesthesia (less than 1 MAC) cause less respiratory depression than other anaesthetic agents. Alveolar PO_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 alveolar PO_2 (PAO_2). The increased utilisation of oxygen when metabolic rate is raised such as with postoperative shivering or malignant hyperpyrexia also causes a reduction in alveolar PO_2.

If the PaO_2 falls to less than 60mmHg 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 and this effect extends into the post-operative period.

Following induction of anaesthesia there is a rapid reduction in FRC that results in airway closure - small airways, particularly in dependant parts of the lung, collapse and remain closed throughout the respiratory cycle. This results in some alveoli not being ventilated at all (true shunt). Ventilation/perfusion (V/Q) mismatch is also increased.

Figure 4. *For an otherwise healthy subject, the thick horizontal line shows the extent to which oxygen delivery can be reduced without reducing oxygen consumption and causing signs of hypoxia (supply independent oxygenation). (A-B). Below the postulated critical delivery (C) oxygen consumption becomes supply-dependent and there are signs of hypoxia. The position of point C depends on the maximum O_2 extraction possible.*

Atelectasis (collapsed alveoli) also develops rapidly in the dependant lung regions and results in true shunt. As explained earlier, airway closure, V/Q mismatch and shunt will cause the oxygen saturation in the pulmonary veins to be less than in the pulmonary capillaries of ventilated alveoli. 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. Volatile anaesthetic agents suppress hypoxic pulmonary vasoconstriction, and blood flow to underventilated or collapsed alveoli is not reduced. Many anaesthetic agents depress cardiac output and therefore decrease oxygen delivery.

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.

THE PRACTICAL USE OF OXYGEN
Inspired oxygen concentration
The efficiency of oxygenation during anaesthesia is reduced due to hypoventilation and venous admixture. An inspired oxygen in the range of 25%-30% is usually effective in restoring the PaO_2 to normal when hypoxaemia is due to hypoventilation. (figure 6) When hypoxaemia is due to venous admixture it is only possible to restore the PaO_2 by increasing the inspired oxygen concentration if the venous admixture does not exceed the equivalent of a 30% shunt. (figure 7) 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).
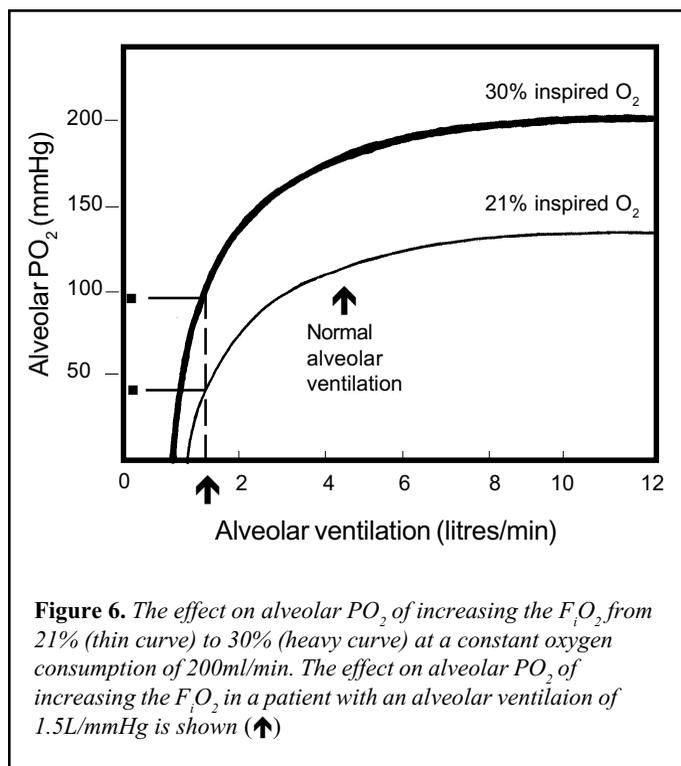
Pre-oxygenation
The small volume of the oxygen stores in the FRC of a patient breathing air means that there will be a rapid fall in oxygen saturation during apnoea (e.g. following induction of anaesthesia, during laryngospasm or during upper airway obstruction). Pre-oxygenation involves the breathing of 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. Although FRC falls on induction of anaesthesia the extra oxygen contained within the FRC provides an essential store of oxygen for periods of apnoea, such as may occur during rapid

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Fig 5. Principal stores of oxygen in the body

	While breathing AIR	While breathing 100% O_2
In the lungs (FRC)	450ml	**3000ml**
In the blood	850ml	950ml
Dissolved or bound in tissues	250ml	300ml
Total	**1550ml**	**4250ml**

Figure 6. *The effect on alveolar PO_2 of increasing the F_iO_2 from 21% (thin curve) to 30% (heavy curve) at a constant oxygen consumption of 200ml/min. The effect on alveolar PO_2 of increasing the F_iO_2 in a patient with an alveolar ventilaion of 1.5L/mmHg is shown (↑)*

sequence induction or difficult intubation. Patients with a small FRC (infants, pregnancy, obesity) or a low haemoglobin concentration and therefore smaller oxygen stores desaturate more rapidly and pre-oxygenation is especially indicated in these patients.

Anoxic gas mixtures
If, during the course of an anaesthetic 100% nitrous oxide is given to the patient in error, the fall in alveolar PO2 will be much more rapid than during apnoea. The alveolar PO2 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 PO2 is therefore more rapid than would occur if it was only being used up by the metabolic needs of the body (250ml/min).

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.
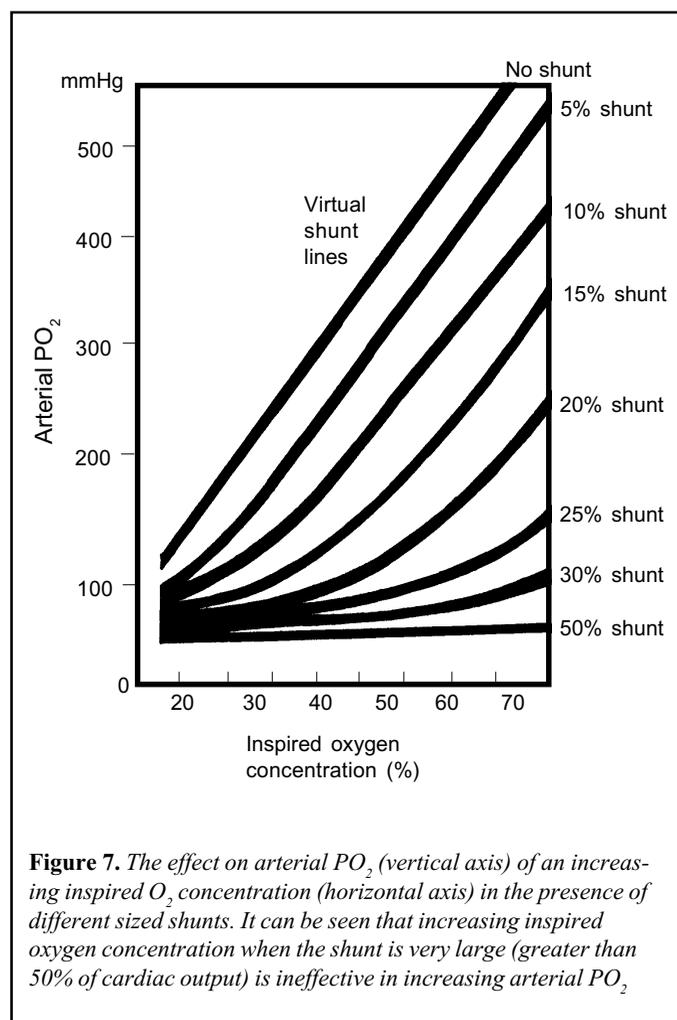
Diffusion hypoxia
Nitrous oxide is forty times more soluble in blood than nitrogen. When nitrous oxide is discontinued at the end of anaesthesia, nitrous oxide diffuses out of the blood into the alveoli in large volumes during the next 2 - 3 minutes.

If the patient is allowed to breathe air at this time the combination of nitrous oxide and nitrogen in the alveoli reduces the alveolar PO2. This is called diffusion hypoxia and is avoided by increasing the inspired concentration of oxygen by the administration of 100% oxygen for 2 –3 minutes after discontinuing nitrous oxide.

Postoperative oxygen
The causes of increased venous admixture (ventilation/ perfusion mismatch, shunt and airway closure) and the abnormal response to hypoxia continue into the postoperative period for a number of 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, desaturate or who are considered to be at special risk (eg. ishaemic heart disease).

Figure 7. *The effect on arterial PO_2 (vertical axis) of an increasing inspired O_2 concentration (horizontal axis) in the presence of different sized shunts. It can be seen that increasing inspired oxygen concentration when the shunt is very large (greater than 50% of cardiac output) is ineffective in increasing arterial PO_2*

Postoperatively, on the ward, episodes of airway obstruction during sleep are common and may aggravate borderline oxygenation due to the above factors. This is due to the use of opioid analgesia and a change in sleep pattern that occurs on the second and third postoperative nights. It is clear that 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. It is especially important to give it overnight to patients at special risk (ischaemic heart disease). Postoperative pain should be effectively treated (see Update 7) as patients in pain following abdominal or thoracic surgery will be reluctant to breathe deeply. If opioid analgesics are indicated, hypoventilation should be anticipated, and oxygen given.

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. There is little evidence to support this and should never prevent its use in treating severe hypoxia.

High concentrations of oxygen will 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. When air and oxygen is used, the nitrogen present is absorbed more slowly and prevents the alveolus from collapsing.

Oxygen therapy may rarely depress ventilation in patients suffering from severe chronic obstructive airways disease. Some of these patients lose their sensitivity to carbon dioxide and rely on hypoxia to stimulate breathing. In these patients, when high concentrations of oxygen are given, serious hypoventilation and hypercapnia can result due to the fact that their hypoxia is reversed. This is extremely rare.

In the second part of this article we plan to discuss the more practical aspects of oxygen production and storage and the equipment needed to safely administer oxygen to patients.

References:

1.   Nunn JF. Applied Respiratory Physiology (3rd Edition). Butterworths 1987

2.   West JB. Respiratory Physiology (4th Edition). Williams and Wilkins 1990