

Factors influencing oxygen availability

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This review gives an account of some of the factors affecting the transport of oxygen from the lungs until its final discharge in the tissues. The sequence of physiological and metabolic processes to be described may be considered collectively as the 'coarse adjustment' of oxygen transport. The 'fine adjustment' will be discussed in the succeeding chapter which surveys the local factors influencing distribution of oxygen from the microcirculation.

Three terms which will doubtless be used more than once during this Symposium are worthy of definition. 'Oxygen availability' consists of two main components: blood flow and oxygen content (which is the product of haemoglobin concentration and oxygen saturation). By means of the Fick equation it can be shown that 'oxygen consumption' equates with the product of blood flow and arteriovenous difference for oxygen. Finally, 'oxygen debt' is the term used to describe the ability of certain tissues, notably muscle, to survive for short periods in the absence of oxygen. This factor may be expressed quantitatively as the product of the reduction in oxygen consumption during a period of hypoxia or ischaemia and its duration.

Oxygen transport

The oxygen transport mechanism is devised in such a way as to combine a large reserve of oxygen together with the capacity for rapid oxygen exchange both in the lungs and in the tissues. The progression of transfer processes has been likened to a cascade (Flenley, 1967) with the partial pressure of oxygen remaining high until the oxygen passes from arterial to capillary blood. The oxygen gradient between capillary blood and the tissues determines the oxygen tension of the mitochondrion which, in turn, determines substrate utilization. Since capillary blood oxygen tension is difficult to measure in clinical practice, mixed venous oxygen tension (or saturation) is often used as a measure of the overall adequacy of oxygen transport and utilization (Goldman, *et al*, 1968; Hutter and Moss, 1970; Verdouw *et al*, 1975; Parr

et al, 1975). Recently, apparatus has been developed which allows continuous measurement and display of mixed venous oxygen saturation in 'at-risk' or critically ill patients (Polanyi, 1974).

If arterial oxygen tension is maintained stable, mixed venous oxygen saturation varies directly with cardiac output and inversely with oxygen consumption. In certain clinical situations, eg, after cardiac surgery, oxygen consumption remains largely unaltered (Raison *et al*, 1970) and under these circumstances mixed venous oxygen saturation is an excellent guide to changes in cardiac output. In other clinical situations, the value of mixed venous oxygen saturation may be less striking since a number of factors may be changing simultaneously, eg, arterial oxygen content and oxygen consumption (Pardy and Dudley, 1977). This is particularly true in the presence of sepsis. Furthermore mixed venous oxygen saturation may conceal changes in regional oxygenation and for this reason, if regional variation in supply is suspected, additional measurements must be made of local oxygen delivery.

Oxygen dissociation

The importance of oxygen dissociation from haemoglobin in determining tissue oxygenation has been appreciated for many years. In an otherwise normal subject with a normal conformation of oxyhaemoglobin dissociation, arterial oxygen tension may fall to 4.0 kPa (30 mm Hg) before there is biochemical evidence of hypoxia; below 2.7 kPa (20 mm Hg) normal substrate metabolism cannot be sustained and death ensues within a very short time. The earliest biochemical change indicating generalized hypoxia is lacticacidaemia although dysfunction of individual organs may be more promptly identified. For example, in a recent study on dogs subjected to haemorrhagic shock (Fronck *et al*, 1974), increase in ornithine carbamoyl transferase activity, which has a high degree of hepatic specificity, was shown to be a more sensitive indicator of imminent refractory shock than lacticacidaemia.

Changes in the shape and position of the oxygen dissociation curve may result from alterations in pH, PCO_2 and temperature (Finch and Lenfant, 1972). More recently attention has turned to the relationship between 2:3 diphosphoglycerate (2:3 DPG) and oxygen dissociation. Diphosphoglycerate is a haemoglobin ligand, and when its level in the red blood cell falls oxygen binding increases and there is a shift to the left of the oxygen dissociation curve with a consequent impairment of oxygen release to the tissues. Shifts in oxyhaemoglobin dissociation are conveniently described as changes in P_{50} (the oxygen partial pressure at which haemoglobin is 50 per cent saturated under standard conditions of pH and temperature), a fall in P_{50} indicating a shift to the left and a rise a shift to the right.

Amongst the causes of acquired abnormalities in haemoglobin dissociation, hypophosphataemia, acidosis and the transfusion of stored blood are the commonest. Hypophosphataemia is not unusual in critically ill patients who are inadvertently receiving phosphate-poor intravenous infusions or phosphate-binders such as aluminium hydroxide, or in the course of haemodialysis (Lichtman *et al*, 1969; Travis *et al*, 1971; Watkins *et al*, 1974; Furlan *et al*, 1975). Acidosis reduces the formation of DPG in the red cell, and in states of chronic acidosis the opposing action of these two mechanisms on oxygen dissociation is balanced. In the event of acutely induced correction of acidosis, however, the increase in pH adds to the low DPG level and produces a marked reduction in P_{50} . Such circumstances may follow the establishment of mechanical ventilation or the administration of sodium bicarbonate. The reduction in P_{50} will be corrected only slowly as new DPG is formed. Stored blood, particularly in acid-citrate dextrose preservative, is low in organic phosphate and infused red cells may take as long as 24 to 48 hours to acquire a normal complement of DPG (fig 1). Blood stored in citrate-phosphate dextrose is to be preferred, particularly if large quantities are to be administered (Jesch *et al*, 1975).

The acute response to reduction in P_{50} and impairment of oxygen discharge to the tissues is a small reduction in mixed venous oxygen tension but in due course cardiac output must increase. The magnitude of the increase is often not fully appreciated. For example, a fall of 0.3 kPa (2 mm Hg) in mixed venous oxygen tension may produce a rise in cardiac output of over 1 litre per minute. In terms of P_{50} a fall of just over 0.5 kPa (4 mm Hg) will require a doubling of cardiac output to maintain the same oxygen supply. In critically ill patients, this may impose a considerable load on an already stressed myocardium; the transfusion of blood with a high 2:3 DPG content has been shown to result in an im-

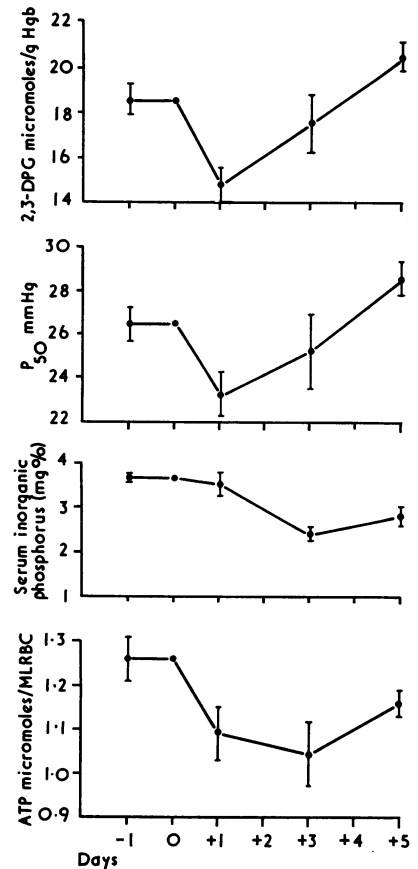


Fig 1 2:3 DPG, P_{50} , inorganic phosphorus and ATP in a group of patients subjected to open heart surgery. 2:3 DPG fell immediately after surgery due, in part, to blood transfusion. Inorganic phosphorus fell later and in association with the fall in ATP (Young *et al*, 1973).

provement in myocardial performance (Dennis *et al*, 1975).

Reduction in oxygen availability

Clinical and laboratory experience has revealed that the body can tolerate a fall of 50 per cent in any of the three components of oxygen availability—blood flow, haemoglobin concentration and oxygen saturation. The general rule is that the reduction of a single component is followed by compensatory changes in the others to restore the *status quo* and maintain tissue oxygenation. If all three components decrease

simultaneously, as may occur in acute trauma, reductions of as little as 30 per cent may prove intolerable unless rapidly corrected (Freeman and Nunn, 1963).

Reduction in blood flow

Reduction in blood flow is the central feature of the shock syndrome (Ledingham and Parratt, 1976). Amongst the main effects induced by hypovolaemic shock, perhaps the most obvious are redistribution of blood flow, changes in the constituents and properties of blood, and shifts in and between the body fluid compartments. Redistribution of blood flow results from reflex neurogenic mechanisms, the release of vasoactive substances into the circulation, and the phenomenon of 'autoregulation'. The precise interrelationship of the several vasoactive substances released into the circulation during generalized hypoxia or ischaemia is uncertain. Pharmacological studies, however, have shown that blockade of catecholamines and angiotensin II greatly modifies the general systemic vascular response to shock (Parratt, 1973; Morton *et al*, 1977) while blockade of histamine and prostaglandins largely prevents the pulmonary vascular response (Parratt and Sturgess, 1977). Autoregulation contributes to the redistribution of blood flow away from less vital to the more vital areas of the body, eg, the brain and the heart (fig 2). Such is the effectiveness of this protective mechanism in privileged organs that it has proved difficult, for example, to establish that the cardiac failure of shock has an ischaemic basis (Ledingham,

1976). In clinical practice the normal physiological responses of the circulation, including autoregulation, may be rendered ineffective by the presence of atherosclerotic vascular disease. Under these circumstances, the pressure/flow relationship becomes linear and organs such as the heart are therefore more vulnerable to ischaemic damage.

The acute changes in vascular resistance during the early stages of shock may be complicated by secondary intravascular changes related to the duration of vasoconstriction, stagnation of the circulation, release of substances from the formed elements of the blood, notably the platelets, and a number of miscellaneous factors, eg, endotoxaemia. The combined effect of these disturbances may be to convert a reversible physiological response into a refractory pathological state, the end result of which is tissue necrosis and defects in coagulation.

Acute reduction in haemoglobin

Acute reduction in haemoglobin without reduction in blood volume may be associated with remarkably little change in oxygen transport because of the accompanying increase in cardiac output (Gruber *et al*, 1976). Studies by Messmer and his colleagues (1973) have confirmed that tissue oxygenation in a number of organs, including the liver, remains essentially unchanged with a reduction in haematocrit to 20 per cent. On the other hand, chronic anaemia is not associated with a rise in cardiac output until the haemoglobin falls below 7g/100ml. More moderate degrees of anaemia are associated with elevation of DPG and decrease in haemoglobin oxygen affinity (fig 3).

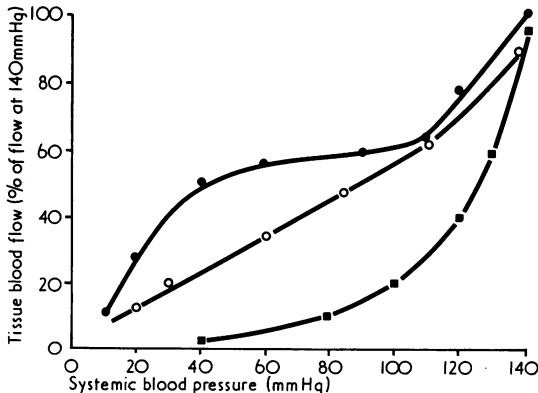


Fig 2 The relationship between systemic arterial (perfusion) pressure and tissue blood flow in organs demonstrating either a passive pressure-flow pattern (■—■; eg, skin) or a vascular autoregulation (●—●; eg, heart and brain). Autoregulation is probably absent in the heart and brain when the major arteries are atheromatous; under these conditions the pressure-flow relationship is probably linear (○—○).

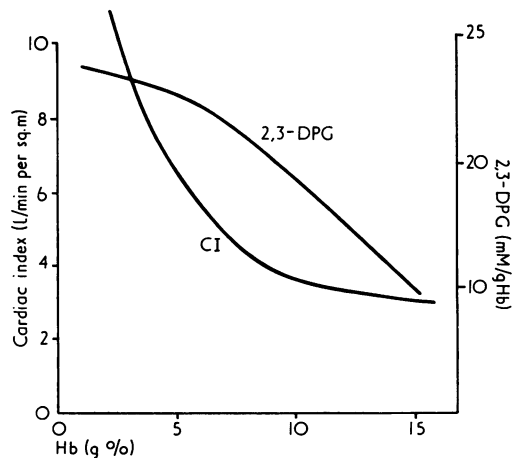


Fig 3 Relationship between haemoglobin, cardiac output and 2:3 DPG in chronic anaemia (quoted in Finch and Lenfant, 1972).

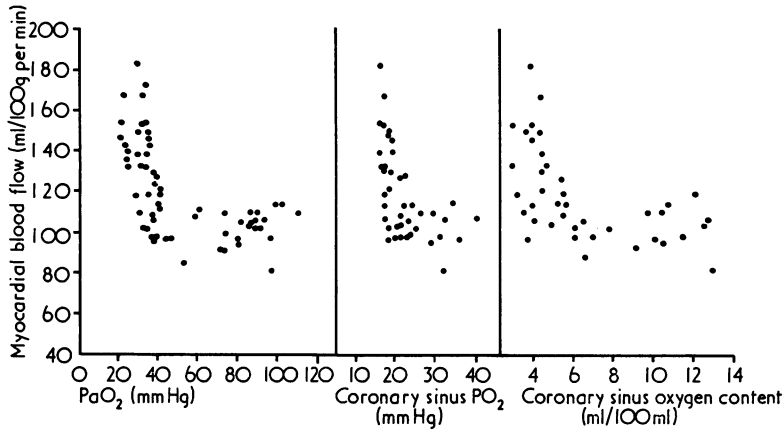


Fig 4 The relationship between myocardial blood flow and PaO_2 , coronary sinus PO_2 and coronary sinus oxygen content. Myocardial blood flow was increased when the PaO_2 fell below 5.3 k Pa (40 mm Hg) equivalent to a coronary sinus PO_2 of 2.4 k Pa (18 mm Hg) or an oxygen content of 5.0 ml/100 ml coronary sinus blood. The results for PaO_2 were obtained from 27 animals and for coronary sinus PO_2 and oxygen content from 22 animals.

Hypoxaemia

Hypoxaemia (or a reduction in PaO_2) produces a host of different reactions depending upon the severity and duration of the hypoxic insult. In organs such as the heart and brain, the worse effects of hypoxaemia, as in shock, are buffered by vascular responses. In the heart, the increase in blood flow evoked by PaO_2 values of 4 kPa (30 mm Hg) (fig 4) is such that oxygen availability to the myocardium is only slightly reduced, and the only sign of impending doom may be the onset of heart block due to hypoxia of the conducting bundles. At these levels of PaO_2 lactic acidosis is occurring in muscles and hepatic dysfunction is present. In yet other organs, hypoxaemia induces vasoconstriction, eg, the lung and the gut (Heath, 1977; Gilmour *et al*, 1977).

Increase in oxygen availability

When hypoxia of anaemic or stagnant origin presents

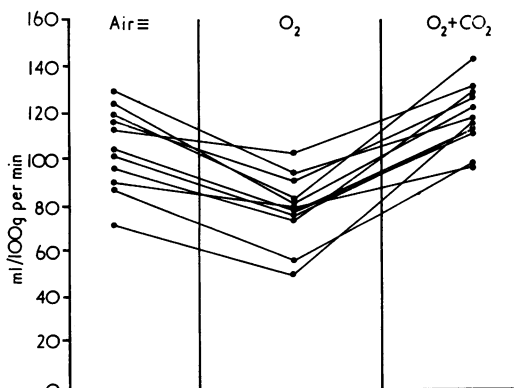


Fig 5 Reduction in normal myocardial blood flow with oxygen at increased pressure. Carbon dioxide reversed the vasoconstrictor action of oxygen.

clinically the normal course of action involves correction of the relevant deficit—red blood cell or blood volume repletion. In the case of local ischaemia, surgical restoration of blood flow is indicated. In certain conditions, eg, acute peripheral vascular disease and myocardial ischaemia, surgical intervention may not be possible and attempts have been made to improve tissue oxygenation using hyperbaric oxygen. An examination of the details of some of these studies may shed some light on the role of oxygen in the control of blood flow.

The normal vascular response to raised arterial oxygen tension is vasoconstriction (fig 5). The vasoconstrictor effect is demonstrable in all organs and the reduction in blood flow is such that mean tissue oxygen availability is little altered in spite of a high arterial oxygen tension. This effect is generally regarded as a protective mechanism against oxygen toxicity in tissues with an otherwise normal blood flow. The interesting observation, however, is that vasoconstriction may also be detected in ischaemic tissues (Schraibman and Ledingham, 1969) (fig 6).

In experimental studies on dogs breathing oxygen at 2 atmospheres absolute, acute ligation of the left anterior descending coronary artery resulted in a lower infarct blood flow and more marked lactate production than in dogs breathing an air equivalent (Ledingham *et al*, 1973). In a more recent study (Ledingham *et al*, 1977), hyperbaric oxygen was administered at 1.5-2 hours after acute coronary artery ligation, a situation which is more relevant to any possible clinical application in patients with acute myocardial infarction. Under these circumstances hyperbaric oxygen decreased cardiac output, and blood flow to both normal and ischaemic myocardial regions. Oxygen consumption by, and availability to, the ischaemic zone were not changed significantly and no changes were observed in lactate handling and in ST-segment depression using epi-

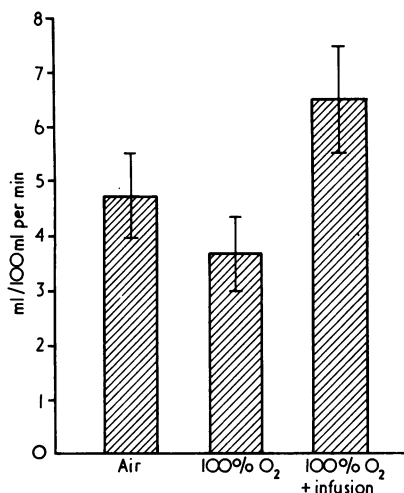


Fig 6 Reduction in foot blood flow in patients with ischaemic vascular disease. Reversal of oxygen effect followed retrograde intravenous infusion of tolazoline.

cardial mapping. These observations suggest that the arteriolar wall is more sensitive to the intravascular vasoconstrictor effect of oxygen than extravascular vasodilatory influences normally present in ischaemic tissue, eg, adenosine, adenosine diphosphate, potassium, lactate and dioxide.

Both in normal and ischaemic tissues the constrictor effect of oxygen may be overcome by pharmacological means, eg, with the carbon dioxide in the normal myocardium (fig 5) and with retrograde infusion of the alpha-blocking agent tolazoline in the ischaemic peripheral circulation (fig 6). The combination of these effects would therefore appear to be an increase in both arterial oxygen tension and blood flow.

In summary, control of oxygen availability to the tissues is a complex mechanism which is just beginning to be understood but a detailed knowledge of which should prove rewarding to scientist and clinician alike.

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