Some major points on the causes of Hypoxia, the Effects of Hyperventilation and Breath Holding Times

Source Kings College London tutorials:

http://www.kcl.ac.uk/teares/gktvc/vc/dental/year1/lectures/rbmsmajorpoints/hypoxiaandhyperventilation.htm

The causes of hypoxia

Cells use oxygen to obtain their energy and may not function adequately if their supply of oxygen is impeded; this is called hypoxia which is a contraction of hypo-oxia or low level of oxygen. Many cells can respire anaerobically but the cells in the brain cannot and they need a constant supply of oxygen. A shortage of oxygen in the brain progressively produces inappropriate behaviour, unconsciousness and death which can occur within a few minutes if the brain is completely deprived of oxygen. There are many ways in which hypoxia can be produced but they can be divided into 4 types, each of which has fairly similar effects, because of the way the body works. This handout will be mainly concerned with the causes of hypoxia and will consider the effects only briefly; a later handout will go further into the effects. Please note that the space devoted to each cause in this handout reflects the number of words needed to explain it, not its importance.

Hypoxic hypoxia

This unfortunately named form of hypoxia occurs when the arterial partial pressure of oxygen (PaO_2) is reduced so that the blood leaves the lungs without its haemoglobin being fully saturated. Hypoxic hypoxia can be produced in many ways: if there is a low partial pressure of oxygen in the inspired air, as at high altitudes, the PAO_2 and the PaO_2 will fall. Anything that reduces the ventilation will produce hypoxic hypoxia: weakness of the respiratory muscles as in poliomyelitis will reduce the ventilation and some drugs, such as general anaesthetics and analgesics (pain relievers), acting on the respiratory centre can reduce the activity of the respiratory muscles. It may become more difficult for the breathing to occur; this may be because it is more difficult to expand the lungs when the compliance is reduced by, for example, fibrosis or it may be the result of narrowed airways, as in asthma or bronchitis, increasing the work needed to move the air. The alveolar ventilation may be reduced if the dead space is increased because less of the air that is inhaled reaches the alveoli where gaseous exchange occurs.

Even if the PAO_2 is normal, the PaO_2 will be reduced if the rate of diffusion between the air and the blood is reduced, which can happen if the membrane becomes thicker, as in pulmonary oedema when interstitial fluid accumulates between the epithelial and endothelial cells and may even enter the alveoli; pulmonary oedema can be produced by left sided heart failure (what is left sided heart failure and how does it produce pulmonary oedema?). In emphysema, the walls of individual alveoli break down, forming large air sacs, whose total surface area is less than for the larger number of smaller alveoli, and the reduction in surface area reduces the rate of diffusion of the gases between the air and the blood; there are other problems in emphysema. Carbon dioxide diffuses more rapidly than oxygen because of its greater solubility in water so, if the impediment to diffusion is slight, there may be adequate diffusion of carbon dioxide and a normal $PaCO_2$ while there is insufficient diffusion of oxygen and a reduced PaO_2.

Hypoxic hypoxia can be produced also if blood goes through the lungs without going past an alveolus so that some blood reaches a pulmonary vein without giving off carbon dioxide or picking up oxygen; this is called a right-to-left shunt. Hypoxia can also be produced by mismatches between the ventilation and the perfusion of the lungs.

In hypoxic hypoxia the haemoglobin leaving the lungs is not fully saturated. When the blood goes through the tissues 50 ml.l-1 will be removed by the average resting tissue as normal, so that more than 50 g.l-1 of the haemoglobin in venous blood may be deoxygenated, producing cyanosis which is a blue coloration of the tissues due to the presence of large amounts of deoxygenated haemoglobin.

Most forms of hypoxic hypoxia can be corrected by giving the patients air containing a higher than normal level of oxygen (hyperbaric oxygen) to breathe. This will raise the alveolar partial pressure of oxygen and, thus, the arterial partial pressure, so increasing the percentage saturation of the haemoglobin. Giving hyperbaric oxygen will be of limited use in right to left shunts because the blood going past the alveoli is fully saturated already; there will be an increase in the amount of oxygen carried in solution but this is small compared to the amount carried on the haemoglobin.

Anaemic hypoxia

Please note the English spelling of anaemia. In anaemic hypoxia the concentration of functional haemoglobin is reduced; what is the normal haemoglobin concentration? Many factors can produce anaemia which may be the result of a reduced synthesis of red blood cells. Among the factors that can reduce red blood cell production (erythropoiesis) are deficiencies of iron, vitamin B12, folate or copper. Iron is required for the synthesis of haemoglobin of which it is a component; in iron deficiency anaemia, the cells tend to be small and contain reduced amounts of haemoglobin so this form of anaemia is called a microcytic (small celled) hypochromic (pale coloured) anaemia. Deficiencies of vitamin B12, folate or copper produce anaemia by stopping red cells dividing so that few cells are produced but those cells are large with plenty of haemoglobin (a macrocytic hyperchromic anaemia). Anaemia can develop in some diseases of the kidney because the hormone that stimulates red cell production (erythropoietin) comes from the kidney; the cells in this form of anaemia will be normal (normocytic anaemia). A normocytic anaemia can arise, also, from the excessive loss of red blood cells such as after a large haemorrhage or because of chronic (long lasting) small haemorrhages due to, for example, parasitic worms in the gut. There are also conditions, such as hereditary spherocytosis, where the red cells have short lives, so producing anaemia. Carbon monoxide combines with haemoglobin, making it unable to carry oxygen, so carbon monoxide poisoning is a form of anaemic hypoxia.

The PAO_2 is determined by the alveolar ventilation and the oxygen consumption, both of which are normal in anaemia, so the PAO_2 is normal and such haemoglobin as is present, will be fully saturated but the oxygen content of the blood will be reduced because there is less haemoglobin than normal.

Giving hyperbaric oxygen to anaemic people will be of limited benefit because the haemoglobin leaving the lungs is fully saturated and the extra amount that would be carried in solution is small compared to the amount on the haemoglobin; the problem is that there is not enough haemoglobin. The amount of deoxygenated haemoglobin in the blood leaving the tissues will be no higher than normal so anaemic patients will not be cyanosed. Indeed, if an anaemic person is exposed also to hypoxic hypoxia, she will be less likely to develop cyanosis than a normal person. Cyanosis occurs when there is more than 50 g.l^{-1} of deoxygenated haemoglobin in venous blood which will occur in a normal man when his haemoglobin is less than saturated; if the anaemic subject had, for example, only half the normal level of haemoglobin, she would not become cyanosed until only of her haemoglobin carried oxygen.

Stagnant hypoxia

Stagnant hypoxia is also called static hypoxia; it is a reduction in the supply of oxygen to tissues produced by a reduced blood flow. See your lecture notes on the cardiovascular course for the various causes of reduced blood flow. The reduced blood flow may be because of inadequate blood flow along the artery to one organ and only that organ will be affected; alternatively, the cardiac output may be reduced and all organs throughout the body may be affected. There is nothing wrong with the lungs in stagnant hypoxia, so the PaO_2 and $PaCO_2$ are normal and the blood leaving the lungs is fully saturated with oxygen; giving the patients air with a high level of oxygen in it to breathe would be of limited value because the amount of oxygen carried in solution is slight, compared to the amount carried on haemoglobin.

The tissues will remove more oxygen from each litre of blood flowing through them, which compensates for the reduced flow, so cyanosis will occur in the affected organs despite the normal arterial partial pressure of oxygen.

Cytotoxic hypoxia

Cytotoxic hypoxia, which is called also *histotoxic hypoxia*, occurs when the respiring cells within the tissues are prevented from using oxygen. The names, cytotoxic and histotoxic, mean poisoning (toxic) of the cells (cyto) or tissues (histo); please note the derivation and that, therefore, there are two t's and two o's in cytotoxic and histotoxic. Examples of cytotoxic hypoxia include poisoning by cyanide, which combines with the cytochrome chain and prevents oxygen being used, and deficiencies of some of the B group of vitamins, which are involved in the chemical pathways used by respiring cells. Carbon monoxide produces an anaemic hypoxia, not a cytotoxic hypoxia, because it makes haemoglobin unable to carry oxygen, rather than by interfering directly with the use of oxygen by respiring cells. In cytotoxic hypoxia, the PaO_2 is normal and the haemoglobin leaving the lungs is fully saturated so giving these patients oxygen enriched air would not be of value. These patients will not be cyanosed as their arterial blood is fully saturated and the tissues will remove less oxygen than normal from the blood.

The effects of hyperventilation

Hyperventilation is an increase in the breathing above the level needed to keep the $PACO_2$ constant; in hyperventilation the $PACO_2$ falls. Hyperventilation should be distinguished from hyperpnoea, which occurs in exercise when the carbon dioxide production is increased, and is an increase in ventilation that stops the $PACO_2$ from rising. Pain and anxiety cause hyperventilation so it is important for dentists to understand and recognise the effects of hyperventilation. As well as reducing the $PACO_2$, hyperventilation makes the PAO_2 rise but subjects who hyperventilate from a Douglas bag containing 5% CO_2 in air, which will prevent the $PACO_2$ falling during the hyperventilation, will show few of the effects of hyperventilation. Therefore most of the effects of hyperventilation are due to the fall in $PACO_2$; however the dry mouth and coughing seen during and after hyperventilation persist when hyperventilating with 5% CO_2 in air so they are not due to a fall in the $PACO_2$. The dry mouth is produced by the high flow of air over the mucosa making saliva evaporate, and a similar effect will occur throughout the respiratory tract. The drying of the mucous membranes will stimulate irritant receptors that reflexly induce coughing.

Effects on the breathing

The normal stimulus for breathing is the partial pressure of carbon dioxide which will fall during hyperventilation. Therefore it becomes increasingly difficult to hyperventilate as time goes by; muscle fatigue may also contribute to this. After hyperventilation, breathing may slow down or even stop because of the low partial pressure of carbon dioxide.

After prolonged hyperventilation, breathing may be intermittent (Cheyne-Stokes breathing), because of the differences in the way oxygen and carbon dioxide are carried in the body fluids. There are approximately 500 ml/l of carbon dioxide in blood, and most of it is in the form of hydrogen carbonate ions (HCO_3^-). These ions are able to cross the capillary endothelium so they will be found throughout the extracellular fluid with little in intracellular fluid because of the negative potential inside cells. The volume of extracellular fluid (plasma plus interstitial fluid) is approximately 16 l, so there are at least 8 l of carbon dioxide in the body (16 l x 500 ml/l). If prolonged hyperventilation reduced the amount of carbon dioxide by, for example, half, there would be 4 l left in the body and 4 l more would have to be produced before the amount of carbon dioxide in the body returned to normal. The body produces 200 ml/min of carbon dioxide at rest so it would take 20 minutes for the amount of carbon dioxide to return to normal after such a severe degree of hyperventilation.

The solubility of oxygen in the body fluids is low, so there will be only small amounts of oxygen in the cells and interstitial fluid, compared to the amount bound to haemoglobin in the blood. The concentration of oxygen in arterial blood is approximately 200 ml/l and it will be lower in venous blood; the blood volume is approximately 5 l so the amount of oxygen in the blood will be no more than 1 l (5 l x 200 ml/l). There will be some oxygen also in the lungs; the volume of the functional residual capacity is around 2.5 l and the air within it, even though it will have a higher than normal concentration of oxygen after hyperventilation, can be no more than 20% oxygen. Therefore, there will be approximately

0.5 l of oxygen in the lungs (2.5 l x 20/100), giving a total amount of oxygen in the body of 1.5 l. The oxygen will be consumed at 250 ml/min at rest so would last for 6 minutes; in practice, hypoxia will stimulate the breathing long before the oxygen is used up when the partial pressure of carbon dioxide is still very low. The hypoxia will stimulate a few breaths which will reduce the hypoxic stimulation and, because the carbon dioxide is still low, the breathing will stop again. The amount of oxygen in the body will fall again until the hypoxia stimulates breathing once more, giving intermittent breathing which will continue until the partial pressure of carbon dioxide has returned to normal.

The change in pH and its effects

The blood pH will rise during hyperventilation because the reaction:

$$CO_2 + H_2O \longrightarrow H^+ + HCO_3^-$$
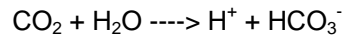
will move to the left as the hyperventilation reduces the concentration of carbon dioxide. The plasma proteins contain some carboxyl and amino groups that will lose hydrogen ions as the pH rises.

$$R\text{-}COOH \longrightarrow R\text{-}COO^- + H^+ \qquad R\text{-}NH_3^+ \longrightarrow R\text{-}NH_2 + H^+$$
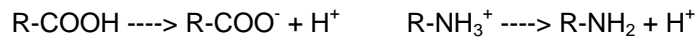
Consequently, the plasma proteins will become more negatively and less positively charged during hyperventilation. Approximately half the calcium ions in the plasma are carried bound to proteins and the increasing negativity of the proteins will make more calcium bind to them during hyperventilation, so the concentration of free calcium will now fall.

The reduced free calcium concentration will have an effect on the threshold of nerve fibres. When a nerve fibre is depolarised, the membrane becomes more permeable to sodium ions which rush in making the inside more positive. At the same time as the sodium ions go in, potassium ions will leave the cell because the depolarisation means that the electrical potential which holds the potassium inside the cell has reduced. For small depolarisations that do not reach the threshold, the number of potassium ions going out is greater than the number of sodium ions going in, so the cell becomes more negative and returns to the resting membrane potential: the threshold has not been reached. As the depolarisations get larger, the inward current of sodium increases faster than the outward current of potassium ions and eventually a potential is reached where there are more sodium ions coming in than potassium going out, so the cell becomes more positive and an action potential is produced: the cell has been depolarised beyond its threshold. At rest and for small depolarisations, the current of sodium ions is inhibited by calcium ions so that during hyperventilation, when the free calcium concentration falls, the inward current of sodium ions increases. Therefore, the threshold will be reached more easily and eventually action potentials will occur spontaneously.

Spontaneous action potentials in afferent fibres produce tingling, pins and needles or other strange sensations in the hands, feet and other extremities; normal sensations are not produced because the pattern of action potentials in the nerve fibres are unusual. If the optic nerve is affected, flashes of light will be seen and ringing in the ears may arise from spontaneous action potentials in the auditory nerve.

If efferent nerve fibres are involved, the muscles they supply will contract involuntarily, explaining the difficulty in writing. The contraction is due to action potentials arising in the nerves, not in the muscle fibres themselves: if the facial nerve is tapped where it emerges from the parotid gland in someone who is hyperventilating, the muscles of the face will contract, giving a marked grimace (Chvostek's sign) even though the muscles themselves were not tapped. In hyperventilation the hands and feet are particularly affected and become flexed because there are larger amounts of flexor than of extensor muscles; these contractions are referred to as carpo-pedal spasm. Muscle contractions due to a low calcium concentration are generally known as tetany, which can be confused in speech with the plural of tetanus. Severe tetany can be fatal because the muscle adducting the vocal cords, the lateral crico-arytenoid, may be affected, closing the airway.

The cardiovascular changes

Carbon dioxide is a vasodilator, so the low level of carbon dioxide in the body will have a direct effect on arterioles, constricting them and reducing the blood flow to the organs they supply. Carbon dioxide also stimulates the vasomotor centre so the low level of carbon dioxide will produce less activity in sympathetic constrictor fibres, making arterioles dilate. Organs which normally have a high level of sympathetic activity, such as the skin, will show the vasodilatation and the faces of subjects who are hyperventilating may be red; organs like the brain in which the arterioles have very little sympathetic activity to be inhibited, will obviously show the vasoconstriction, because of the direct effect of the low carbon dioxide. The brain becomes hypoxic but this has less effect on the cerebral arterioles than the low partial pressure of carbon dioxide, so the blood flow remains low despite the hypoxia, producing dizziness and tunnel vision. In the brain there may be a reactive hyperaemia when the hyperventilation is stopped and the dilatation of the meningeal arterioles can allow the arterial pulsations to reach the meninges causing the pulsing headache which may occur after the hyperventilation.

There is also a marked tachycardia (acceleration of the heart rate) during hyperventilation. Part of this may arise from the exertion involved in hyperventilation, but the tachycardia is less marked after hyperventilating with 5% CO_2, suggesting it is related to the low levels of carbon dioxide. There are stretch receptors in the lung which can affect the heart rate and they will be stimulated more intensely and more often during hyperventilation, but if they were the sole cause of the tachycardia, the heart rate would be the same after hyperventilating with 5% CO_2 as after hyperventilating with air. If vasodilatation occurred in many organs, there might be a drop in arterial pressure which could produce a tachycardia through the baroreceptor reflex but measurements of arterial blood pressure during voluntary hyperventilation suggest that the arterial pressure does not fall. If the hyperventilation is due to an incorrect setting of an artificial ventilator that works by positive pressure, there will be a low arterial pressure because the positive pressure artificial ventilation impedes the venous return. In other cases, it appears most likely that the tachycardia arises from either a change in nervous activity going to the sino-atrial node (inhibition of the vagus or stimulation of the sympathetic fibres) or from effects of the low free calcium ion concentration on the membrane potentials of sino-atrial node cells, similar to the effects on nerve fibres.

Breath holding times

The time for which people can hold their breaths, which is known as the breath holding time, tells us something about the control of breathing. People can hold their breath for a shorter time after breathing 5% CO_2 in air than after breathing normal air because their PACO$_2$ will be higher at the beginning of the breath hold after they have been breathing the 5% CO_2 than after inhaling normal air; therefore the degree of stimulation of the central chemoreceptors at which it becomes impossible to hold the breath any longer will be reached earlier after breathing 5% CO_2 than after breathing air.

People can hold their breath for longer after breathing 100% oxygen than after breathing normal air; therefore hypoxia, as well as the raised PaCO$_2$, contributes to the inability to hold ones breath any longer, despite breathing 100% oxygen not affecting the ventilation rate. The greater amount of oxygen in the lungs after breathing 100% oxygen keeps the blood leaving the lungs fully saturated for longer into the breath hold, thus delaying the onset of hypoxia, than after breathing normal air. It is the extra oxygen in the lungs, not the blood, that has the major effect because the amount carried in solution is small compared to the amount bound to haemoglobin and the haemoglobin leaves the lungs fully saturated even after breathing normal air.

The breath holding time is longer in people who are fully inhaled than in people who are fully exhaled. Can you explain this?