

Oxygen transport: the relation between oxygen delivery and consumption

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The unifying concept of oxygen transport has until recently been neglected by both cardiologists and respiratory physicians. With the increasing part played by both disciplines in the care of the critically ill, however, this attitude is changing. The primary function of the heart and lungs is to generate a flow of oxygenated blood to the tissues to sustain aerobic metabolism. The main requirements of this system are that it should be energy efficient, so that unnecessary cardiorespiratory work is avoided, and that it should be sensitive to the fluctuating demands of cellular metabolism. Secondly, metabolic demand and distribution should be matched regionally at rest, during exercise, and in different disease states. Thirdly, oxygen should be able to pass efficiently across the extravascular tissue matrix. The mechanisms controlling oxygen distribution are incompletely understood, but are almost certainly important in determining clinical outcome in the critically ill patient.¹

Although the relation between oxygen delivery (\dot{D}_{O_2}) and consumption (\dot{V}_{O_2}) has not been clearly established, these variables are often measured to define a population of critically ill patients in whom \dot{V}_{O_2} is limited by \dot{D}_{O_2} , the state of so called "pathological supply dependency."² During recent years many of the publications on critical care, and indeed practice in leading intensive care units, have emphasised the importance of raising \dot{D}_{O_2} to "supranormal" levels in an attempt to satisfy the increased metabolic demands of these patients. This practice has been justified by the observation that increased \dot{D}_{O_2} improves oxygen debt and outcome in postoperative surgical patients requiring intensive care.³ No one would dispute that restoring blood volume to improve \dot{D}_{O_2} in the severely hypovolaemic patient must be beneficial. Controlled trials, however, examining the influence of such strategies on clinical outcome in patients with more complex conditions, suffering from sepsis, cardiovascular collapse, and hypoxic hypoxaemia, have produced conflicting data. Perhaps the concept of global oxygen delivery has failed to emphasise the importance of the regional distribution of blood flow, particularly to the splanchnic and renal vascular beds, which may be more important in determining clinical outcome.¹

This article reviews current ideas about the relation between \dot{D}_{O_2} and \dot{V}_{O_2} , the physio-

logical mechanisms controlling regional \dot{D}_{O_2} , and their relevance to critical illness and currently used therapeutic interventions.

Physiology of oxygen transport

GLOBAL OXYGEN DELIVERY

Under normal resting conditions global \dot{D}_{O_2} (defined as the product of cardiac output and arterial oxygen content) is more than adequate to meet tissue oxygen demands for aerobic metabolism (fig 1). Oxygen consumption or uptake (\dot{V}_{O_2}) is determined by cellular requirements and is classically considered to be independent of \dot{D}_{O_2} unless the latter falls below a critical level ($c\dot{D}_{O_2}$; fig 2A, point B). Below this point further reductions in \dot{D}_{O_2} result in a fall in \dot{V}_{O_2} .⁴ The slope of the line relating uptake and delivery defines the oxygen extraction ratio (ERO_2), which is an index of the efficiency of total tissue extraction of oxygen from the extracellular environment. Thus above $c\dot{D}_{O_2}$ \dot{V}_{O_2} is supply independent and ERO_2 falls progressively as \dot{D}_{O_2} rises. Below $c\dot{D}_{O_2}$ a state of so called supply dependency of oxygen uptake exists, the extent of which is determined by the slope of the line (ERO_2). Individual organs have different values of ERO_2 , which may vary with stress and in different disease states. A more complete understanding of the global and regional \dot{D}_{O_2} - \dot{V}_{O_2} relationships would be a major advance in the management of the critically ill.⁵

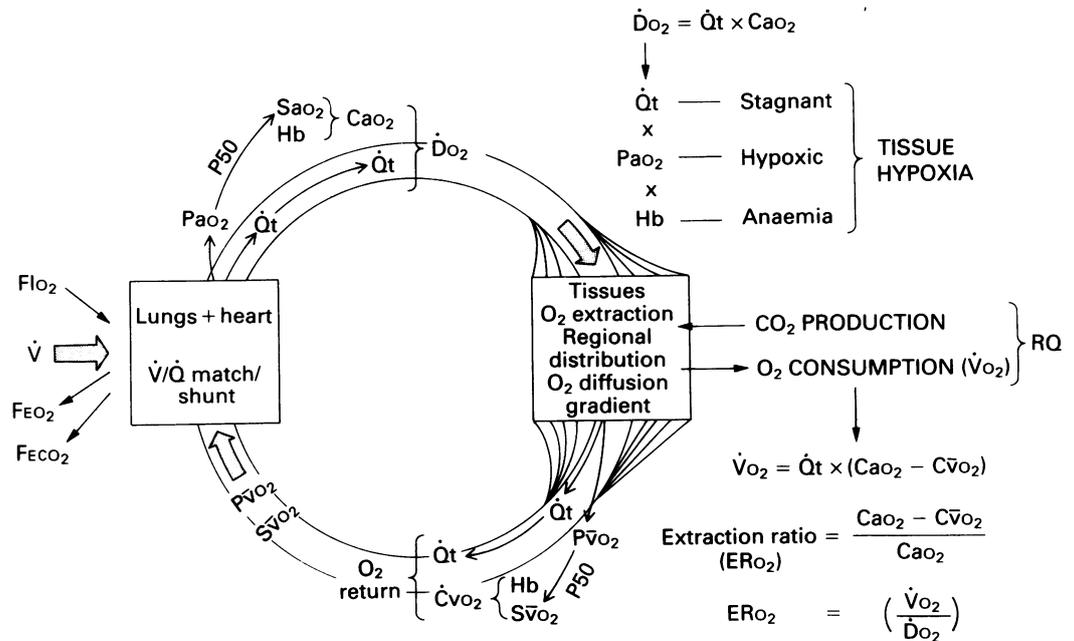
TISSUE OXYGEN DELIVERY

Oxygen delivery to individual cells is usually considered in terms of convective and diffusive oxygen transport. *Convective oxygen transport* refers to the bulk movement of oxygen in blood and includes the regional distribution of cardiac output to individual organs and the mechanisms regulating the tissue microcirculation. This is determined by a complex interaction of endothelial, neural, and metabolic influences on arteries, small resistance arterioles, and precapillary sphincters.⁶ Nevertheless, in the normal state and in clinical conditions convective transport depends predominantly on cardiac output. *Diffusive oxygen transport* refers to the transfer of oxygen molecules from blood through the extracellular matrix down the capillary-intracellular oxygen tension (PO_2) gradient and it depends on arterial oxygen tension (PaO_2). Analysis of \dot{D}_{O_2}

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Figure 1 Diagrammatic representation of oxygen transport. \dot{V} —ventilation; F_{IO_2}/F_{EO_2} —fractional inspired and mixed expired oxygen concentration; F_{ECO_2} —fractional mixed expired carbon dioxide concentration; \dot{Q}_t —cardiac output; P_{aO_2}/P_{vO_2} —partial pressure of arterial/venous oxygen tension; S_{aO_2}, S_{vO_2} —% saturation of arterial/venous blood; Ca_{O_2}/Cv_{O_2} —oxygen content of arterial/mixed venous blood; Hb —haemoglobin concentration; RQ —respiratory quotient; \dot{D}_O_2 —oxygen delivery.

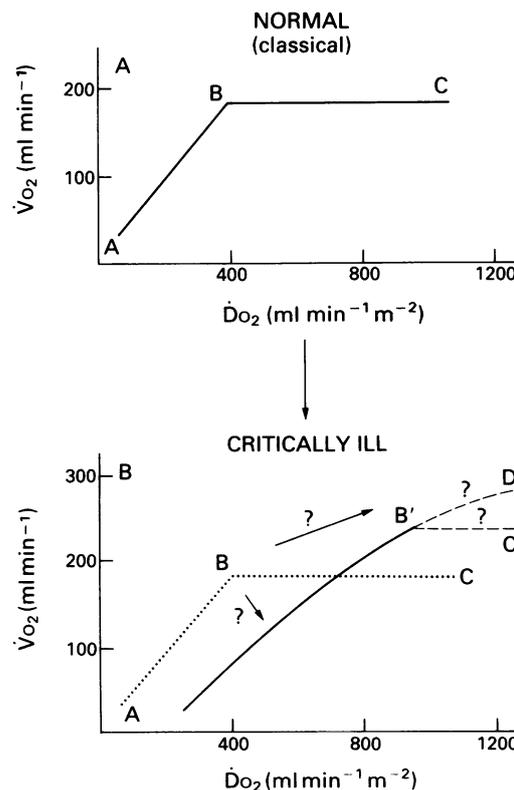


should evaluate both mechanisms as failure of either component results in tissue hypoxia.

The relative importance of convective and diffusive oxygen transport in limiting $\dot{V}O_2$ is controversial. As the oxygen content of blood perfusing a limb at different flow rates is gradually reduced, $\dot{V}O_2$ and ER_{O_2} are greater for a given \dot{D}_O_2 under low flow conditions.⁷ This suggests that $\dot{V}O_2$ is diffusion limited rather than convection limited in progressive hypoxaemia. In contrast, other workers have shown that the point at which $\dot{V}O_2$ falls is similar whether \dot{D}_O_2 is decreased by progressive anaemia, hypoxaemia, or a reduction in blood flow, and that $\dot{V}O_2$

correlates with \dot{D}_O_2 but not with venous PO_2 .^{4,8} These observations would suggest a dominant role for convective transport. To clarify this paradox the theoretical relation between tissue oxygen supply and uptake was examined recently by using the Krogh tissue cylinder model⁹ (fig 3). In this hypothetical model, provided that the intercapillary distances were less than 80 μm , $\dot{V}O_2$ began to fall at a similar level of \dot{D}_O_2 ($c\dot{D}_O_2$), independent of whether \dot{D}_O_2 was progressively reduced by anaemia, hypoxaemia, or a fall in blood flow. As the intercapillary distances were progressively increased above 80 μm there was a rightward shift in $c\dot{D}_O_2$ and a flattening of the response gradient. These changes in the $\dot{V}O_2$ - \dot{D}_O_2 relationship were more dramatic when the reduction in \dot{D}_O_2 was achieved by hypoxaemia than with anaemia or a fall in flow. This suggests that the relative contributions of convective and diffusive transport are determined by capillary density, which may vary between organs, with tissue oedema, and with disease states. This theoretical analysis may explain the earlier contradictory results.

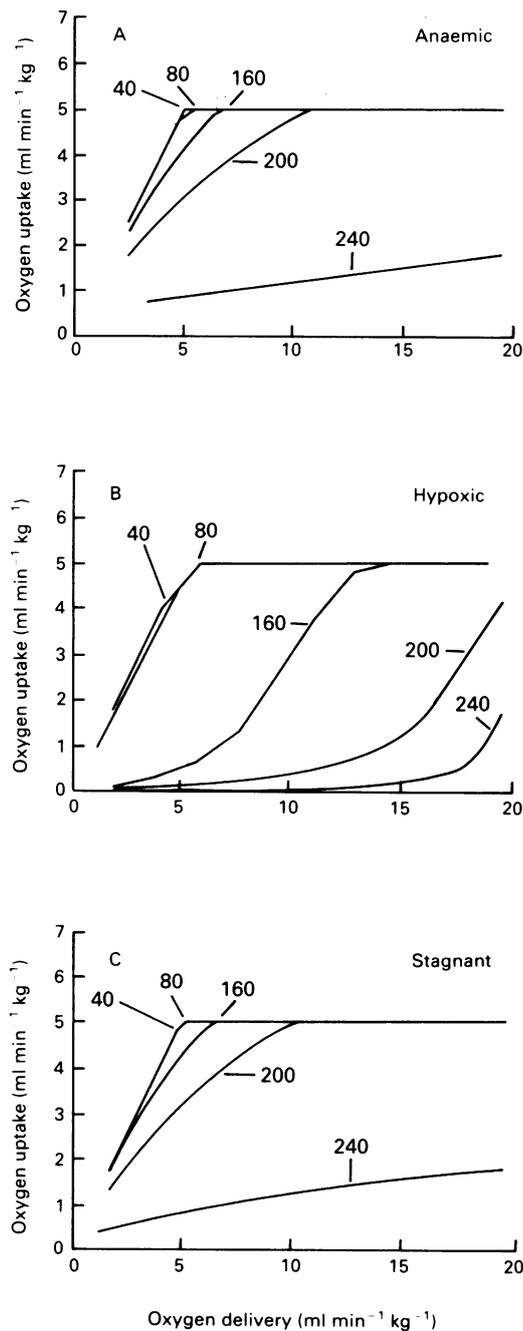
Figure 2 A—The normal (classical) oxygen delivery (\dot{D}_O_2)—oxygen uptake ($\dot{V}O_2$) relationship. Point B represents the critical \dot{D}_O_2 , A-B the supply dependent phase, B-C the supply independent phase. B—“Pathological” supply dependency; A-B’ shows a curvilinear relationship. At high levels of \dot{D}_O_2 , does the relationship remain supply dependent (B’-D) or become independent (B’-C’)?



Relation between oxygen supply and oxygen consumption

Defining the \dot{D}_O_2 - $\dot{V}O_2$ relationship in individual subjects over a sufficiently wide range of values is extremely difficult for practical and ethical reasons. Consequently, plotting complete \dot{D}_O_2 - $\dot{V}O_2$ relationships has been impossible, particularly in healthy individuals, though clinical requirements have permitted some progress to be made in patients with certain disease states. This lack of data has generated many hypotheses, but no scientifically secure conclusion regarding the phenomenon of supply dependency of oxygen uptake. Our present understanding is founded on evidence from (a) exercise in healthy human volunteers, (b) animal experiments and patients undergoing surgery, and (c) critically ill patients.

Figure 3 Predicted effect of changes in intercapillary distance (perfused capillary density) on critical oxygen delivery. Reductions in oxygen delivery were achieved by (A) progressive anaemia, (B) hypoxia, (C) stagnant hypoxia. The numbers on the plots correspond to the intercapillary distances in micrometres. When intercapillary distances were short (40–80 μm), similar levels of critical oxygen delivery were seen for all three forms of hypoxia. When intercapillary distances were over 80 μm tissue oxygen uptake ($\dot{V}\text{O}_2$) was reduced to a greater extent by hypoxic hypoxia than by anaemic or stagnant hypoxia. (Reproduced from Schumacker and Samsel by courtesy of the *Journal of Applied Physiology*.⁹)



EVIDENCE FROM EXERCISE IN HEALTHY HUMAN VOLUNTEERS

The cardiorespiratory system is extremely effective at augmenting $\dot{D}\text{O}_2$ to satisfy sudden increases in metabolic demand required during exercise. Immediate increases in cardiac output can rapidly increase the basal $\dot{D}\text{O}_2$ five fold in the healthy individual. As $\dot{V}\text{O}_2$ may increase 10 fold, however, during maximal exercise and $\text{E}\text{R}\text{O}_2$ also rises at the onset of exercise, a progressive widening of the arteriovenous oxygen difference occurs.¹⁰ At rest the $\text{E}\text{R}\text{O}_2$ is about 0.3 but can increase to 0.8 during maximal exercise in healthy, well trained subjects. This is attributed to an improvement in diffusive oxygen transport mediated by increases in nutritive capillary densities. When the metabolic demands of increasing exercise can no longer be sustained by increases in $\dot{D}\text{O}_2$ or $\text{E}\text{R}\text{O}_2$ the anaerobic threshold is reached and blood lactate concentrations rise. The $\text{E}\text{R}\text{O}_2$ at

the anaerobic threshold is about 0.6, which implies that above this level oxygen uptake becomes diffusion limited.¹¹ $\text{E}\text{R}\text{O}_2$ is improved by training, which suggests an improvement in the diffusion reserve (resulting from increased numbers of mitochondria or microvessels) or more efficient regional distribution of blood flow to the active tissues.¹²

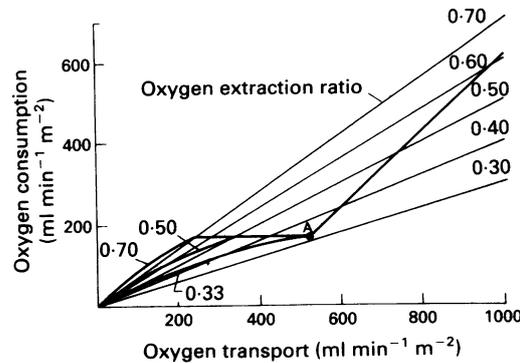
EVIDENCE FROM ANIMALS AND PATIENTS UNDERGOING SURGERY

The response of the cardiopulmonary system to decreasing oxygen availability is more complex. The evidence for the classical two phase relationship between $\dot{V}\text{O}_2$ and $\dot{D}\text{O}_2$ (fig 2A)⁴ rests almost exclusively on animal studies. These have shown that $\text{c}\dot{D}\text{O}_2$ varies from 6 to 10 ml/kg/min, with an $\text{E}\text{R}\text{O}_2$ of 0.5–0.8.^{13,14} In the only study in relatively healthy human subjects under normal conditions, a biphasic relationship between $\dot{V}\text{O}_2$ and $\dot{D}\text{O}_2$ was observed in 58 patients undergoing coronary artery bypass surgery after the induction of anaesthesia, but before the start of cardiac bypass.¹⁵ Analysis of 99 $\dot{D}\text{O}_2/\dot{V}\text{O}_2$ points revealed that $\dot{V}\text{O}_2$ was constant for values of $\dot{D}\text{O}_2$ from 330 to 700 ml min⁻¹ m⁻². Below the $\text{c}\dot{D}\text{O}_2$ (330 ml min⁻¹ m⁻²), which was similar to that found in animal studies, $\dot{V}\text{O}_2$ fell with decreasing $\dot{D}\text{O}_2$. The $\dot{V}\text{O}_2$ in these patients was substantially lower than the basal levels recorded in animals and this was attributed to anaesthesia. At the $\text{c}\dot{D}\text{O}_2$ the apparent $\text{E}\text{R}\text{O}_2$ was only 0.33, a figure well below that observed in animal experiments.

EVIDENCE FROM CRITICALLY ILL PATIENTS

In the critically ill most investigators have reported a modified $\dot{D}\text{O}_2$ - $\dot{V}\text{O}_2$ relationship, suggesting that under pathological conditions $\dot{D}\text{O}_2$ and $\dot{V}\text{O}_2$ continue to increase above the physiological level for $\text{c}\dot{D}\text{O}_2$ (fig 2B). Therefore $\dot{V}\text{O}_2$ remains supply limited at a normal or even increased $\dot{D}\text{O}_2$. In addition, $\text{E}\text{R}\text{O}_2$ does not increase, as is observed during exercise, or with progressive reductions in $\dot{D}\text{O}_2$, as reported in animal experiments. The resulting single phase, curvilinear relationship is termed pathological supply dependency (fig 2B) and implies that a reduction in $\dot{D}\text{O}_2$ cannot be compensated for by an increase in $\text{E}\text{R}\text{O}_2$; $\dot{V}\text{O}_2$ therefore must fall. This relationship has been reported both in animal models of sepsis and during critical illness in man. It was first observed in patients with the adult respiratory distress syndrome (ARDS)^{16,17} and was subsequently identified in patients with septic and hypovolaemic shock,^{18,19} congestive cardiac failure,²⁰ pulmonary hypertension,²¹ and chronic obstructive airways disease.²² The linear relationship has important clinical implications, because with a rightward shift and downward displacement of the $\dot{V}\text{O}_2$ - $\dot{D}\text{O}_2$ relationship, as illustrated in figure 2B, $\dot{V}\text{O}_2$ is reduced at a normal $\dot{D}\text{O}_2$. At a simplistic level, this suggests that an increase in total $\dot{D}\text{O}_2$ by manipulation of the circulation may be beneficial. If, however, $\dot{V}\text{O}_2$ is diffusion limited treatment should be directed at improving $\text{P}\text{a}\text{O}_2$ rather than increasing $\dot{D}\text{O}_2$. Factors affecting the gradient and movement of the $\dot{D}\text{O}_2$ - $\dot{V}\text{O}_2$

Figure 4 Hypothetical oxygen delivery ($\dot{D}O_2$)-oxygen uptake ($\dot{V}O_2$) relationship. Point A represents the average values for $\dot{D}O_2$, $\dot{V}O_2$ found in normal subjects at rest.¹⁰ To the right of point A lies the regression line fitted to the values of $\dot{D}O_2$ and $\dot{V}O_2$ from the progressive exercise data of Astrand et al¹⁰; it represents the condition where $\dot{V}O_2$ is the independent variable as $\dot{D}O_2$ rises to meet increased cellular energy requirements and shows the increasing oxygen extraction ratio (ERO_2). To the left of point A is the portion of the relationship where $\dot{V}O_2$ is the dependent variable, which is more difficult to define because of the lack of data comparable to that on exercise in healthy human subjects. The actual ERO_2 in normal man is unknown and three possible pathways for different ERO_2 values (0.33, 0.50, and 0.70) are illustrated. (Reproduced from Dantzker et al by courtesy of the American Review of Respiratory Disease.²³)



relationship in health and disease clearly require further investigation to determine the prognostic significance and implications of such changes. The basis for the belief that the curvilinear relationship identified in pathological supply dependency is distinct from the classical biphasic relationship reported in health is tenuous.

IS THE $\dot{V}O_2$ - $\dot{D}O_2$ RELATIONSHIP BIPHASIC OR LINEAR?

Despite the biphasic $\dot{V}O_2$ - $\dot{D}O_2$ relationship in animal experiments, it has recently been suggested that in man both the physiological and the pathological relationships are linear.²³ In a recent review Dantzker and colleagues proposed the hypothetical interaction of $\dot{D}O_2$ and $\dot{V}O_2$ shown in figure 4. Experiments during exercise provide strong evidence to support that part of the hypothetical line to the right of point A.¹⁰ Below point A the classical relationship would demand ERO_2 values of 0.5-0.7 to achieve the plateau phase. In human studies, however, the maximum values for ERO_2 both in disease states (0.25-0.45) and in relative health (0.33)¹⁵ are much lower. These low ERO_2 values argue against the existence of the point $c\dot{D}O_2$ and a plateau phase. If a curvilinear relationship similar to that observed in "pathological supply dependency" existed in healthy individuals this would satisfy the requirement for cardiorespiratory efficiency as it implies a much smaller reserve of oxygen transport.²³

An alternative explanation is that the curvilinear relationship between supply and demand represents the distillation of a series of points lying on a family of organ specific supply-demand curves. These points would be determined by the regional distribution of flow between organs each having different and varying $\dot{V}O_2$ - $\dot{D}O_2$ relationships.

Clinical implications of the global $\dot{D}O_2$ - $\dot{V}O_2$ relationship

Patients admitted to an intensive care unit who show the pattern of pathological supply dependency have a 70% mortality, compared with a 30% mortality in those who do not.²⁴ Similarly, in mechanically ventilated patients with sepsis the prognosis was found to be worse if $\dot{V}O_2$ increased in response to a rise in $\dot{D}O_2$ produced by an infusion of prostacyclin (that is, pathological supply dependency).²⁵ Shoemaker et al,³ in a large series of postoperative patients admit-

ted to intensive care, empirically set "supranormal" $\dot{D}O_2$ and $\dot{V}O_2$ targets and reported an improvement in outcome.

This evidence has resulted in the current vogue for "goal directed" treatment requiring that the cardiac index should be >4.5 l $\text{min}^{-1} \text{m}^{-2}$, $\dot{D}O_2 >600$ ml $\text{min}^{-1} \text{m}^{-2}$, $\dot{V}O_2 >170$ ml $\text{min}^{-1} \text{m}^{-2}$, and venous oxygen saturation (SvO_2) $>70\%$.^{3,9} This approach to management assumes that the following conditions pertain: (a) $\dot{V}O_2$ can be increased by raising $\dot{D}O_2$ to supranormal levels; (b) an increase in $\dot{V}O_2$ reduces tissue hypoxia; (c) an increase in $\dot{D}O_2$ improves outcome. The validity of these statements depends on the individual pathological process and whether there is a true deficit of either convective or diffusive oxygen transport. The importance of these two factors in oxygen delivery is examined by considering two groups of patients.

STUDIES IN PATIENTS WITH CHRONIC OBSTRUCTIVE AIRWAYS DISEASE

Patients with hypoxic chronic obstructive airways disease have both a failure of arterial oxygenation and abnormalities of cardiac output. Pathological supply dependency has been reported in both chronic obstructive airways disease²² and pulmonary hypertension.²¹ Three years after the development of peripheral oedema in hypoxaemic cor pulmonale survival is less than 50%.²⁶ Can this reduced survival be attributed to compromised oxygen diffusion due to reduced P_{aO_2} or to reduced $\dot{D}O_2$ from a failure of convective transport? In a study examining 50 patients with severe chronic obstructive airways disease $\dot{D}O_2$ and the cardiac index had no prognostic significance, whereas a clear benefit was associated with increased P_{aO_2} and venous oxygen tension (P_{vO_2}).²⁷ Acute oxygen therapy produces a fall in cardiac index and $\dot{D}O_2$ but an increase in P_{vO_2} , implying improved tissue oxygenation.²⁷ Long term oxygen therapy aimed at improving arterial oxygen saturation (SaO_2) produces no significant haemodynamic benefit or increase in $\dot{D}O_2$, but does improve survival in patients with hypoxaemic cor pulmonale. Reversal of arterial hypoxaemia (>8.7 kPa) appears to be the key prognostic factor.^{26,28,29} This suggests that for this population of patients the diffusive component of oxygen transport is more important than the convective component.

STUDIES IN CRITICALLY ILL PATIENTS

The position in the critically ill appears to be different. Several reports have suggested that improving $\dot{V}O_2$ by increasing $\dot{D}O_2$ to a point well above $c\dot{D}O_2$ may confer clinical benefit.^{30,31} Empirical studies by Shoemaker and colleagues showed that increasing cardiac output, $\dot{D}O_2$, $\dot{V}O_2$, and blood volume above normal in postoperative patients improved outcome.³ Maintaining a high $\dot{D}O_2$ also improves $\dot{V}O_2$ and reverses lactic acid production.³² These studies suggest that a high $\dot{D}O_2$ should be maintained whenever possible, but this generalisation cannot allow for either specific aspects of the underlying pathology or the possible complications of strategies used to increase $\dot{D}O_2$. In

ARDS attempts to increase $\dot{D}O_2$ by raising filling pressures with volume expansion will have detrimental effects due to increased alveolar capillary permeability. Any increase in pulmonary artery occlusion pressure will increase lung water, further impairing gas exchange and lung compliance and leading to an increase in the fractional inspired oxygen (FIO_2) requirement and airway pressures. The same increase in vascular permeability, albeit less clinically apparent, affects all tissues. Therefore volume loading may increase extravascular tissue water and potentially compromise diffusive oxygen transport.³³

A second consideration in ARDS is the frequent need for positive end expiratory pressure (PEEP) to reduce the alveolar-arterial oxygen gradient and FIO_2 requirements. The effect of increasing PEEP on $\dot{D}O_2$ is unpredictable but usually a net fall occurs owing to reduced cardiac output even if Pao_2 rises. This pattern of response provides an interesting model with which to study the relative contribution of diffusive and convective transport. Carlile and Gray investigated the effect of opposite changes in cardiac output and Pao_2 on $\dot{D}O_2$, $\dot{V}O_2$ and Pvo_2 and showed that in these circumstances $\dot{V}O_2$ was not supply dependent.³⁴

MEASUREMENT ERRORS: MATHEMATICAL AND PHYSIOLOGICAL LINKAGE

The conflicting evidence concerning supply dependency in the critically ill may be explained by the different methods used for measuring $\dot{V}O_2$. Studies in patients after surgery and in those with sepsis and ARDS have shown that, although $\dot{D}O_2$ correlated well with $\dot{V}O_2$ calculated from cardiac output and difference in arteriovenous oxygen content (indirect Fick method), the correlation was much weaker when $\dot{V}O_2$ was calculated from direct measurements of ventilatory minute volume and inspired and mixed expired oxygen concentration by mass spectrometer or metabolic cart.³⁵⁻³⁷ It was suggested that the $\dot{D}O_2/\dot{V}O_2$ relationship seen when $\dot{V}O_2$ is calculated by the indirect Fick method is an artefact related to the use of common variables (cardiac output and arterial oxygen content) in the calculation of both $\dot{V}O_2$ and $\dot{D}O_2$.³⁸ Errors in measuring the two variables are therefore effectively coupled, producing apparent supply dependency. The effect of this mathematical coupling depends on the size of the errors in the measurement of the variables concerned.³⁹ In studies with a small range of $\dot{D}O_2$ the problems are exaggerated.³⁹ If measurement errors are large, as may be the case during mechanical ventilation, the chance that a true pathological supply dependency exists is diminished. Theoretical examination, however, suggests that the linear relationship between $\dot{D}O_2$ and $\dot{V}O_2$ cannot be ascribed entirely to mathematical coupling.

Physiological coupling may also be responsible for generating a false association between variables. If, for example, inotropic support is used to increase $\dot{D}O_2$, most of the agents available not only increase cardiac output but also stimulate metabolism, thereby increasing $\dot{V}O_2$ directly.⁴⁰ Data obtained in such circumstances could be misinterpreted as evidence of supply dependency. Such treatment could

hardly be viewed as beneficial as it is similar to fever in its effect on $\dot{V}O_2/\dot{D}O_2$. Pain, anxiety, endogenous catecholamine release, and physical activity produce similar changes.

Doubts about a simple global supply dependency relationship have also been raised by personal observations in patients with severe sepsis characterised by systemic hypotension with high cardiac output and $\dot{D}O_2$. In these patients with much reduced systemic vascular resistance treatment with noradrenaline increased not only arterial pressure but also the incidence of clinical indices of organ function. Independent measurements of $\dot{V}O_2$ by indirect calorimetry using a mass spectrometer and of $\dot{D}O_2$ from thermodilution cardiac output and arterial oxygen content showed that, with the introduction of noradrenaline, while $\dot{D}O_2$ remained unchanged or even fell, $\dot{V}O_2$ increased (DFT, unpublished observations). This evidence of an inverse relation between $\dot{D}O_2$ and $\dot{V}O_2$ in certain circumstances could be explained by regional redistribution of flow and would suggest that such changes may be more important than absolute increases in $\dot{D}O_2$.

Clinical implications of regional $\dot{D}O_2$ - $\dot{V}O_2$ relationships

In the critically ill patient the regional distribution to the organs of the total oxygen delivered varies considerably with the underlying pathological process. Both clinical and theoretical evidence shows that Pao_2 is more important than $\dot{D}O_2$ in maintaining tissue oxygenation, particularly in respiratory failure with hypoxaemia.^{7,9} In these circumstances treatment that improves peripheral distribution and cellular utilisation of oxygen is more appropriate.

Induction of endotoxaemia or septicaemia in animal experiments has shown that the $c\dot{D}O_2$ is higher and the ERO_2 reduced to a greater extent in the splanchnic than in the skeletal muscle circulation.⁵ Splanchnic perfusion is selectively reduced by the endogenous vasoconstrictors released in critical illness and the gut mucosa is further compromised by the frequent failure to sustain enteral feeding. The fall in regional $\dot{D}O_2$ with increased metabolic demands and reduced ERO_2 results in ischaemia of the splanchnic organs, particularly the gut. This renders the gut mucosa "leaky," allowing absorption of endotoxin and translocation of bacteria into the portal circulation. This sequence of events means that a massive toxic load enters the portal circulation, which first overwhelms the liver defences and then promotes capillary endothelial damage in the lung (ARDS) and the development of multisystem organ failure. The most common cause of late death in the intensive care unit is multisystem organ failure, and recent evidence has shown that treatment aimed at maintaining or improving splanchnic perfusion and tissue oxygenation reduces mortality and improves outcome.¹

Therapeutic strategies to manipulate $\dot{D}O_2$ - $\dot{V}O_2$ relationships

INOTROPIC SUPPORT

Catecholamines, including dobutamine and adrenaline, improve cardiac output and are

reported to improve survival in septic shock.⁴¹ In addition, they may have important effects on regional vascular resistance, thereby improving oxygen diffusion and tissue ERO_2 . Dobutamine, however, may reduce splanchnic perfusion at the doses required to increase global DO_2 in sepsis, emphasising the desirability of measuring regional perfusion if therapeutic benefits are to be assured.⁴ Inotropes may also induce physiological linkage, increasing cardiac work and VO_2 .⁴²⁻⁴⁵ The new adrenergic and dopaminergic agent dopexamine hydrochloride has no α adrenergic effects and may selectively increase renal and splanchnic blood flow.^{44,45} The potential value of region specific inotropic agents is considerable but needs further evaluation.

VOLUME INFUSION

Many trials have examined the effects of volume loading to increase cardiac output by raising filling pressures. Volume loading has been shown to increase cardiac output and total DO_2 and to improve disease outcome post-operatively.³ Nevertheless, there are two major problems with the indiscriminate use of this strategy. Firstly, complications occur in patients with increased vascular permeability, as already discussed. Secondly, many critically ill patients, particularly those with sepsis, have severely impaired myocardial contractility, with flat myocardial function curves, so that the stroke volume and hence gain in cardiac output from an increase in filling pressure is minimal. This results in all the disadvantages of volume loading in exchange for trivial improvements in DO_2 .

VASODILATORS

Vasodilators increase oxygen transport without increasing cardiac work or producing the problems of physiological linkage,⁴⁶ but in many critically ill patients systemic vascular resistance is already low, and poor organ perfusion resulting from systemic hypotension is a major concern. Even if vasodilators are tolerated without overt haemodynamic compromise, their effects on regional distribution are unpredictable and in certain circumstances may jeopardise blood flow in vital organs, even though overall DO_2 is increased.⁴⁶ The use of vasodilators to reveal covert oxygen debt by showing whether VO_2 increases in response to DO_2 has been recommended,²⁵ but no convincing evidence exists to show that vasodilators improve outcome.

PERIPHERAL CIRCULATION

Manoeuvres that shift the oxygen dissociation curve to the right will increase tissue oxygen uptake. In this regard the adverse effects of a raised temperature and acidosis are well known but the importance of correcting hypophosphataemia is frequently overlooked.⁴⁷

Most methods for improving tissue oxygenation by influencing the microcirculation are at present experimental. The endothelium has been shown to have an important influence on vascular tone and vasoreactivity through the release of both constricting and relaxing factors. The endothelial cell damage associated

with septic shock and ARDS is likely to have an important influence on tissue perfusion. The most important of the endothelium derived relaxing factors is nitric oxide. Recent studies have shown that inhibition of the synthesis of endothelium derived relaxing factors may be beneficial in maintaining vascular tone in septic shock.⁴⁸ Anti-endotoxin antibody has recently been shown to reduce mortality in patients with Gram negative bacteraemia and particularly those with septic shock, though the mechanism of action in terms of oxygen transport and regional perfusion is unclear.⁴⁹ Other antioxidants, such as prostaglandin E_1 , may improve DO_2 and VO_2 but have no influence on mortality.⁵⁰

FACTORS INFLUENCING VO_2

It is important to avoid factors which raise metabolic demand, with an inevitable increase in VO_2 and DO_2 , but which may aggravate rather than relieve tissue hypoxia. Principal among these are infection, a high temperature, drugs (β agonists), excess physical activity (physiotherapy, restlessness, shivering, fighting ventilator), sympathetic overactivity (pain, anxiety), and the feeding regimen (excess intravenous glucose).

Measures of the adequacy of tissue oxygenation

LACTATE CONCENTRATION

Blood lactate concentration may be raised or normal in the presence or absence of hypoxia because the metabolic pathways utilising glucose during aerobic energy production may be blocked at several points.⁵¹ If phosphofructokinase is inhibited, glucose utilisation is prevented without an increase of lactate. In contrast, in the hypermetabolism of sepsis inactivation of pyruvate dehydrogenase prevents utilisation of pyruvate in the citric acid cycle, resulting in production of lactate, accumulation of pyruvate, and aerobic metabolism of fat and protein.⁵² Recent studies have shown that endotoxin can directly inactivate pyruvate dehydrogenase, resulting in lactate production in the absence of tissue hypoxia.⁵³ With an unfavourable cellular redox state, normal DO_2 may be associated with high lactate concentrations, but on the other hand if compensatory reductions in $[\text{ATP}]/[\text{ADP}][\text{Pi}]$ or $[\text{NAD}^+]/[\text{NADH}]$ occur then low lactate concentrations may be found with tissue hypoxia.⁵⁴ Lactate is therefore not a reliable reflection of tissue hypoxia.

The blood lactate concentration also represents a balance between production, as shown by perfusion, and consumption by hepatic, cardiac, and skeletal muscle metabolism.² Clinically, arterial lactate concentrations are reported to vary inversely with DO_2 ,⁵¹ but 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.²⁰ Clearly, the value of a single lactate concentration in the assessment of tissue hypoxia is at best question-

able.⁵⁵ Serial lactate measurements, particularly if corrected for pyruvate, may be of greater value.

TONOMETRY

Much of the evidence presented here has suggested the probable importance of regional distribution of $\dot{D}O_2$, particularly to the splanchnic bed. The introduction of the gastrointestinal tonometer to measure the intramucosal pH of the gut (pHi) promises to be an important advance. This may provide an early warning of inadequate splanchnic tissue oxygenation and guide subsequent treatment.⁵⁶ Recent reports have shown that a low pHi is associated with a poor prognosis, but if pHi increases with treatment the outcome is improved.¹

Future developments

Further advances in the understanding of oxygen transport require the development of suitable techniques for measuring regional blood flow and tissue oxygenation. Examination of serial muscle biopsy specimens to study the histological changes, endothelial architecture, lactate concentrations, and ATP turnover may help to explain the microcirculatory changes controlling tissue perfusion.⁵⁷ Magnetic resonance spectroscopy is a non-invasive method by which intracellular aerobic and anaerobic energy metabolism may be studied.⁵⁸ Phosphorus-31 is a naturally occurring isotope concerned with energy transfer within the cell. ³¹P-magnetic resonance spectroscopy generates spectral peaks corresponding to the resonance of the phosphate bonds (α , β , γ) of ATP, inorganic phosphate (P_i), and phosphocreatine (PCr), from which intracellular pH (pHi), oxidative phosphorylation, the rate of mitochondrial electron transport, and creatine kinase kinetics may be calculated.⁵⁹ Despite appreciable technical difficulties and the practical problems presented by patients in intensive care, magnetic resonance spectroscopy promises considerable advances in the study of both aerobic and anaerobic metabolism and the metabolic response to critical illness. Positron emission tomography permits the non-invasive measurement of regional blood flow and organ function and should allow the response of the microcirculation to stress, hypoxaemia, and treatment to be assessed.⁶⁰

Conclusion

Despite a bewildering array of publications, many aspects of oxygen transport remain an enigma. The relationship between $\dot{D}O_2$ and $\dot{V}O_2$ has not been clearly established and the current vogue of therapeutic manipulation is of unproved value in determining outcome in many conditions. Part of the confusion relates to problems in measuring $\dot{V}O_2$, and future studies should report independently calculated values from the analysis of inspired and expired gas. In critically ill patients it is essential to define clearly the population and the pathological abnormality under study and to iden-

tify and account for potentially confounding metabolic factors. The recognition that tissue hypoxia varies between and within individual organs is focusing attention on the importance of regional oxygen delivery and the need for direct assessment of tissue oxygenation.⁶¹ Recent technological advances should allow further aspects of the enigma to be unravelled.

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