Some major points on the Effects of Hypoxia

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

Cells obtain their energy from oxygen. Most cells have a limited ability to respire anaerobically but brain cells do not; not only do brain cells stop working if no oxygen is present but they are also killed if they are deprived of oxygen for a few minutes. The body has many responses to hypoxia that tend to reduce its severity. In an earlier lecture we noticed that there were 4 different ways in which hypoxia could be produced and the way in which the hypoxia is produced affects how the body responds.

Arterial partial pressure of oxygen, haemoglobin saturation and cyanosis

In hypoxic hypoxia, the arterial partial pressure of oxygen (PaO2) is reduced and the haemoglobin is not fully saturated. In other forms of hypoxia, the arterial partial pressure is normal so the haemoglobin is fully saturated. In anaemic hypoxia there is little haemoglobin so that, despite such haemoglobin as there is being fully saturated, there is a small amount of oxygen carried in the blood.

Normal arterial blood contains 200ml/l of oxygen and only gives up 50ml/l as it goes through the average resting tissue, so it leaves the tissues with 150ml/l at a partial pressure of 5kPa. This reserve, however, is smaller than it seems because there has to be a partial pressure gradient to drive the oxygen from the blood to the working cells so, in practice, not all the oxygen can be removed from the blood as it goes through the tissues. Also, some tissues remove more than 50ml/l and when tissues are active they will remove more oxygen than at rest, further reducing the size of this reserve.

In hypoxic and anaemic hypoxias, there will be less oxygen than normal in the blood entering the organs, so there will be less oxygen than normal in the blood leaving the organs. In stagnant hypoxia there is 200ml/l of oxygen in arterial blood but the blood flow through the tissues is reduced, so the tissues will remove more oxygen from each unit volume of blood; again there will be a reduced amount of oxygen in the blood leaving the organs. In cytotoxic hypoxia, the organs cannot use the oxygen that is brought to them, so there will be more oxygen than normal in the blood leaving the organ. In hypoxic and stagnant hypoxias, the low level of oxygen in capillary blood makes the affected organs go blue, a condition called cyanosis, but this does not occur in anaemic hypoxia. The blueness is due to the presence of more than 50g/l of deoxygenated haemoglobin in capillary blood; in normal people this will occur when one third of their haemoglobin is deoxygenated but in anaemic people with lower levels of haemoglobin a greater proportion of their haemoglobin would have to be deoxygenated before there would be 50g/l of it in their blood so anaemic people will not be cyanosed. For example, if an anaemic patient had only 75g/l of haemoglobin in her blood instead of the usual 150g/l, cyanosis would occur when two thirds of her haemoglobin was deoxygenated instead of the usual one third. Furthermore, if an anaemic patient is exposed additionally to hypoxic hypoxia, she will become cyanosed only at a much more severe degree of hypoxia than would a normal person. Therefore the presence of cyanosis indicates that hypoxia is present but the absence of cyanosis does not mean that there is no hypoxia.

Can you treat hypoxia by giving patients 100% oxygen to breathe? This would be effective in hypoxic hypoxia. In other forms of hypoxia the blood leaving the lungs is fully saturated with oxygen; though some oxygen can be carried in solution, the amount is small so that the benefit of giving 100% oxygen would be slight and it could also lead to the loss of the Haldane effect, which would raise the level of carbon dioxide in the tissues, as was discussed in an earlier lecture. Also in right-to-left shunts, though it is a form of hypoxic hypoxia, the blood going past functional alveoli leaves the lung fully saturated.

The rate of ventilation

In most forms of hypoxic hypoxia, the partial pressure of carbon dioxide will be raised and the partial pressure of oxygen will be lowered because, whatever is preventing oxygen entering the blood, will also stop carbon dioxide leaving the blood. Both the raised pressure of carbon dioxide, which is largely detected at the central chemoreceptor in the brainstem, and the reduced partial pressure of oxygen, which stimulates the peripheral chemoreceptors in the carotid bodies, can increase the ventilation. The increase in ventilation produced by hypoxia and hypercapnia (a raised partial pressure of carbon dioxide) acting together, is greater than the sum of the increases produced by the hypoxia and the hypercapnia acting on their own. The rise in the ventilation will reduce the partial pressure of carbon dioxide and increase the partial pressure of oxygen, returning the partial pressures of these gases towards normal; note that these mechanisms cannot return the partial pressures right back to normal because that would remove the stimulus which is increasing the ventilation.

The main receptors for carbon dioxide are the central chemoreceptors, in the brain stem, which are stimulated by hydrogen ions in the cerebral extracellular fluid, rather than directly by the partial pressure of carbon dioxide in arterial blood. The capillaries in the brain are very impermeable, forming the blood-brain barrier; not even small ions can go between the endothelial cells, so the pH of the extracellular fluid can be different from the pH of the plasma. Carbon dioxide is lipid soluble and can cross endothelial cell membranes, so the concentration of carbon dioxide in the plasma and extracellular fluid will be the same; because of the equilibrium:-

$$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$$

the pH of the extracellular fluid will be determined by the carbon dioxide concentration but not be directly affected by the plasma pH as the hydrogen ions cannot cross the barrier. The Henderson-Hasselbalch equation can be applied to the equilibrium to give:-

$$pH = pK + \log_{10} \frac{[HCO_3^-]}{[CO_2]}$$

so the pH of the extracellular fluid is determined by the concentrations of both hydrogen carbonate ions and carbon dioxide. The extracellular fluid exchanges freely with the cerebrospinal fluid which fills the ventricles of the brain and the subarachnoid space; the cerebrospinal fluid is not a filtrate but an active secretion and its composition can be changed. When the partial pressure of carbon dioxide is raised, the pH of the cerebrospinal fluid will fall but, if the rise in carbon dioxide is prolonged, there may be an increase in the concentration of hydrogen carbonate ions, bringing the pH back to normal, so the central chemoreceptors are no longer stimulated. The patients will still be hypoxic so their peripheral chemoreceptors will be stimulated and keep the ventilation high. This can be a problem if the patients are given air with an increased partial pressure of oxygen to breathe; normally this would help the patients by increasing their alveolar and arterial partial pressures of oxygen but, if the hypoxia is driving the ventilation, the raised level of oxygen will reduce the ventilation, so there will be little increase in the amount of oxygen in the blood but the reduction in ventilation will increase the partial pressure of carbon dioxide even more.

If the partial pressure of oxygen in the inspired air is low, as at high altitudes, there will be hypoxia without a rise in the partial pressure of carbon dioxide and the ventilation will be increased by the hypoxia stimulating the peripheral chemoreceptors. Small decreases in the partial pressure of oxygen do not increase the ventilation; increases occur only when the partial pressure in arterial blood has fallen to somewhat below 10kPa, which corresponds to a partial pressure of 15kPa in inspired air or to altitudes of 3000 metres. This is a useful property because the haemoglobin is fully saturated above 10kPa so that increases in ventilation would not increase the amount of oxygen in arterial blood. Also, any increase in ventilation that did occur would reduce the partial pressure of carbon dioxide which is undesirable.

When the hypoxia is severe enough to increase the ventilation, the partial pressure of carbon dioxide in the alveolar air and arterial blood does fall and a low partial pressure of carbon dioxide (hypocapnia) reduces the ventilation; the combination of hypoxia stimulating the ventilation and hypocapnia slowing it, increases the ventilation only slightly. This phenomenon can be demonstrated in the laboratory: if subjects are given air with a low partial pressure of oxygen to breathe, their ventilation increases and their end tidal partial pressure of carbon dioxide, which is a measure of the alveolar partial pressure of carbon dioxide, falls; if the air has a small amount of carbon dioxide added to it, so that the end tidal carbon dioxide remains constant, the ventilation will increase more than if there were no carbon dioxide in the inspired air. If people remain at high altitudes for a few days, their ventilation increases throughout this time so that it is higher 3 to 4 days after they reached these altitudes than it was on first arriving there; this is one component of the acclimatisation to high altitudes. Initially the increased ventilation reduced the partial pressure of carbon dioxide, making the cerebrospinal fluid alkaline, which reduces the ventilation. It has been suggested that the slow increase in the breathing during acclimatisation arises because the concentration of hydrogen carbonate ions in the cerebrospinal fluid decreases during acclimatisation, bringing the pH of the cerebrospinal fluid back to normal, so that the slowing due to the low partial pressure of carbon dioxide is lost and the full effect of the hypoxia is seen. This is not universally accepted: not all experiments show the pH of the cerebro-spinal fluid declining at the same time as the ventilation increases. If people are given hypoxic gas mixtures containing a little carbon dioxide, the ventilation will increase because of the hypoxia but the carbon dioxide in the inspired air will prevent the alveolar partial pressure of carbon dioxide falling. The ventilation of these people slowly increases over several hours, which suggests that the increase of the breathing is due to hypoxia, not pH changes.

In the other types of hypoxia (anaemic, stagnant and cytotoxic), the arterial partial pressure of oxygen is not reduced, so there will be no increase in the ventilation because the carotid bodies respond more to the partial pressure than to the amount of oxygen in the blood. The absence of an increase in the ventilation is an advantage because the haemoglobin is fully saturated when it leaves the lungs, so an increase in the ventilation would not increase the amount of oxygen carried in the blood, but it would reduce the arterial partial pressure of carbon dioxide which is not raised in these forms of hypoxia.

The red blood cell count

Prolonged hypoxia induces a slow rise in the red blood cell count (polycythaemia), which will increase the amount of haemoglobin in the blood, so increasing the amount of oxygen that the blood can carry at any partial pressure of oxygen; this increases the amount of oxygen being carried to the tissues. A disadvantage of polycythaemia is that the blood becomes more viscous, making it flow less readily. The increase in the red blood cell count is due to more red blood cells being formed; their destruction continues at normal rates. When new red cells enter the circulation they still contain ribosomes and strands of the messenger ribonucleic acid that was used to form their haemoglobin; therefore stains which bind to ribonucleic acid (acidophilic stain) show up the strands as a net, so the new cells are called reticulocytes. When the rate of red cell formation (erythropoiesis) increases, the number of reticulocytes in the blood increases, which is called a reticulocytosis.

The increase in the rate of red cell production is produced by the effect of hypoxia on the kidney. The kidney secretes a renal erythrogenic factor, or erythrogenin, into the blood stream where it acts on a plasma protein, called erythropoietinogen, to produce erythropoietin which stimulates the red bone marrow to make more red cells.

The shape of the dissociation curve

Changes in the pH and the partial pressure of carbon dioxide move the dissociation curve. A reduction in the alveolar ventilation to half its normal value, for example, would reduce the alveolar and arterial partial pressures of oxygen to approximately 7.5kPa and increase the partial pressure of carbon dioxide to around 10.5kPa. If the position of the dissociation curve did not move, the amount of oxygen in arterial blood would be around 175ml/l but the movement of the curve (the Bohr effect) would reduce this figure to 160ml/l; you may find it helpful to look at a dissociation curve in one of your textbooks while reading this. As the tissues take 50ml of oxygen from each litre of blood passing through them, the amount of

oxygen left in the blood as it leaves the tissues will be 125ml/l if the curve did not move and 110ml/l if the curve moves to the right; the partial pressures at which oxygen is released from the haemoglobin will be 4.4kPa if the curve had not moved but will be 4.8kPa after the Bohr shift occurs; this rise in pressure means there is a higher gradient driving the oxygen from the blood to the organs, improving the supply of oxygen.

In stagnant hypoxia the reduced blood flow means that more carbon dioxide has to be added to each unit volume of blood flowing through the tissues, raising the partial pressure of carbon dioxide in the tissues. This is undesirable but it has the compensatory advantage that the raised partial pressure of carbon dioxide will move the oxygen dissociation curve to the right which favours the delivery of oxygen to the tissues.

If the partial pressure of carbon dioxide falls in hypoxic hypoxia, the dissociation curve will move to the left which will increase the amount of oxygen carried by the blood as it leaves the lungs but will also reduce the partial pressure at which the oxygen is released from the haemoglobin. This is undesirable because it reduces the partial pressure gradient driving oxygen from the blood into the tissues, reducing the supply of oxygen to the working cells. When the arterial blood becomes alkaline, as it will if the partial pressure of carbon dioxide falls, there is an increased formation inside the red cells of 2,3-diphosphoglycerate (2,3-DPG) which binds to haemoglobin, moving the dissociation curve to the right. The formation of 2,3-diphosphoglycerate occurs when the low partial pressure of carbon dioxide has shifted the curve to the left and one of 2,3-diphosphoglycerate's main functions may be to prevent or reduce this leftwards movement of the dissociation curve; as the formation of 2,3-diphosphoglycerate is increased when the pH is high, it will not be formed when the partial pressure of carbon dioxide is high, which will reduce the pH, and the curve has already moved to the right.

Anaemia does not affect the pCO2 or pH so it will not generally alter the shape of the dissociation curve but remember that carbon monoxide poisoning is a form of anaemic hypoxia because it makes the haemoglobin unable to combine with oxygen. Also, carbon monoxide poisoning shifts the dissociation curve to the left so that, as well as reducing the amount of oxygen carried on haemoglobin, it makes the haemoglobin less willing to release the oxygen that it does have. Thus a patient who has 50% of his haemoglobin bound to carbon monoxide will be in a worse position than an anaemic patient with only half the normal concentration of haemoglobin. (What is the normal haemoglobin concentration?)

Blood flow through the tissues

Turning to the effects of hypoxia on blood flow, a reduction in the partial pressure of oxygen in the tissues will cause dilatation of arterioles, increasing the blood flow, so that the tissues need to remove less oxygen from each litre of blood flowing through them. If anaerobic metabolism occurs, hydrogen ions will be produced which add to the vasodilatation and further increase the supply of oxygen to the tissues. The hypoxia dilates precapillary sphincters as well as arterioles, so that more capillaries will be open, reducing the distance the oxygen has to cover getting from capillaries to the respiring cells, so that the diffusion of oxygen is increased; in chronic (prolonged) hypoxia new capillaries are formed, further reducing the distance over which diffusion has to occur.

In stagnant hypoxia and most forms of hypoxic hypoxia the concentration of carbon dioxide in the tissues will rise and contribute to the vasodilatation increasing the blood flow. The increased blood flow will help to carry away the carbon dioxide so that the partial pressure of carbon dioxide would not be as high as it otherwise would be. In those forms of hypoxic hypoxia with a low carbon dioxide partial pressure, the fall in carbon dioxide's partial pressure can lead to a vasoconstriction which may be more potent in some organs than the effect of the hypoxia. As well as the direct effect of the blood gases on arterioles, there may also be reflexes due to stimulation of chemoreceptors. When considering these reflexes, remember that many organs can manage without oxygen for a long time and it is only the brain and heart that require a continuous supply of oxygen. Hypoxic stimulation of the carotid bodies produces a bradycardia, which reduces the cardiac output, by vagal stimulation and a vasoconstriction, which spares the coronary and cerebral circulations, by sympathetic stimulation. This response can be beneficial if you stop breathing completely because the blood then circulates mainly to the brain and heart which cannot manage without oxygen while the other organs that can respire anaerobically receive very little

blood flow, so the oxygen that is in the blood will go preferentially to the organs that cannot manage without it; also the reduced cardiac output will reduce the work the heart has to do, so reducing its oxygen needs. A similar effect is obtained in the diving response, where stimulation of the face or upper respiratory tract can produce a slowing of the heart (bradycardia). Stimulation of the aortic chemoreceptors may produce a slight tachycardia.

Stimulation of the carotid body usually increases the ventilation which will stimulate the lung stretch receptors more often and more intensely; the stretch receptors produce a tachycardia (increase the heart rate) and inhibit vasoconstrictor fibres. This will increase the flow of blood through tissues which can compensate for the reduced concentration of oxygen in the blood; it is a useful response where the breathing is continuing but the partial pressure of oxygen in the blood is reduced. During acclimatisation to high altitudes, the cardiac output, unlike the ventilation, returns to normal; the stroke volume falls but the tachycardia persists; the fall in cardiac output may be associated with the rise in the haematocrit.

The partial pressure of carbon dioxide in arterial blood may be either reduced or elevated in hypoxic hypoxia and these changes can produce reflex effects on the cardiovascular system. A raised partial pressure of carbon dioxide will stimulate the vasomotor centre, producing a generalised vasoconstriction which is called the central effect of carbon dioxide and is the opposite to the direct, or local, effect on the arterioles. Conversely, a low partial pressure of carbon dioxide can produce a vasodilatation by inhibiting sympathetic vasoconstrictor fibres and may also have a direct effect on the pacemaker cells of the heart, producing a tachycardia, as in hyperventilation. Hypoxia can also stimulate the defence reaction in which there is vasoconstriction within most organs, but vasodilatation in skeletal muscle; there is also a tachycardia in the defence reaction.

Hypoxia can also release adrenaline from the adrenal medulla which can produce a tachycardia and vasoconstriction in organs where adrenaline stimulates alpha receptors but vasodilatation in organs, such as skeletal muscle, that have many ß receptors. In summary, the response of blood vessels to hypoxia is complicated and the changes vary according to the organ and circumstances involved.

Changes in pH

If the partial pressure of carbon dioxide rises in hypoxia, the pH will fall which is called a respiratory acidosis. At high altitudes the increased ventilation reduces the partial pressure of carbon dioxide, raising the pH so producing a respiratory alkalosis. The kidney returns the pH towards normal by altering the hydrogen carbonate concentration in the plasma but does not affect the partial pressure of carbon dioxide. Hydrogen carbonate ions are filtered at the glomerulus and reabsorbed in the tubule; the mechanism producing the reabsorption was covered in the renal course. Briefly, carbon dioxide in the tubular cells is turned into hydrogen ions and hydrogen carbonate ions. The hydrogen carbonate ions go into the blood while the hydrogen ions go into the tubule where they combine with a hydrogen carbonate ion, turning it into carbon dioxide which goes into the cell. Effectively, this mechanism reabsorbs hydrogen carbonate ions; one ion has been removed from the tubule and one added to the blood.

If fewer hydrogen ions are secreted than there are hydrogen carbonate filtered, fewer hydrogen carbonate ions will be returned to the blood than were filtered so the plasma concentration of hydrogen carbonate ions will fall, reducing the pH. Conversely, if more hydrogen ions are secreted than there are hydrogen carbonate filtered, the plasma concentration of hydrogen carbonate ions will rise increasing the plasma pH. The number of hydrogen ions secreted is determined by the partial pressure of carbon dioxide; the higher is the pressure, the more hydrogen ions are secreted.

In a respiratory acidosis the partial pressure of carbon dioxide is high so more hydrogen ions are secreted, more hydrogen carbonate ions are put back into the blood and the pH will rise back towards normal; conversely in a respiratory alkalosis there will be a fall in hydrogen ion secretion and hydrogen carbonate ions returned to the blood, making the pH fall.

The brighter ones of you may have realised from the equation above that in a respiratory acidosis, the hydrogen carbonate ion concentration will rise, increasing the amount of the ion filtered, so both the hydrogen ion secretion and the hydrogen carbonate filtration will have increased. However, looking at the Henderson-Hasselbalch equation will show you that the ratio of the hydrogen carbonate concentration to the carbon dioxide concentration will fall; therefore the rise in the hydrogen carbonate filtered is smaller than the rise in the hydrogen ion secretion. So there will still be more hydrogen ions secreted into the tubule and hydrogen carbonate put into the blood than there was hydrogen carbonate filtered. Similarly, in a respiratory alkalosis there will be a large fall in the hydrogen ion secretion but only a small fall in the hydrogen carbonate concentration.