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REVIEW SERIES

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

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Early detection and correction of tissue hypoxia is essential if progressive organ dysfunction and death are to be avoided. However, hypoxia in individual tissues or organs caused by disordered regional distribution of oxygen delivery or disruption of the processes of cellular oxygen uptake and utilisation cannot be identified from global measurements. Regional oxygen transport and cellular utilisation have an important role in maintaining tissue function. When tissue hypoxia is recognised, treatment must be aimed at the primary cause. Supplemental oxygen may be life saving in some situations but cannot correct inadequate oxygen delivery caused by a low cardiac output or impaired ventilation. Recent innovations include artificial oxygen carrying proteins and "haemoglobin" molecules designed to improve tissue blood flow by reducing viscosity. Regulating cell metabolism using different substrates or drugs has so far been poorly explored but is an exciting area for further research. A minimum level of global oxygen delivery and perfusion pressure must be maintained in the critically ill patient with established "shock", but advances in the understanding and control of regional distribution and other "downstream" factors in the oxygen cascade are needed to improve outcome in these patients.

Although traditionally interested in conditions affecting gas exchange within the lungs, the respiratory physician is increasingly, and appropriately, involved in the care of critically ill patients and therefore should be concerned with systemic as well as pulmonary oxygen transport. Oxygen is the substrate that cells use in the greatest quantity and upon which aerobic metabolism and cell integrity depend. Since the tissues have no storage system for oxygen, a continuous supply at a rate that matches changing metabolic requirements is necessary to maintain aerobic metabolism and normal cellular function. Failure of oxygen supply to meet metabolic needs is the feature common to all forms of circulatory failure or "shock". Prevention, early identification, and correction of tissue hypoxia are therefore necessary skills in managing the critically ill patient and this requires an understanding of oxygen transport, delivery, and consumption.

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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 (DO_2) 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 (VO_2) and ensure that aerobic metabolism is maintained.

Recognition of inadequate global DO_2 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 (SVO_2), as well as organ specific features such as oliguria and impaired level of consciousness, suggest inadequate DO_2. Serial lactate measurements can indicate both progression of the underlying problem

Abbreviations: SO_2, oxygen saturation (%); PO_2, oxygen partial pressure (kPa); PIO_2, inspired PO_2; PEO_2, mixed expired PO_2; $PECO_2$, mixed expired PCO_2; PAO_2, alveolar PO_2; PaO_2, arterial PO_2; SaO_2, arterial SO_2; SvO_2, mixed venous SO_2; Qt, cardiac output; Hb, haemoglobin; CaO_2, arterial O_2 content; CvO_2, mixed venous O_2 content; VO_2, oxygen consumption; VCO_2, CO_2 production; O_2R, oxygen return; DO_2, oxygen delivery; Vi/e, minute volume, inspiratory/expiratory.

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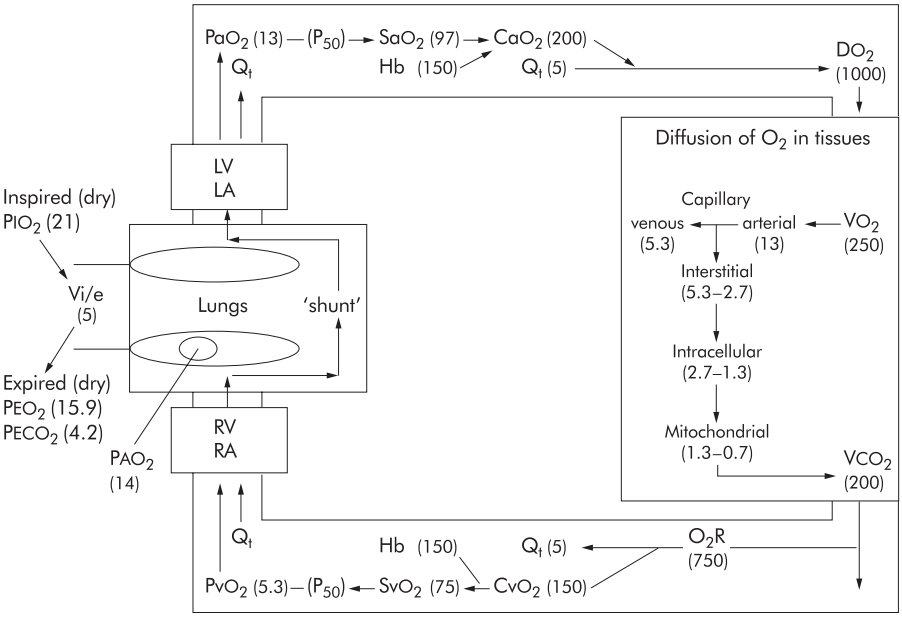

Figure 1 Oxygen transport from atmosphere to mitochondria. Values in parentheses for a normal 75 kg individual (BSA 1.7 m^2) breathing air (FIO_2 0.21) at standard atmospheric pressure (P_B 101 kPa). Partial pressures of O_2 and CO_2 (PO_2, PCO_2) in kPa; saturation in %; contents (CaO_2, CvO_2) in ml/l; Hb in g/l; blood/gas flows (Qt, Vi/e) in l/min. P_{50} = position of oxygen haemoglobin dissociation curve; it is PO_2 at which 50% of haemoglobin is saturated (normally 3.5 kPa). DO_2 = oxygen delivery; VO_2 = oxygen consumption, VCO_2 = carbon dioxide production; PIO_2, PEO_2 = inspired and mixed expired PO_2; $PECO_2$ = mixed expired PCO_2; PAO_2 = alveolar PO_2.

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 DO_2 produces global tissue ischaemia and impairs liver function.

Table 1 illustrates the calculation of DO_2 from the oxygen content of arterial blood (CaO_2) 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) DO_2 may be compromised by anaemia, oxygen desaturation, and a low cardiac output, either singly or in combination; (2) global DO_2 depends on oxygen saturation rather than partial pressure and there is therefore little extra benefit in increasing PaO_2 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 DO_2, 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.[1] 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.[2] With the appropriate Hb achieved by transfusion, and since the oxygen saturation (SaO_2) can usually be maintained above 90% with supplemental oxygen (or if necessary by intubation and mechanical ventilation), cardiac output is the variable that is most often manipulated to achieve the desired global DO_2 levels.

OXYGEN CONSUMPTION

Global oxygen consumption (VO_2) 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:

$$VO_2 = Qt \times (CaO_2 - CvO_2)$$

Table 1 Relative effects of changes in PaO_2, haemoglobin (Hb), and cardiac output (Qt) on oxygen delivery (DO_2)

	FIO_2	PaO_2 (kPa)	SaO_2 (%)	Hb (g/l)	Dissolved O_2 (ml/l)	CaO_2 (ml/l)	Qt (l/min)	DO_2 (ml/min)	DO_2 (% change)‡
Normal*	0.21	13.0	96	130	3.0	170	5.3	900	0
Patient†	0.21	6.0	75	70	1.4	72	4.0	288	– 68
↑FIO_2	0.35	9.0	92	70	2.1	88	4.0	352	+ 22
↑↑FIO_2	0.60	16.5	98	70	3.8	96	4.0	384	+ 9
↑Hb	0.60	16.5	98	105	3.8	142	4.0	568	+48
↑Qt	0.60	16.5	98	105	3.8	142	6.0	852	+50

$DO_2 = CaO_2 \times Qt$ ml/min, CaO_2 = (Hb × SaO_2 × 1.34) + (PaO_2 × 0.23) ml/l where FIO_2 = fractional inspired oxygen concentration; PaO_2, SaO_2, CaO_2 = 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 CaO_2 for normal PaO_2 (ie <14 kPa). *Normal 75 kg subject at rest. †Patient with hypoxaemia, anaemia, reduced cardiac output, and evidence of global tissue hypoxia. ‡Change in DO_2 expressed as a percentage of the preceding value.

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Directly measured V_{O_2} 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 V_{O_2} and D_{O_2} to avoid problems of mathematical linkage.[3]

The amount of oxygen consumed (V_{O_2}) as a fraction of oxygen delivery (D_{O_2}) defines the oxygen extraction ratio (OER):

$OER = V_{O_2}/D_{O_2}$

In a normal 75 kg adult undertaking routine activities, V_{O_2} 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 (S_{VO_2}) measured in the pulmonary artery represents the pooled venous saturation from all organs. It is influenced by changes in both global D_{O_2} and V_{O_2} and, provided the microcirculation and the mechanisms for cellular oxygen uptake are intact, a value above 70% indicates that global D_{O_2} 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 V_{O_2}. The metabolic rate increases during physical activity, with shivering, hyperthermia and raised sympathetic drive (pain, anxiety). Similarly, certain drugs such as adrenaline[4] and feeding regimens containing excessive glucose increase V_{O_2}. Mechanical ventilation eliminates the metabolic cost of breathing which, although normally less than 5% of the total V_{O_2}, 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 V_{O_2}.

RELATIONSHIP BETWEEN OXYGEN CONSUMPTION AND DELIVERY

The normal relationship between V_{O_2} and D_{O_2} is illustrated by line ABC in fig 2. As metabolic demand (V_{O_2}) increases or D_{O_2} diminishes (C–B), OER rises to maintain aerobic metabolism and consumption remains independent of delivery. However, at point B—called critical D_{O_2} (cD_{O_2})—the maximum OER is reached. This is believed to be 60–70% and beyond this point any further increase in V_{O_2} or decline in D_{O_2} must lead to tissue hypoxia.[5] In reality there is a family of such V_{O_2}/D_{O_2} relationships with each tissue/organ having a unique V_{O_2}/D_{O_2} 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 *v* 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 D_{O_2}, demonstrating so called "supply dependency" and the presence of a covert oxygen debt that would be relieved by further increasing D_{O_2}.[6]

The relationship between global D_{O_2} and V_{O_2} in critically ill patients has received considerable attention over the past two decades. Shoemaker and colleagues demonstrated a relationship between D_{O_2} and V_{O_2} in the early postoperative phase that

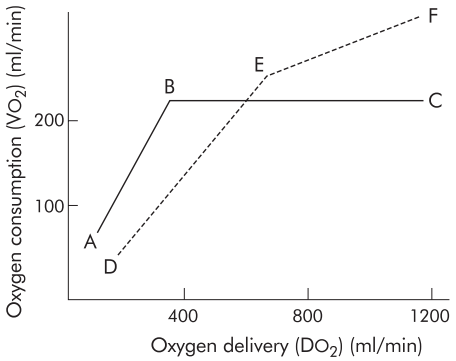

Figure 2 Relationship between oxygen delivery and consumption.

had prognostic implications such that patients with higher values had an improved survival.[7] A subsequent randomised placebo controlled trial in a similar group of patients showed improved survival if the values for D_{O_2} (>600 ml/min/m^2) and S_{VO_2} (>70%) that had been achieved by the survivors in the earlier study were set as therapeutic targets ("goal directed therapy").[8]

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 V_{O_2} and prevent multiple organ failure. D_{O_2} was increased using vigorous intravenous fluid loading and inotropes, usually dobutamine. The mathematical linkage caused by calculating both V_{O_2} and D_{O_2} using common measurements of Qt and Ca_{O_2}[3] and the "physiological" linkage resulting from the metabolic effects of inotropes increasing both V_{O_2} and D_{O_2} were confounding factors in many of these studies.[9] 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".[10 11] Interestingly, these studies also found that those patients who neither increased their D_{O_2} 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 catheters[12] may reflect the adverse effects of their use in attempting to achieve supranormal levels of D_{O_2}.

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.[13–16] 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

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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 Do_2; those with septic, anaphylactic, and neurogenic shock (group 2) have a problem with the distribution of Do_2 between and within organs—that is, abnormalities of regional Do_2 in addition to any impairment of global Do_2. 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 Do_2 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 Do_2 alone will be ineffective. Global Do_2 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 Do_2.[17] 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 Do_2 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 Do_2 and Svo_2 being normal or raised.[18] In these circumstances, improving peripheral distribution and cellular oxygen utilisation will be more effective than further increasing global Do_2. 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.[19]

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).[20] 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.[21] 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.[22]

Figure 3 Example of tissue ischaemia and necrosis from extensive microvascular and macrovascular occlusion in a patient with severe meningococcal sepsis.

The clinical implications of disordered regional blood flow distribution vary considerably with the underlying pathological process. In the critically ill patient splanchnic 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 Do_2 increased to a greater extent in splanchnic tissue than in skeletal muscle.[23] This tendency to splanchnic 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 splanchnic perfusion reduces the incidence of multiple organ failure and mortality.[24]

Although increasing global Do_2 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 Do_2. In a group of critically ill patients prostacyclin increased both Do_2 and Vo_2 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

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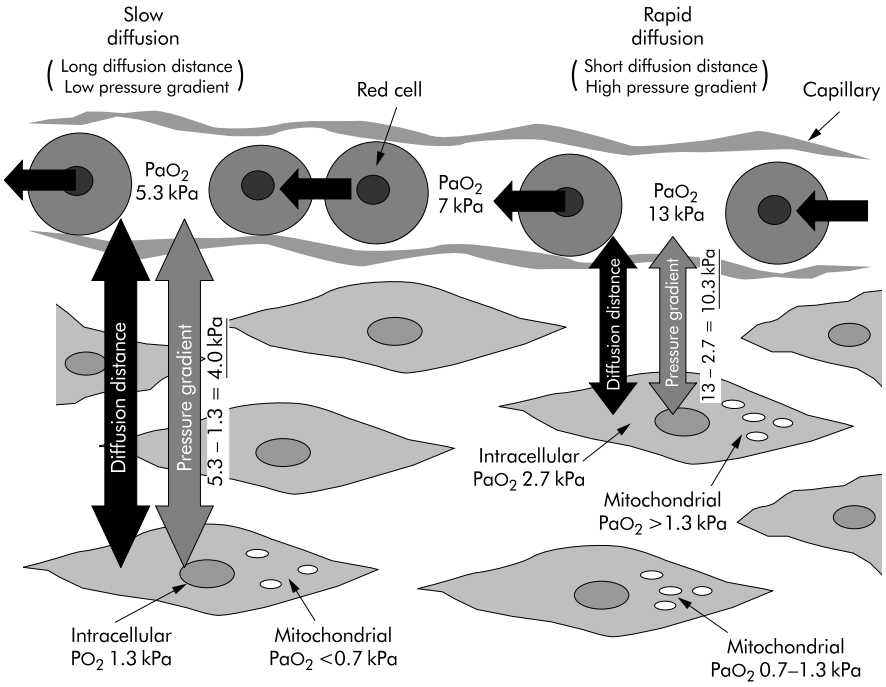

Figure 4 Diagram showing the importance of local capillary oxygen tension and diffusion distance in determining the rate of oxygen delivery and the intracellular P_{O_2}. On the left there is a low capillary P_{O_2} and pressure gradient for oxygen diffusion with an increased diffusion distance resulting in low intracellular and mitochondrial P_{O_2}. On the right the higher P_{O_2} pressure gradient and the shorter diffusion distance result in significantly higher intracellular P_{O_2} values.

dobutamine may reduce splanchnic perfusion, dopexamine hydrochloride has dopaminergic and β-adrenergic but no α-adrenergic effects and may selectively increase renal and splanchnic blood flow.[25]

OXYGEN TRANSPORT FROM CAPILLARY BLOOD TO INDIVIDUAL CELLS

The delivery of oxygen from capillary blood to the cell depends on:

- factors that influence diffusion (fig 4);
- the rate of oxygen delivery to the capillary (D_{O_2});
- the position of the oxygen-haemoglobin dissociation relationship (P_{50});
- the rate of cellular oxygen utilisation and uptake (V_{O_2}).

The sigmoid oxygen-haemoglobin dissociation relationship is influenced by various physicochemical factors and its position is defined by the Pa_{O_2} at which 50% of the Hb is saturated (P_{50}), normally 3.5 kPa. An increase in P_{50} or rightward shift in this relationship reduces the Hb saturation (Sa_{O_2}) for any given Pa_{O_2}, thereby increasing tissue oxygen availability. This is caused by pyrexia, acidosis, and an increase in intracellular phosphate, notably 2,3-diphosphoglycerate (2,3-DPG). The importance of correcting hypophosphataemia, often found in diabetic ketoacidosis and sepsis, is frequently overlooked.[26]

Mathematical models of tissue hypoxia show that the fall in cellular oxygen resulting from an increase in intercapillary distance is more severe if the reduction in tissue D_{O_2} is caused by "hypoxic" hypoxia (a fall in Pa_{O_2}) rather than "stagnant" (a fall in flow) or "anaemic" hypoxia (fig 5).[27] Studies in patients with hypoxaemic respiratory failure have also shown that it is Pa_{O_2} rather than D_{O_2}—that is, diffusion rather than convection—that has the major influence on outcome.[9]

Thus, tissue oedema due to increased vascular permeability or excessive fluid loading may result in impaired oxygen diffusion and cellular hypoxia, particularly in clinical situations associated with arterial hypoxaemia. In these situations, avoiding tissue oedema may improve tissue oxygenation.

OXYGEN DELIVERY AT THE TISSUE LEVEL

Individual organs and cells vary considerably in their sensitivity to hypoxia.[28] 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.[29] 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

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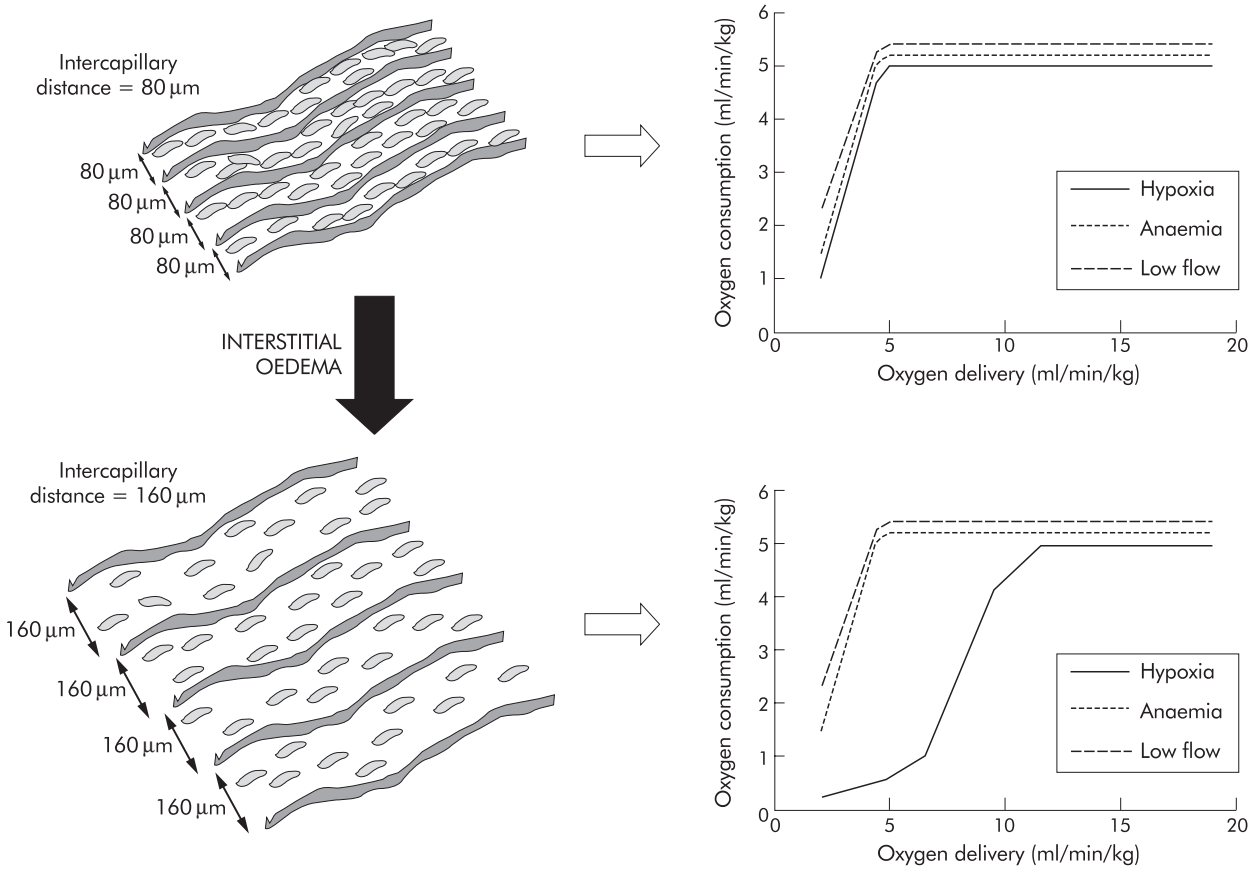

Figure 5 Influence of intercapillary distance on the effects of hypoxia, anaemia, and low flow on the oxygen delivery-consumption relationship. With a normal intercapillary distance illustrated in the top panels the D_{O_2}/V_{O_2} relationship is the same for all interventions. However, in the lower panels an increased intercapillary distance, as would occur with tissue oedema, reducing D_{O_2} by progressive falls in arterial oxygen tension results in a change in the D_{O_2}/V_{O_2} relationship with V_{O_2} falling at much higher levels of global D_{O_2}. This altered relationship is not seen when D_{O_2} is reduced by anaemia or low blood flow.

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 Pa_{O_2} 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 the 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.[30] It may be raised or normal during hypoxia because the metabolic pathways utilising glucose during aerobic metabolism may be blocked at several points.[31] 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.[32] Similarly, a normal D_{O_2} 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.[33] Thus, the value of a single lactate measurement in the assessment of tissue hypoxia is limited.[34] 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.[35] 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.[24] In the future NMR spectroscopy may allow direct non-invasive measurement of tissue energy status and oxygen utilisation.[36]

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

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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 (Km_{O_2})

Enzyme	Substrate	Km_{O_2}
Glucose oxidase	Glucose	57
Xanthine oxidase	Hypoxanthine	50
Tryptophan oxygenase	Tryptophan	37
Nitric oxide synthase	L-arginine	30
Tyrosine hydroxylase	Tyrosine	25
NADPH oxidase	Oxygen	23
Cytochrome aa3	Oxygen	0.05

ATP synthesis are induced.[37] 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.[17 28] 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.[28] 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 (Km_{O_2}),[28] 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. Cellular 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.[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.[38] In cardiac cells anaerobic glucose utilisation protects cell membrane integrity by maintaining energy dependent K^+ channels.[39] During hypoxic stress endothelial and vascular smooth muscle cells increase glucose transport through the expression of membrane glucose transporters (GLUT-1 and GLUT-4) and the production of glycolytic enzymes, thereby increasing anaerobic glycolysis and maintaining energy production.[38] 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.[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.[40 41] 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.[42] 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".[43] 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-κB), 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.[40] Erg-1 protein is also rapidly induced by hypoxia leading to transcription of tissue factor, which triggers prothrombotic events.[41]

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 splanchnic 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 hypoxaemia.
- 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_2}/V_{O_2} 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.

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REFERENCES

1 **Harrison MJG**, Kendall BE, Pollock S, *et al.* Effect of haematocrit on carotid stenosis and cerebral infarction. *Lancet* 1981;ii:114–5.
2 **Hebert PC**, Wells G, Blajchman MA, *et al.* A multicentre, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;**340**:409–17.
3 **Archie JP**. Mathematic coupling of data. A common source of error. *Ann Surg* 1981;**193**:296–303.
4 **Fellows IW**, Bennett T, MacDonald IA. The effects of adrenaline upon cardiovascular and metabolic functions in man. *Clin Sci* 1985;**69**:215–22.
5 **Schumacher PT**, Cain SM. The concept of a critical DO_2. *Intensive Care Med* 1987;**13**:223.
6 **Bihari D**, Smithies M, Gimson A, *et al.* The effect of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. *N Engl J Med* 1987;**317**:397–403.
7 **Shoemaker WC**, Appel PL, Waxman K, *et al.* Clinical trial of survivors' cardiorespiratory patterns as therapeutic goals in critically ill postoperative patients. *Crit Care Med* 1982;**10**:398–403.
8 **Shoemaker WC**, Appel PL, Kram HB, *et al.* Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988;**94**:1176–86.

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9 **Leach RM**, Treacher DF. The relationship between oxygen delivery and consumption. *Disease-a-Month* 1994;**40**:301–68.
10 **Hayes MA**, Timmins AC, Yau E, *et al*. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994;**330**:1712–22.
11 **Gattinoni L**, Brazzi L, Pelosi P, *et al*. A trial of goal-orientated haemodynamic therapy in critically ill patients. *N Engl J Med* 1995;**333**:1025–32.
12 **Connors AF**, Speroff T, Dawson NV, *et al*. The effectivenss of right heart catheterisation in the initial care of critically ill patients. *JAMA* 1996;**276**:889–97.
13 **Boyd O**, Grounds M, Bennett ED. A randomised clinical trial of the effect of deliberate peri-operative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 1993;**270**:2699–708.
14 **Sinclair S**, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture; randomised control trial. *BMJ* 1997;**315**:909–12.
15 **Wilson J**, Woods I, Fawcett J, *et al*. Reducing the risk of major elective surgery: randomised control trial of preoperative optimising of oxygen delivery. *BMJ* 1999;**318**:1099–103.
16 **Lobo SMA**, Salgado PF, Castillo VGT, *et al*. Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. *Crit Care Med* 2000;**28**:3396–404.
17 **Duling BR**. Oxygen, metabolism, and microcirculatory control. In: Kaley G, Altura BM, eds. *Microcirculation*. Volume 2. Baltimore: University Park Press, 401–29.
18 **Curtis SE**, Cain SM. Regional and systemic oxygen delivery/uptake relations and lactate flux in hyperdynamic, endotoxin-treated dogs. *Am Rev Respir Dis* 1992;**145**:348–54.
19 **Mulvany MJ**, Aalkjaer C, Heagerty AM, *et al*, eds. *Resistance arteries, structure and function*. Amsterdam: Elsevier Science, 1991.
20 **Karimova A**, Pinsky DJ. The endothelial response to oxygen deprivation: biology and clinical implications. *Intensive Care Med* 2001;**27**:19–31.
21 **Petros A**, Bennett A, Vallance P. Effect of nitric oxide synthase inhibitors on hypotension in patients with septic shock. *Lancet* 1991;**338**:1557–8.
22 **Bernard GR**, Vincent J-L, Laterre P-F, *et al*. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;**344**:699–709.
23 **Nelson DP**, Samsel RW, Wood LDH, *et al*. Pathological supply dependence of systemic and intestinal O_2 uptake during endotoxaemia. *J Appl Physiol* 1988;**64**:2410–9.
24 **Gutierrez G**, Palizas F, Doglio G, *et al*. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992;**339**:195–9.
25 **Stephan H**, Sonnatag H, Henning H, *et al*. Cardiovascular and renal haemodynamic effects of dopexamine: comparison with dopamine. *Br J Anaesth* 1990;**65**:380–7.
26 **Clebaux T**, Detry B, Reynaert M, *et al*. Re-estimation of the effects of inorganic phosphates on the equilibrium between oxygen and hemoglobin. *Intensive Care Med* 1992;**18**:222–5.
27 **Schumacker PT**, Samsel RW. Analysis of oxygen delivery and uptake relationships in the Krogh tissue model. *J Appl Physiol* 1989;**67**:1234–44.
28 **Robin ED**. Of men and mitochondria: coping with hypoxic dysoxia. *Am Rev Respir Dis* 1980;**122**:517–31.
29 **Bradley SG**. Cellular and molecular mechanisms of action of bacterial endotoxins. *Ann Rev Microbiol* 1979;**33**:67–94.
30 **Vincent J-L**, Roman A, De Backer D, *et al*. Oxygen uptake/supply dependency. *Am Rev Respir Dis* 1990;**142**:2–7.
31 **Cain SM**, Curtis SE. Experimental models of pathologic oxygen supply dependence. *Crit Care Med* 1991;**19**:603–11.
32 **Vary TC**, Siegel JH, Nakatani T, *et al*. Effects of sepsis on activity of pyruvate dehydrogenase complex in skeletal muscle and liver. *Am J Physiol* 1986;**250**:E634–9.
33 **Wilson DF**, Erecinska M, Drown C, *et al*. Effect of oxygen tension on cellular energetics. *Am J Physiol* 1973;**233**:C135–40.
34 **Silverman HJ**. Lack of a relationship between induced changes in oxygen consumption and changes in lactate levels. *Chest* 1991;**100**:1012–5.
35 **Mohsenifar Z**, Amin D, Jasper AC, *et al*. Dependence of oxygen consumption on oxygen delivery in patients with chronic congestive heart failure. *Chest* 1987;**92**:447–56.
36 **Leach RM**, Sheehan DW, Chacko VP, *et al*. Energy state, pH, and vasomotor tone during hypoxia in precontracted pulmonary and femoral arteries. *Am J Physiol* 2000;**278**:L294–304.
37 **Hochachka PW**, Buck LT, Doll CJ, *et al*. Unifying theory of hypoxia tolerance: molecular/metabolic defense and rescue mechanisms for surviving oxygen lack. *Proc Natl Acad Sci USA* 1996;**93**:9493–8.
38 **Cartee GD**, Dounen AG, Ramlai T, *et al*. Stimulation of glucose transport in skeletal muscle by hypoxia. *J Appl Physiol* 1991;**70**:1593–600.
39 **Paul RJ**. Smooth muscle energetics. *Ann Rev Physiol* 1989;**51**:331–49.
40 **Semenza GL**. Hypoxia-inducible factor 1: master regulator of O_2 homeostasis. *Curr Opin Genet Dev* 1998;**8**:588–94.
41 **Yan S-F**, Lu J, Zou YS, *et al*. Hypoxia-associated induction of early growth response-1 gene expression. *J Biol Chem* 1999;**274**:15030–40.
42 **Archer SL**, Weir EK, Reeve HL, *et al*. Molecular identification of O_2 sensors and O_2-sensitive potassium channels in the pulmonary circulation. *Adv Exp Med Biol* 2000;**475**:219–40.
43 **Leach RM**, Hill HS, Snetkov VA, *et al*. Divergent roles of glycolysis and the mitochondrial electron transport chain in hypoxic pulmonary vasoconstriction of the rat: identity of the hypoxic sensor. *J Physiol* 2001;**536**:211–24.

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