The pulmonary physician in critical care • 2: Oxygen delivery and consumption in the critically ill

R M Leach, D F Treacher

OXYGEN TRANSPORT

Oxygen transport describes the process by which oxygen from the atmosphere is supplied to the tissues as shown in fig 1 in which typical values are quoted for a healthy 75 kg individual. The phases in this process are either convective or diffusive: (1) the convective or “bulk flow” phases are alveolar ventilation and transport in the blood from the pulmonary to the systemic microcirculation: these are energy requiring stages that rely on work performed by the respiratory and cardiac “pumps”; and (2) the diffusive phases are the movement of oxygen from alveolus to pulmonary capillary and from systemic capillary to cell: these stages are passive and depend on the gradient of oxygen partial pressures, the tissue capillary density (which determines diffusion distance), and the ability of the cell to take up and use oxygen.

This review will not consider oxygen transport within the lungs but will focus on transport from the heart to non-pulmonary tissues, dealing specifically with global and regional oxygen delivery, the relationship between oxygen delivery and consumption, and some of the recent evidence relating to the uptake and utilisation of oxygen at the tissue and cellular level.

OXYGEN DELIVERY

Global oxygen delivery (DO₂) is the total amount of oxygen delivered to the tissues per minute irrespective of the distribution of blood flow. Under resting conditions with normal distribution of cardiac output it is more than adequate to meet the total oxygen requirements of the tissues (VO₂) and ensure that aerobic metabolism is maintained.

Recognition of inadequate global DO₂ can be difficult in the early stages because the clinical features are often non-specific. Progressive metabolic acidosis, hyperlactataemia, and falling mixed venous oxygen saturation (SvO₂), as well as organ specific features such as oliguria and impaired level of consciousness, suggest inadequate DO₂. Serial lactate measurements can indicate both progression of the underlying problem and the need for increased oxygen delivery.

Abbreviations: SO₂, oxygen saturation (%); PO₂, oxygen partial pressure (kPa); PCO₂, inspired PO₂; Pao₂, mixed expired PO₂; PICO₂, mixed expired PCO₂; Pao₂, alveolar PO₂; PaO₂, arterial PO₂; SaO₂, arterial SO₂; Svo₂, mixed venous SO₂; QI, cardiac output; Hb, haemoglobin; CaO₂, arterial O₂ content; Cvo₂, mixed venous O₂ content; VO₂, oxygen consumption; VenO₂, CO₂ production; QI, arterial O₂ return; DO₂, oxygen delivery; Vi/e, minute volume, inspiratory/expiratory.
and the response to treatment. Raised lactate levels (>2 mmol/l) may be caused by either increased production or reduced hepatic metabolism. Both mechanisms frequently apply in the critically ill patient since a marked reduction in DO2 produces global tissue ischaemia and impairs liver function.

Table 1 illustrates the calculation of DO2 from the oxygen content of arterial blood (CaO2) and cardiac output (Qt) with examples for a normal subject and a patient presenting with hypoxaemia, anaemia, and a reduced Qt. The effects of providing an increased inspired oxygen concentration, red blood cell transfusion, and increasing cardiac output are shown. This emphasises that: (1) DO2 may be compromised by anaemia, oxygen desaturation, and a low cardiac output, either singly or in combination; (2) global DO2 depends on oxygen saturation rather than partial pressure and there is therefore little extra benefit in increasing PaO2 above 9 kPa since, due to the sigmoid shape of the oxyhaemoglobin dissociation curve, over 90% of haemoglobin (Hb) is already saturated with oxygen at that level. This does not apply to the diffusive component of oxygen transport that does depend on the gradient of oxygen partial pressure.

Although blood transfusion to polycythaemic levels might seem an appropriate way to increase DO2, blood viscosity increases markedly above 100 g/l. This impairs flow and oxygen delivery, particularly in smaller vessels and when the perfusion pressure is reduced, and will therefore exacerbate tissue hypoxia. Recent evidence suggests that even the traditionally accepted Hb concentration for critically ill patients of approximately 100 g/l may be too high since an improved outcome was observed if Hb was maintained between 70 and 90 g/l with the exception of patients with coronary artery disease in whom a level of 100 g/l remains appropriate. With the appropriate Hb achieved by transfusion, and since the oxygen saturation (SaO2) can usually be improved by intubation and mechanical ventilation), cardiac output is the variable that is most often manipulated to achieve the desired global DO2 levels.

**OXYGEN CONSUMPTION**

Global oxygen consumption (VO2) measures the total amount of oxygen consumed by the tissues per minute. It can be measured directly from inspired and mixed expired oxygen concentrations and expired minute volume, or derived from the cardiac output (Qt) and arterial and venous oxygen contents:

\[
\text{VO}_2 = \text{Qt} \times \left( \text{CaO}_2 - \text{CvO}_2 \right)
\]

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**Table 1 Relative effects of changes in PaO2, haemoglobin (Hb), and cardiac output (Qt) on oxygen delivery (DO2)**

<table>
<thead>
<tr>
<th></th>
<th>FiO2</th>
<th>PaO2 (kPa)</th>
<th>SaO2 (%)</th>
<th>Hb (g/l)</th>
<th>Dissolved O2 (ml/l)</th>
<th>CaO2 (ml/l)</th>
<th>Qt (l/min)</th>
<th>DO2 (ml/min)</th>
<th>DO2 (% change)†</th>
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<tbody>
<tr>
<td>Normal*</td>
<td>0.21</td>
<td>13.0</td>
<td>96</td>
<td>130</td>
<td>3.0</td>
<td>170</td>
<td>5.3</td>
<td>900</td>
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<tr>
<td>Patient†</td>
<td>0.21</td>
<td>6.0</td>
<td>75</td>
<td>70</td>
<td>1.4</td>
<td>72</td>
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<td>2.1</td>
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<tr>
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<td>16.5</td>
<td>98</td>
<td>105</td>
<td>3.8</td>
<td>142</td>
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<tr>
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<td>3.8</td>
<td>142</td>
<td>6.0</td>
<td>852</td>
<td>+50</td>
</tr>
</tbody>
</table>

\[
\text{DO}_2 = \text{CaO}_2 \times \text{Qt} \text{ml/min}, \text{CaO}_2 = \left( \text{Hb} \times \text{SaO}_2 \times 1.34 \right) + \left( \text{PaO}_2 \times 0.23 \right) \text{ml/l} \text{where FiO}_2 = \text{fractional inspired oxygen concentration; PaO}_2 = \text{partial pressure, saturation and content of oxygen in arterial blood; Qt = cardiac output. 1.34 ml is the volume of oxygen carried by 1 g of 100% saturated Hb. PaO}_2 (kPa) < 0.23 is the amount of oxygen in physical solution in 1 l of blood, which is less than <3% of total CaO2 for normal PaO2 (ie <14 kPa). *Normal 75 kg subject at rest. †Patient with hypoxaemia, anaemia, reduced cardiac output, and evidence of global tissue hypoxia. ‡Change in DO2 expressed as a percentage of the preceding value.}
Directly measured VO₂ is slightly greater than the derived value that does not include alveolar oxygen consumption. It is important to use the directly measured rather than the derived value when studying the relationship between VO₂ and DO₂ to avoid problems of mathematical linkage.¹

The amount of oxygen consumed (VO₂) as a fraction of oxygen delivery (DO₂) defines the oxygen extraction ratio (OER): OER = VO₂/DO₂

In a normal 75 kg adult undertaking routine activities, VO₂ is approximately 250 ml/min with an OER of 25% (fig 1), which increases to 70–80% during maximal exercise in the well-trained athlete. The oxygen not extracted by the tissues returns to the lungs and the mixed venous saturation (SVO₂) measured in the pulmonary artery represents the pooled venous saturation from all organs. It is influenced by changes in both global DO₂ and VO₂ and, provided the microcirculation and the mechanisms for cellular oxygen uptake are intact, a value above 70% indicates that global DO₂ is adequate.

A mixed venous sample is necessary because the saturation of venous blood from different organs varies considerably. For example, the hepatic venous saturation is usually 40–50% but the renal venous saturation may exceed 80%, reflecting the considerable difference in the balance between the metabolic requirements of these organs and their individual oxygen deliveries.

CLINICAL FACTORS AFFECTING METABOLIC RATE AND OXYGEN CONSUMPTION
The cellular metabolic rate determines VO₂. The metabolic rate increases during physical activity, with shivering, hyperthermia, and raised sympathetic drive (pain, anxiety). Similarly, certain drugs such as adrenaline and feeding regimens containing excessive glucose increase VO₂. Mechanical ventilation eliminates the metabolic cost of breathing which, although normally less than 5% of the total VO₂, may rise to 30% in the catabolic critically ill patient with respiratory distress. It allows the patient to be sedated, given analgesia and, if necessary, paralysed, further reducing VO₂.

RELATIONSHIP BETWEEN OXYGEN CONSUMPTION AND DELIVERY
The normal relationship between VO₂ and DO₂ is illustrated by line ABC in fig 2. As metabolic demand (VO₂) increases or DO₂ diminishes (C–B), OER rises to maintain aerobic metabolism and consumption remains independent of delivery. However, at point B—called critical DO₂ (cDO₂)—the maximum OER is reached. This is believed to be 60–70% and beyond this point any further increase in VO₂ or decline in DO₂ must lead to tissue hypoxia.² In reality there is a family of such VO₂/DO₂ relationships with each tissue/organ having a unique VO₂/DO₂ relationship and value for maximum OER that may vary with stress and disease states. Although the technology currently available makes it impracticable to determine these organ specific relationships in the critically ill patient, it is important to realise that conclusions drawn about the genesis of individual organ failure from the “global” diagram are potentially flawed.

In critical illness, particularly in sepsis, an altered global relationship is believed to exist (broken line DEF in fig 2). The slope of maximum OER falls (DE > AB), reflecting the reduced ability of tissues to extract oxygen, and the relationship does not plateau as in the normal relationship. Hence consumption continues to increase (E–F) to “supranormal” levels of DO₂, demonstrating so called “supply dependency” and the presence of a covert oxygen debt that would be relieved by further increasing DO₂.³

The relationship between global DO₂ and VO₂ in critically ill patients has received considerable attention over the past two decades. Shoemaker and colleagues demonstrated a relationship between DO₂ and VO₂ in the early postoperative phase that had prognostic implications such that patients with higher values had an improved survival.⁴ A subsequent randomised placebo controlled trial in a similar group of patients showed improved survival if the values for DO₂ (>600 ml/min/m²) and SVO₂ (>70%) that had been achieved by the survivors in the earlier study were set as therapeutic targets (“goal directed therapy”).⁵

This evidence encouraged the use of “goal directed therapy” in patients with established (“late”) septic shock and organ dysfunction in the belief that this strategy would increase VO₂ and prevent multiple organ failure. DO₂ was increased using vigorous intravenous fluid loading and inotropes, usually dobutamine. The mathematical linkage caused by calculating both VO₂ and DO₂ using common measurements of Qt and CaO₂ and the “physiological” linkage resulting from the metabolic effects of inotropes increasing both VO₂ and DO₂ were confounding factors in many of these studies. This approach was also responsible for a considerable increase in the use of pulmonary artery catheters to direct treatment. However, after a decade of conflicting evidence from numerous small, often methodologically flawed studies, two major randomised controlled studies finally showed that there was no benefit and possibly harm from applying this approach in patients with established “shock”.⁶⁻⁷ Interestingly, these studies also found that those patients who neither increased their DO₂ spontaneously nor in response to treatment had a particularly poor outcome. This suggested that patients with late “shock” had “poor physiological reserve” with myocardial and other organ failure caused by fundamental cellular dysfunction. These changes would be unresponsive to Shoemaker’s goals that had been successful in “early” shock. Indeed, one might predict that, in patients with the increased endothelial permeability and myocardial dysfunction that typifies late “shock”, aggressive fluid loading would produce widespread tissue oedema impairing both pulmonary gas exchange and tissue oxygen diffusion. The reported increase in mortality associated with the use of pulmonary artery catheters⁸ may reflect the adverse effects of their use in attempting to achieve supranormal levels of DO₂.

SHOULD GOAL DIRECTED THERAPY BE ABANDONED?
Recent studies examining perioperative “optimisation” in patients, many of whom also had significant pre-existing cardiopulmonary dysfunction, have confirmed that identifying and treating volume depletion and poor myocardial performance at an early stage is beneficial.⁹⁻¹⁰ This was the message from Shoemaker’s studies 20 years ago, but unfortunately it was overinterpreted and applied to inappropriate patient populations causing the confusion that has only recently been resolved. Thus, adequate volume replacement in relatively volume depleted perioperative patients is entirely appropriate. However, the strategy of using aggressive fluid replacement...
and vasoactive agents in pursuit of supranormal “global” goals does not improve survival in patients presenting late with incipient or established multiorgan failure. This saga highlights the difference between “early” and “late” shock and the concept well known to traumatologists as the “golden hour”. Of the various forms of circulatory shock, two distinct groups can be defined: those with hypovolaemic, cardiogenic, and obstructive forms of shock (group 1) have the primary problem of a low cardiac output impairing DO₂; those with septic, anaphylactic, and neurogenic shock (group 2) have a problem with the distribution of DO₂ between and within organs—that is, abnormalities of regional DO₂ in addition to any impairment of global DO₂. Sepsis is also associated with cellular/metabolic defects that impair the uptake and utilisation of oxygen by cells. Prompt effective treatment of “early” shock may prevent progression to “late” shock and organ failure. In group 1 the peripheral circulatory response is physiologically appropriate and, if the global problem is corrected by intravenous fluid administration, improvement in myocardial function or relief of the obstruction, the peripheral tissue consequences of prolonged inadequacy of global DO₂ will not develop. However, if there is delay in instituting effective treatment, then shock becomes established and organ failure supervenes. Once this late stage has been reached, manipulation of the “global” or convective components of DO₂ alone will be ineffective. Global DO₂ should nonetheless be maintained by fluid resuscitation to correct hypovolaemia and inotropes to support myocardial dysfunction.

REGIONAL OXYGEN DELIVERY

Hypoxia in specific organs is often the result of disordered regional distribution of blood flow both between and within organs rather than inadequacy of global DO₂. The importance of regional factors in determining tissue oxygenation should not be surprising since, under physiological conditions of metabolic demand such as exercise, alterations in local vascular tone ensure the necessary increase in regional and overall blood flow—that is, “consumption drives delivery”. It is therefore important to distinguish between global and regional DO₂ when considering the cause of tissue hypoxia in specific organs. Loss of normal autoregulation in response to humoral factors during sepsis or prolonged hypotension can cause severe “shunting” and tissue hypoxia despite both global DO₂ and SvO₂ being normal or raised. In these circumstances, improving peripheral distribution and cellular oxygen utilisation will be more effective than further increasing global DO₂. Regional and microcirculatory distribution of cardiac output is determined by a complex interaction of endothelial, neural, metabolic, and pharmacological factors. In health, many of these processes have been intensively investigated and well reviewed elsewhere.

Until recently the endothelium had been perceived as an inert barrier but it is now realised that it has a profound effect on vascular homeostasis, acting as a dynamic interface between the underlying tissue and the many components of flowing blood. In concert with other vessel wall cells, the endothelium not only maintains a physical barrier between the blood and body tissues but also modulates leucocyte migration, angiogenesis, coagulation, and vascular tone through the release of both constrictor (endothelin) and relaxing factors (nitric oxide, prostacyclin, adenosine). The differential release of such factors has an important role in controlling the distribution of regional blood flow during both health and critical illness. The endothelium is both exposed to and itself produces many inflammatory mediators that influence vascular tone and other aspects of endothelial function. For example, nitric oxide production is increased in septic shock following induction of nitric oxide synthase in the vessel wall. Inhibition of nitric oxide synthesis increased vascular resistance and systemic blood pressure in patients with septic shock, but no outcome benefit could be demonstrated. Similarly, capillary microthrombosis following endothelial damage and neutrophil activation is probably a more common cause of local tissue hypoxia than arterial hypoxaemia (fig 3). Manipulation of the coagulation system, for example, using activated protein C may reduce this thrombotic tendency and improve outcome as shown in a recent randomised, placebo controlled, multicentre study in patients with severe sepsis.

The clinical implications of disordered regional blood flow distribution vary considerably with the underlying pathophysiological process. In the critically ill patient splanchic perfusion is reduced by the release of endogenous vasoconstrictors and the gut mucosa is frequently further compromised by failure to maintain enteral nutrition. In sepsis and experimental endotoxaemia the oxygen extraction ratio is reduced and the critical DO₂ increased to a greater extent in splanchic tissue than in skeletal muscle. This tendency to splanchic ischaemia renders the gut mucosa “leaky”, allowing translocation of endotoxin and possibly bacteria into the portal circulation. This toxic load may overwhelm hepatic clearance producing widespread endothelial damage. Treatment aimed at maintaining or improving splanchic perfusion reduces the incidence of multiple organ failure and mortality.

Although increasing global DO₂ may improve blood flow to regionally hypoxic tissues by raising blood flow through all capillary beds, this is an inefficient process and, if achieved using vasoactive drugs, may adversely affect regional distribution, particularly to the kidneys and splanchnic beds. The potent α receptor agonist noradrenaline is frequently used to counteract sepsis induced vasodilation and hypotension. The increase in blood pressure may improve perfusion to certain hypoxia sensitive vital organs but may also compromise blood flow to other organs, particularly the splanchnic bed. The role of vasodilators is less well defined: tissue perfusion is frequently already compromised by systemic hypotension and a reduced systemic vascular resistance, and their effect on regional distribution is unpredictable and may impair blood flow to vital organs despite increasing global DO₂. In a group of critically ill patients prostacyclin increased both DO₂ and VO₂, and this was interpreted as indicating that there was a previously unidentified oxygen debt. However, there is no convincing evidence that vasodilators improve outcome in critically ill patients. An alternative strategy that attempts to redirect blood flow from overperfused non-essential tissues such as skin and muscle tissues to underperfused “vital” organs by exploiting the differences in receptor population and density between different arteries is theoretically attractive. While
Oxygen delivery at the tissue level

Individual organs and cells vary considerably in their sensitivity to hypoxia. Neurons, cardiomyocytes, and renal tubular cells are exquisitely sensitive to a sudden reduction in oxygen supply and are unable to survive sustained periods of hypoxia, although ischaemic preconditioning does increase tolerance to hypoxia. Following complete cessation of cerebral perfusion, nuclear magnetic resonance (NMR) measurements show a 50% decrease in cellular adenosine triphosphate (ATP) within 30 seconds and irreversible damage occurs within 3 minutes. Mechanisms have developed in other tissues to survive longer without oxygen: the kidneys and liver can tolerate 15–20 minutes of total hypoxia, skeletal muscle 60–90 minutes, and vascular smooth muscle 24–72 hours. The most extreme example of hypoxic tolerance is that of hair and nails which continue to grow for several days after death.

Variation in tissue tolerance to hypoxia has important clinical implications. In an emergency, maintenance of blood flow to the most hypoxia sensitive organs should be the primary goal. Hypoxic brain damage after cardiorespiratory collapse will leave a patient incapable of independent life even if the other organ systems survive. Although tissue death may not occur as rapidly in less oxygen sensitive tissues, prolonged failure to make the diagnosis has equally serious consequences. For example, skeletal muscle may survive severe ischaemia for several hours but failure to remove the causative arterial embolus will result in muscle necrosis with the release into the circulation of myoglobin and other toxins and activation of the inflammatory response.

Tolerance to hypoxia differs in health and disease. In a septic patient inhibition of enzyme systems and oxygen utilisation reduces hypoxic tolerance. Methods aimed at enhancing metabolic performance including the use of alternative substrates, techniques to inhibit endotoxin induced cellular damage, and drugs to reduce oxidant induced intracellular damage are currently under investigation. Ischaemic preconditioning of the heart and skeletal muscle is recognised both in vivo and in experimental models. Progressive or
repeated exposure to hypoxia enhances tissue tolerance to oxygen deprivation in much the same way as altitude acclimatisation. An acclimatised mountaineer at the peak of Mount Everest can tolerate a PaO2 of 4–4.5 kPa for several hours, which would result in loss of consciousness within a few minutes in a normal subject at sea level.

What is the critical level of tissue oxygenation below which cellular damage will occur? The answer mainly depends on the patient’s circumstances, comorbid factors, and the duration of hypoxia. For example, young previously healthy patients with acute respiratory distress syndrome tolerate prolonged hypoxaemia with saturations as low as 85% and can recover completely. In the older patient with widespread atheroma, however, prolonged hypoxaemia at such levels would be unacceptable.

RECOGNITION OF INADEQUATE TISSUE OXYGEN DELIVERY

The blood lactate concentration is an unreliable indicator of tissue hypoxia. It represents a balance between tissue production and consumption by hepatic and, to a lesser extent, by cardiac and skeletal muscle. It may be raised or normal during hypoxia because the metabolic pathways utilising glucose during aerobic metabolism may be blocked at several points. Inhibition of phosphofructokinase blocks glucose utilisation without an increase in lactate concentration. In contrast, endotoxin and sepsis may inactivate pyruvate dehydrogenase, preventing pyruvate utilisation in the Krebs cycle resulting in lactate production in the absence of hypoxia. Similarly, a normal DO2 with an unfavourable cellular redox state may result in a high lactate concentration, whereas compensatory reductions in energy state [ATP]/[ADP][Pi] or [NAD]/[NADH] may be associated with a low lactate concentration during hypoxia. Thus, the value of a single lactate measurement in the assessment of tissue hypoxia is limited. The suggestion that pathological supply dependency occurs only when blood lactate concentrations are raised is incorrect as the same relationship may be found in patients with normal lactate concentrations. Serial lactate measurements, particularly if corrected for pyruvate, may be of greater value.

Measurement of individual organ and tissue oxygenation is an important goal for the future. These measurements are difficult, require specialised techniques, and are not widely available. At present only near infrared spectroscopy and gastric tonometry have clinical applications in the detection of organ hypoxia. In the future NMR spectroscopy may allow direct non-invasive measurement of tissue energy status and oxygen utilisation.

CELLULAR OXYGEN UTILISATION

In general, eukaryotic cells are dependent on aerobic metabolism as mitochondrial respiration offers greater efficiency for extraction of energy from glucose than anaerobic glycolysis. The maintenance of oxidative metabolism is dependent on complex but poorly understood mechanisms for microvascular oxygen distribution and cellular oxygen uptake. Teleologically, the response to reduced blood flow in a tissue is likely to have evolved as an energy conserving mechanism when substrates, particularly molecular oxygen, are scarce. Pathways that use ATP are suppressed and alternative anaerobic pathways for
ATP synthesis are induced.\textsuperscript{27} This process involves oxygen sensing and transduction mechanisms, gene activation, and protein synthesis.

**CELLULAR METABOLIC RESPONSE TO HYPOXIA**

Although cellular metabolic responses to hypoxia remain poorly understood, the importance of understanding and modifying the cellular responses to acute hypoxia in the critically ill patient has recently been appreciated. In isolated mitochondria the partial pressure of oxygen required to generate high energy phosphate bonds (ATP) that maintain aerobic cellular biochemical functions is only about 0.2–0.4 kPa.\textsuperscript{17–20} However, in intact cell preparations hypoxia induced damage may result from failure of energy dependent membrane ion channels with subsequent loss of membrane integrity, changes in cellular calcium homeostasis, and oxygen dependent changes in cellular enzyme activity.\textsuperscript{38} The sensitivity of an enzyme to hypoxia is a function of its $P_{O_2}$ in mm Hg at which the enzyme rate is half maximum ($K_m O_2$).\textsuperscript{37} and the wide range of values for a variety of cellular enzymes is shown in table 2, illustrating that certain metabolic functions are much more sensitive to hypoxia than others. Celluar tolerance to hypoxia may involve “hibernation” strategies that reduce metabolic rate, increased oxygen extraction from surrounding tissues, and enzyme adaptations that allow continuing metabolism at low partial pressures of oxygen.\textsuperscript{37}

Anaerobic metabolism is important for survival in some tissues despite its inherent inefficiency: skeletal muscle increases glucose uptake by 600% during hypoxia and bladder smooth muscle can generate up to 60% of total energy requirement by anaerobic glycolysis.\textsuperscript{28} In cardiac cells anaerobic glucose utilisation protects cell membrane integrity by maintaining energy dependent K$^+$ channels.\textsuperscript{19} During hypoxic stress endothelial and vascular smooth muscle cells increase glucose transport through the expression of membrane glucose transporters (GLUT1 and GLUT-4) and the production of glycolytic enzymes, thereby increasing anaerobic glycolysis and maintaining energy production.\textsuperscript{37} High energy functions like ion transport and protein production are downregulated to balance supply and demand.

Cellular oxygen utilisation is inhibited by metabolic poisons (cyanide) and toxins associated with sepsis such as endotoxin and other cytokines, thereby reducing energy production.\textsuperscript{29} It is yet to be established whether there are important differences in the response to tissue hypoxia resulting from damage to mitochondrial and other intracellular functions as occurs in poisoning and sepsis, as opposed to situations such as exercise and altitude when oxygen consumption exceeds supply.

**OXYGEN SENSING AND GENE ACTIVATION**

The molecular basis for oxygen sensing has not been established and may differ between tissues. Current evidence suggests that, following activation of a “hypoxic sensor”, the signal is transmitted through the cell by second messengers which then activate regulatory protein complexes termed transcription factors.\textsuperscript{41–43} These factors translocate to the nucleus and bind with specific DNA sequences, activating various genes with the subsequent production of effector proteins. It has long been postulated that the “hypoxic sensor” may involve haem-containing proteins, redox potential or mitochondrial cytochromes.\textsuperscript{44} Recent evidence from vascular smooth muscle suggests that hypoxia induced inhibition of electron transfer at complex III in the electron transport chain may act as the “hypoxic sensor”.\textsuperscript{45} This sensing mechanism is associated with the production of oxygen free radicals (ubiquinone cycle) that may act as second messengers in the activation of transcription factors.

Several transcription factors play a role in the response to tissue hypoxia including hypoxia inducible factor 1 (HIF-1), early growth response 1 (Erg-1), activator protein 1 (AP-1), nuclear factor kappa-B (NF-$\kappa$B), and nuclear factor IL-6 (NF-IL-6). HIF-1 influences vascular homeostasis during hypoxia by activating the genes for erythropoietin, nitric oxide synthase, vascular endothelial growth factor, and glycolytic enzymes and glucose transport thereby altering metabolic function.\textsuperscript{46} Erg-1 protein is also rapidly induced by hypoxia leading to transcription of tissue factor, which triggers prothrombotic events.\textsuperscript{47}

**Key points**

- Restoration of global oxygen delivery is an important goal in early resuscitation but thereafter circulatory manipulation to sustain “supranormal” oxygen delivery does not improve survival and may be harmful.
- Regional distribution of oxygen delivery is vital: if skin and muscle receive high blood flows but the splanchic bed does not, the gut may become hypoxic despite high global oxygen delivery.
- Microcirculatory, tissue diffusion, and cellular factors influence the oxygen status of the cell and global measurements may fail to identify local tissue hypoxia.
- Supranormal levels of oxygen delivery cannot compensate for diffusion problems between capillary and cell, nor for metabolic failure within the cell.
- When assessing $D_O/V_O$ relationships, direct measurements should be used to avoid errors due to mathematical linkage.
- Strategies to reduce metabolic rate to improve tissue oxygenation should be considered.

**Table 2**  Oxygen affinities of cellular enzymes expressed as the partial pressure of oxygen in mm Hg at which the enzyme rate is half maximum ($K_m O_2$)

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>$K_m O_2$</th>
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