Local factors in tissue oxygenation

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Oxygen tension varies from tissue to tissue and is maintained in a dynamic equilibrium between oxygen delivery and oxygen uptake. Both of these factors may vary from time to time, and if PO_2 is measured at a particular point over a period of some hours, slow fluctuations will be observed in most tissues, often with more rapid fluctuations superimposed. A mean level is, however, normally maintained but differs even within a single tissue from place to place. Oxygen uptake reflects local energy requirements and may change relatively slowly in organs such as liver or skin or very rapidly in muscle and brain tissue. To maintain an adequate supply of oxygen to structures with varying requirements there must be an accurate feedback mechanism coupling the need to the delivery system. Local vascular control mechanisms show features characteristic of autoregulation which require a sensor, an effector and a comparator to adjust the blood supply to a suitable value for that particular tissue and time (see fig 1) (Crone, 1975). A large number of factors are involved in the efficient delivery of oxygen to a region and for the fine control of that delivery. Among those of importance are: capillary density, local flow rates, blood viscosity, haemoglobin unloading tensions, the presence of local oxygen buffers such as myoglobin, the oxygen permeability of the vessel wall, the variability of the capillary perfusion pattern and the oxygen diffusion constant in tissue. Several of these factors in turn may be controlled and modified by others. For instance, the unloading tension of oxyhaemoglobin is clearly affected by local pH, CO_2 , 2-3 DPG concentrations and the particular chemical type of the haemoglobin in question. The efficiency of diffusion of oxygen through the tissues depends on the nature of the intercellular matrix, cell density, whether the cells are in physiological or pathological condition, and whether the intercellular spaces are affected by oedema, the presence of microorganisms or necrotic debris. For instance, inflammation may bring a new population of cells to an area which normally has a relatively low oxygen uptake, and inflammatory cells may alter completely the oxygen diffusion profiles. The rate of capillary perfusion also varies not only from time to time in the normal course of physiological adjustment but may be totally altered under pathological conditions.

Changes of oxygen uptake may occur by the process of 'activation', a phenomenon seen chiefly in phagocytes or through the effects of toxins. Pathological processes such as endarteritis, thrombosis or disseminated intravascular coagulation may either block completely or significantly reduce local flow to a tissue. Certain toxins may produce paradoxical effects in that they may reduce flow of blood by causing swelling of vascular endothelium but at the same time reduce oxygen uptake and transitorily cause the oxygen tension in the tissue to rise.

Control of local blood flow

The chief factor in the oxygenation of most tissues is the blood flow in the nutrient capillaries. The rate of flow in these vessels is determined by (a) the arteriolar pressure, (b) the viscosity of the blood, (c) frictional resistance in the capillary bed and (d) the venous back pressure, (e) tissue pressure, and (f) the presence of low pressure bypass vessels. In almost all tissues the capillary bed is in a state of constant change so that at any one time, unless there is a sudden demand for oxygen, probably not more than two-thirds of the capillaries are being perfused. Krogh (1920) postulated and anatomically demonstrated this variability, and more recent techniques have made it possible to demonstrate *in vivo* that his prediction was correct (Bourdeau-Martini *et al*, 1974). Control of flow through the capillaries is exercised at two levels. The first is systemic, operating through central chemo- and baroreceptors and the brain stem vasomotor reflexes, while the second is by local mechanisms. Capillaries may be divided into 'nutrient' or 'exchange' vessels and 'bypass' or 'preferred route' low impedance vessels. The exchange vessels are those that are involved in O_2 delivery but the bypass routes are important in some pathological and physiological emergencies (fig 2).

To be biologically effective capillary blood supply must be closely tailored to the needs of the tissues it is serving. We must therefore conclude that the set points of the oxygen sensors are very variable according to their position in the tissue or that each arteriolar capillary unit has one sensor, strategically placed, and that flow in the unit is geared to the needs of the

Fig 1 Diagram of an autoregulation feedback system

sensor area. A point which is of considerable interest is why it is that certain parts, for instance of the brain or liver, are able to exist permanently at oxygen tensions of approximately 1 mm of mercury, whereas

this same tension, if applied to the whole of the brain, leads to almost immediate extinction of all electrical activity and very rapidly to irreversible changes.

This highlights a problem which occurs in the control of all flow systems where it is usual to find the sensor either within or 'down stream' from the metabolically active area and yet circulatory adjustments must be made through an 'up stream' effector for the flow to be properly regulated. As yet there is no agreement as to what is the form of the sensor in the tissues or how the local flow is modified. Most work on local blood flow has been carried out on voluntary muscle, partly because it is easy to produce very large rapid changes of flow in this tissue and partly because many of the capillaries are arranged in relatively simple parallel arrays (Krogh 1919a, b; Haddy and Scott, 1975). Voluntary muscle can be stimulated to change from a resting to an active state in a few milliseconds and rapidly produces large amounts of metabolites. These tend to be washed out of the active area into the capillaries and venules distal to the site of activity. It has been shown that many of the products of muscle contraction when collected and perfused through the artery do cause changes of local blood flow but it has not been demonstrated that any of them when introduced into or around the 'down stream' section of the vasculature produce any 'up stream' effect (Haddy and Scott, 1975). Factors which have been shown to have an effect are potassium in concentrations of less than 10 mEq/litre, hydrogen ions, ATP, inorganic phosphate and oxygen. Of these only oxygen is known to produce very rapid effects and it is not at all clear whether the other substances are involved in the initiation of changes in vascular tone or in its maintenance or merely assist in some other role. There is some evidence in muscle that potassium may be responsible for the initial vasodilatation and that oxygen lack is responsible for a later long-term increase in flow. A further complication with voluntary muscle is the presence of large numbers of arteriovenous shunts which are under cholinergic nervous control.

Fig 2 Diagrams of an arteriolar-capillary unit under various conditions.

- X Normal—some vessels open, some closed
- Y Hypovolaemia—preferred route only open
- Z Reactive hyperaemia—all vessels open
- A Feedback to fine capillary flow control
- B Preferred route vessel
- C 'Nutrient' capillaries
- D Local flow control mechanism
- AA Arteriole
- V Venule
- S Sensor cell

It has been suggested by Renkin (1966) that the very rapid changes in flow that these arteriovenous shunts bring about may in fact not assist the muscle itself in any way but merely be a means of adjusting the circulatory balance during sudden muscular exercise.

However, Betz *et al* (1973) and Betz (1976) have shown that cerebral arterioles are sensitive to K^+ and H^+ and Ca^{++} although the concentrations used were not physiological and cannot be considered to account necessarily for the physiological control of blood flow.

The need for some autoregulatory mechanism is clear but the details of the mechanisms are more obscure and will be dealt with one by one. The first requirement of any control system is that there should be a sensor which is able to detect deviation from normal. A short-response oxygen sensor is obviously present in such organs as the carotid body where nervous activity can be elicited to rapid changes in oxygen tension, and a long-response one must be present in the kidney where the complex renin-angiotensin and haemopoietin systems are activated by lowered oxygen tension. It is, however, less easy to find hard evidence for oxygen sensors in other tissues although their presence must be inferred. Perhaps the most telling evidence for tissue oxygen sensors other than those which have been mentioned is the increased capillary density in chronic hypoxia (Valdivia, 1962). The oxygen sensor is apparently sensitive to blood or tissue oxygen tension but not to the oxygen capacity of blood. This may lead to a paradoxical situation in chronic hypoxia where the sensor is under continual bombardment because the tissue oxygen tension remains low yet it can only provide signals to stimulate increased capillary growth and hyperplasia of the bone marrow which leads to an increased oxygen capacity in the blood. Although increased blood oxygen capacity may improve oxygenation in the proximal end and middle parts of the capillary, it will not necessarily do so at the lower end of the capillary (fig 3). Thus, the sensor may remain permanently stimulated, but drives an effector mechanism which is partially inappropriate. The cycle of continuing tissue hypoxia and red cell production leads ultimately to the state where the number of red cells is such that the blood viscosity increases to the point where the tissue perfusion rate is reduced due to increased blood viscosity and results in further tissue hypoxia. This vicious cycle of tissue hypoxia and increasing polycythaemia is a feature of aging of mammals evolved at low altitude (Whittembury and Monge, 1972) and is not seen in true high-altitude animals which, although they have a slightly higher haematocrit than the sea-level animals, do not show progressive poly-

Fig 3 Tissue oxygen tension profiles along a capillary. CAP Capillary (a) in hypoxia/ischaemia A Arteriolar end (b) normal profile V Venular end (c) severe polycythaemia

cythaemia and must therefore have an oxygen sensor which is 'set' for a lower tissue PO_2 than that of the sea-level animals.

The nature of the sensor has led to considerable discussion because most of the known attributes of the respiratory enzymes suggests that they are capable of operating effectively at extremely low tensions which are well below those found in tissue. For instance, it has been claimed that cytochrome a-a₃ (cytochrome oxidase) may be the tissue oxygen sensor. Since its K_m for oxygen in mammalian tissue is <0.1 mmHg (10^{-7} M), this suggestion implies that there must either be an extraordinarily steep oxygen gradient between the supply and the respiratory enzyme or some intervening factor which prevents the oxygen reaching cytochrome oxidase. In a recent symposium (Reivich *et al*, 1977) covering the biochemistry of physiological oxygen sensors, a number of suggestions were made as to what these might be. Chance and Wilkstrom (1977) favoured the oxygen reductase, Estabrook (1977) preferred the microsomal enzymes and Gunsalus and Sliger (1977) put forward the suggestion that the mono-oxygenases were the most likely detectors. Among other proposals was the production of local acidity in hypoxia or the lack of production of alkali (Torrance, 1975; Hayes and Torrance, 1975; Torrance, 1977). This suggestion has been made on the basis of the behaviour of the known chemoreceptors but it may not necessarily be relevant to the sensors in tissues outside the specific chemoreceptive cells. On the other hand, cellular mechanisms tend to be conservative and it seems reasonable to suppose that the specialized receptor cells merely demonstrate a general attribute in a rather more obvious fashion. Lahiri (1977) has evidence which suggests that the oxygen sensor may be the binding of molecular

oxygen by a polymeric chromophore group. Fitzgerald (1977) has shown that hypoxia in the carotid body significantly reduces the level of cyclic AMP and if the suggestion of Greengard and Kebabian (1974) concerning the action of endogenous dopamine on the superior cervical ganglion is applicable to the carotid body, one may conclude that in normoxia the dopamine of the type 1 cells of that body may activate an adenylate cyclase-cAMP system somewhere in the axon of the carotid body.

Coburn (1977) has suggested that in smooth muscle cells the O₂-dependent changes in the mechanical tension indicate that the oxygen tension sensor is an oxygenase rather than cytochrome a, a₃ and that the transduction process from the oxygenase to the contractile protein may involve the plasma membrane rather than some variation in energy production and ATP. On the other hand, Berne and Rubio (1977) have demonstrated that reduction in the oxygen supply may produce a change in the relative concentration of the adenine nucleotides (decreased ATP and increased AMP). They suggest that enhanced metabolism may result in the release of a vasodilator metabolite (possibly adenosine) that is linked to the metabolic activity in the tissue and not directly to its PO₂. A wide range of choice is therefore still available for discussion.

Comparator and effector mechanisms

If little is agreed on the subject of oxygen sensors virtually nothing is known of the mechanism of the comparator which is necessary for the maintenance of a constant oxygen supply to a tissue. The importance of the comparator is that it provides a set point about which the oxygen tension is allowed to fluctuate only by a small amount and it controls the mechanism whereby tissue PO₂ can be returned to the appropriate value. It is relatively easy to demonstrate experimentally the existence of the set point by the use of either micro oxygen electrodes (Silver, 1973) or by fluorescent oxygen-sensitive dyes (Longmuir and Knopp, 1973). In either case if the environmental oxygen tension is observed over a period of hours it will be seen that the tension fluctuates not more than $\pm 2\text{--}3$ mmHg. Long-term fluctuations are associated with changes in systemic blood pressure and with waves of arteriolar dilatation and contraction. Superimposed on these waves may be larger short-term changes caused by local muscular contraction or by alterations in position or by some other movement which affects the haemodynamic relationships of that particular region. However much the oxygen tension may be distorted from the set point it is usually rapidly returned to the mean and often overshoots. In most tissues the control is therefore not

exact but is maintained in a state of dynamic equilibrium with a rather slow feedback. By contrast, in essential organs such as the brain, feedback is very much more rapid and this perhaps is not surprising when one considers the extreme oxygen sensitivity of the central nervous system as compared with most other cells in the body. Our own experiments (Silver, 1977) have shown that in the cerebral cortex deviations from the set oxygen tension are usually compensated within about $1\frac{1}{2}$ seconds and similar results have been reported by Moskalenko (1976) who also shows that the compensation is biphasic having a fast and slow component.

The effector mechanism in the control of blood flow has received considerable attention and was originally thought to be either in the form of contractile Rouget cells (pericytes) around capillaries or in the contractility of the capillary walls themselves (Krogh, 1920) or were mediated through 'precapillary sphincters' (Fulton and Lutz, 1940; Chambers and Zweifach, 1944) or the modification of the distal part of the arteriolar wall (Eriksson, 1972). It can be shown that although the walls of the capillaries themselves do not appear to be particularly contractile, it is possible for the nuclear area of the endothelial cell to swell and almost to block the lumen in response to certain types of stimulus, but it is very difficult to demonstrate a specific precapillary sphincter. Clearly arterioles with muscular walls are able to contract but seem to be more involved in systemic than in local autoregulation. Dr D. W. Lübbers (1976, personal communication) has shown very recently in the rat mesentery that stimulation of the wall of a capillary distally may result in the appearance of swelling of the endothelium in the proximal part of the capillary, ie, in the region where one would expect to find a precapillary sphincter.

If a capillary bed is examined with a microscope in preparations such as the rabbit ear chamber, the mesentery or the web of a frog's foot, one sees that capillary flow is variable not only in amount but also in direction. The extremes are of course maximum and nil perfusion, but between these there may be rapid or slow flow or movement which ceases, reverses and subsequently returns to the original pattern. Such ability to change not only the amount but direction of flow indicates either a very fine control or alternatively a certain degree of randomness in supply and demand. In the brain most capillaries appear to be open most of the time, but even here there are fluctuations and there are very low points of oxygen tension within the system (Davies and Brink, 1942; Silver, 1965).

Another possible mechanism for ensuring adequate capillary flow in organs such as muscle, where pressure changes occur frequently, is the so-called

'Bayliss' response, where, in response to decreased transmural pressure, ie, higher tissue pressure in relation to blood pressure, capillary walls relax, and *vice versa* (Haddy and Scott, 1975).

The communication system

While it is obvious that there must be a tissue oxygen sensor, a comparator and an effector, we still have no idea as to what is the connexion between the three. It is supposed that metabolic products or low oxygen tension may act directly or they may act on a sensor which subsequently relays information to the effector (Johnson and Henrich, 1975; Granger *et al*, 1975). The nature of this relay is obscure and it has been postulated (a) that it is nervous, (b) that it is merely diffusion of some messenger substance, or (c) that it may take place by membrane transfer through non-nervous tissues. If this latter is so, the most likely transfer mechanism is either along capillary walls or possibly through glial cells in the central nervous system. So far most experimental attempts to stimulate any kind of communication system directly have always resulted in vasoconstriction rather than in vasodilatation and yet physiologically it is vasodilatation which is the most obvious effect of metabolic activity.

Other vascular factors

It is not only the flow of blood through the tissue which determines the oxygenation of the cells in the vicinity. Other factors are important such as the type of haemoglobin and its particular oxygen unloading characteristics. Most mammalian haemoglobins are sensitive to the pH of the blood, to the level of CO₂ and to the 2-3 DPG concentrations. This latter substance, although very important in man, may be present in some animals such as the sheep without affecting the oxyhaemoglobin unloading tensions. The shape of the oxygen dissociation curve is important as far as the local tissue tensions are concerned and is also important in determining at what level the tissue oxygen sensors must work. For instance, in many animals adapted to living in chronically hypoxic situations the oxygen unloading curve for haemoglobin is shifted to the left. Man is peculiar in that in adapting to high altitude his oxygen dissociation curve is shifted to the right by an increase in 2-3 DPG, although there is, at least initially, a tendency for the blood pH to rise and CO₂ to fall due to overbreathing. True high-altitude animals such as Vicuña, Llama and Guanaco, have a shift to the left which strongly suggests that their tissues must be working at a lower PO₂ than the

average sea-level animal. Some recent reports on blood from Sherpas in the high Himalayas suggests that they too are truly adapted and have shifted their oxyhaemoglobin unloading tensions to the left. This contrasts with the situation in the Andes where most of the people are of mixed Spanish and Indian origin and demonstrate the ordinary sea-level behaviour.

The rate of perfusion of blood through the vessels, the diameter of the capillaries and the relative proportions of cells to plasma are also factors in determining oxygenation of tissues. For instance, the larger the vessel the less relatively is the diffusion area from its surface and therefore the less efficient is its oxygen delivery to the tissue. The faster the flow of blood through an area, the more likely it is that oxyhaemoglobin will emerge in the blood from the distal end of the vessel and the less oxygen will have had time to diffuse into the tissue. On the other hand, unless the flow is maintained above a critical rate cells around the distal end of the capillary will be permanently hypoxic because all the oxygen will have been unloaded before the blood reaches them. Thus a balance must be maintained between the efficiency of oxygen unloading and the danger of hypoxia at the distal end of the capillary. In some specialized tissue such as the heart, although there are long capillaries present these are provided with injections of arteriolar blood along their lengths and the oxygen tension is prevented from falling.

The diameter of blood vessels may be altered by a number of extrinsic factors and an overall control is exerted by the systemic requirements. For instance, in emergencies local autoregulatory mechanisms are overridden by central mechanisms which may result in severe vasoconstriction of 'inessential' organs and the diversion of blood from these organs to vital organs such as the heart and brain.

Pressure effects

The haemostatic pressure in the capillaries is very low (10-15 mmHg) and any external pressure which is above the internal capillary pressure results in compression of the vessels. This assumes considerable clinical significance in the immobile or paralysed patient lying in a hard bed or where pressure bandages have been applied too enthusiastically. Extrinsic pressure resulting in collapse of the capillary bed unless relieved rapidly leads to ischaemic necrosis. Intrinsic pressure can be developed through oedema and in the vicinity of fractures or under conditions of inflammation or allergic oedema there may be an increase of tissue pressure which, if it cannot be relieved, will result in capillary collapse and severe local hypoxia.

Inflammation

Inflammation, as the common response to almost any kind of injury in vascularized tissue, follows a set pattern. Each stage in the inflammatory process produces characteristic changes of oxygen tension. The most obvious of these occur during the periods of vasodilatation when oxygen tension increases briefly and this is then followed by a progressive fall in oxygenation as tissue oedema begins to develop and there is an accumulation of activated oxygen-consuming phagocytic cells. Inflammation in superficial tissues results in an increase in tissue temperature and therefore an increased oxygen uptake due to enhanced metabolism. Furthermore in the later stages of acute inflammation there may be a slowing of flow and haemoconcentration with a result that the distal ends of the capillaries become deeply hypoxic and the venous blood returning from an inflamed area may have an oxygen tension of less than 10. Where infection is involved, if aerobic micro-organisms are present in large numbers, these may also significantly reduce the oxygen tension. Our own measurements show that where toxin-producing organisms such as *Staphylococcus aureus* are involved, there may be a brief period in the later stages of inflammation when oxygen tension suddenly rises due to inhibition of cell respiration by the exotoxin. This is followed almost immediately by a fall as the blood vessels themselves become affected and necrotic endarteritis appears. Similarly, viral endarteritis may produce discrete lesions due to thrombosis or embolism formation or merely to the constriction of arteriolar diameter by the swelling of the endothelium.

Healing tissue

During the process of healing there is a rapid production of new blood vessels, the stimulus for which is unknown, but which appears from recent work (Clark, *et al*, 1976) to be triggered at least in some circumstances by the presence of some substance derived from activated macrophages. New blood vessels tend to grow towards areas of hypoxia and as soon as circulation is developed within them raise the oxygen tension of the tissues in which they form. This may have the result of producing a sudden demand for oxygen among cells which have up to that time been quiescent or glycolytic because of the hypoxic conditions in which they were situated. However, when an adequate oxygen supply has been established at least half of these new capillaries then close down or are only intermittently open, especially if the area becomes fibrosed. In situations of long-term

hypoxia, such as occur in chronic cardiac disease or at high altitude, there is usually a great increase in the number of capillaries in a tissue per unit volume. This leads to a reduction in intercapillary distance and therefore to a reduction in diffusion distance for oxygen from the blood vessel to the most distant cell.

Non-vascular tissue

There are a few tissues in the body which are normally not vascularized such as cartilage, cornea or epidermis. These obtain their oxygen by diffusion either from some special arrangements of vessels near their surface or from the tissue fluid which bathes them. In the case of the cornea most of the oxygen is derived either from the atmosphere or from the vessels of the palpebral conjunctiva when the eyelid is closed, or alternatively from the aqueous humor of the anterior chamber (Barr and Silver, 1973). In the case of cartilage the supply is by diffusion either from the bone on which the cartilage is lying or from other surrounding tissues, or, in the case of joints, from the synovial vessels via the articular fluid. In some large mammals there may be canals through the cartilage containing blood vessels and in all cases there are fluid-filled canals which presumably aid in the delivery of oxygen and nutrients. In avascular tissues there is not of course any autoregulatory mechanism which can increase or decrease the oxygen availability to that area. It seems probable that the growth of new vessels into damaged cartilage or damaged cornea is probably not mediated primarily by an oxygen-sensing device but rather through some product of sensitized macrophages invading the area.

Hypovolaemia

In hypovolaemia, whether or not shock is clinically manifest, the withdrawal of circulation from certain tissues produces profound hypoxia. The skin and splanchnic regions are most obviously affected, but so is healing tissue. Withdrawal of circulation from developing granulation tissue, if prolonged, leads to death of the new fibroblasts but spares pericytes and older cells. Incautious replacement of blood volume by excessive fluid may also lead to a reduction in oxygen in delicate tissues such as the healing wound edge, due to the development of local microoedema.

A feature of severe hypovolaemia is the tendency of blood flow to be maintained, even in vital organs, by perfusion of 'preferred' route capillaries rather than 'nutrient' vessels. This produces areas of severe underperfusion in spite of apparently maintained flow and is exacerbated by any tendency to diffuse intravascular coagulation.

Conclusion

Although the basic principles governing oxygen delivery to tissues are understood, the details of how tissue oxygenation is maintained constant are still obscure.

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