

Oxygen delivery to tissues

R.W. Samsel, P.T. Schumacker

Oxygen delivery to tissues. R.W. Samsel, P.T. Schumacker.

ABSTRACT: For health, well perfused tissues, oxygen uptake is determined primarily by metabolic need rather than by oxygen supply. Tissue hypoxia supervenes when tissue oxygen tension (P_{O_2}) falls below a critical point, and the point where this occurs can be predicted from the systemic oxygen delivery or extraction ratio. A growing body of evidence suggest that tissue oxygen extraction may be impaired in adult respiratory distress syndrome (ARDS) and sepsis. In these syndromes the minimum oxygen delivery needed to maintain a normal oxygen uptake appears to be increased, as tissues become hypoxic despite high levels of delivery. However, controversy surrounds every phase of this observation, from its experimental basis, to potential causes, to its implications for patient care. In this review, we discuss the physiology of oxygen transport, the determinants of tissue oxygenation in normal and pathological states, and the therapeutic implications of oxygen transport.

Eur Respir J., 1991, 4, 1258-1267.

Section of Pulmonary and Critical Care Medicine,
The University of Chicago, Chicago, Illinois, USA.

Correspondence: R.W. Samsel, Dept of Medicine,
Box 83, The University of Chicago, 5841 South
Maryland Avenue, Chicago, Illinois 60637, USA.

Keywords: Adult respiratory distress syndrome;
oxygen consumption; oxygen extraction; oxygen
uptake; pathological supply dependence: sepsis.

Received: January, 1990; accepted after revision
November 11, 1990.

Supported by National Heart, Lung and Blood
Institute grants HL01857, HL32646, and HL01682.

Many critical illnesses still do not have specific, curative therapy, so that care for the critically ill patient often emphasizes supportive therapy. Cardiopulmonary supportive therapy is aimed at keeping tissue respiratory function normal enough to allow healing. Its success or failure hinges on the ability to prevent tissue hypoxia, for tissue hypoxia progresses to systemic cardiovascular collapse. Understanding what determines the threshold of tissue hypoxia is, therefore, the physiological basis of cardiorespiratory support. This review will focus on the relationship between tissue oxygen delivery and consumption, and on the pathological aberrations that disturb normal tissue oxygen utilization. Tissue hypoxia occurs when cellular oxygen delivery does not fulfill cellular oxygen demand. Cellular oxygen delivery involves a co-ordinated sequence of pulmonary oxygen transfer, convection of blood to tissue, and diffusion of oxygen from capillary to cell. Co-ordinating this sequence of processes allows tissues to extract as much as 70% of the delivered oxygen before oxygen consumption becomes limited by delivery. In the last decade, a number of studies have reported that adult respiratory distress syndrome (ARDS) and sepsis can impair oxygen extraction by tissues, distorting the relationship between oxygen delivery and uptake. They have suggested that tissues become hypoxic despite a high mixed venous oxygen content, apparently starving amid plenty. Understanding how these syndromes may alter tissue oxygen extraction may shed light on how they continue to exact such a high toll on patient survival.

The physiology of oxygen transport

Cellular oxygen consumption is determined primarily by metabolic need, provided that metabolic substrates are in good supply. These metabolic substrates, oxygen and fuel in the form of sugars, fats, and their metabolites, rarely limit metabolic oxygen consumption by cells. Rather, adenosine triphosphate (ATP) consumption is the ordinary limiting feature in respiration, and depends on the current metabolic workload of the cell. Tissue oxygen demand is thus operationally defined as tissue oxygen consumption under conditions of substrate excess at the tissue level.

Metabolic need for ATP consumption is sensed by the mitochondrion as adenosine diphosphate (ADP) concentration [1]. Increases in ADP concentration trigger an increase in mitochondrial electron transport, provided that the local oxygen partial pressure exceeds about 0.5 torr [2]. For ATP production to become dependent on oxygen supply rather than metabolic need, the mitochondrial oxygen tension (P_{O_2}) must fall even further; in such cases tissue hypoxia supervenes. If the cardiorespiratory system can ensure that the mitochondrial P_{O_2} remains above this critical level everywhere in the body, oxygen supply should not limit mitochondrial ATP production.

The capillary P_{O_2} is the driving force for the diffusion of oxygen to the cell, and must suffice to carry oxygen from the red cell to the furthest point from any capillary. Maintaining effective oxygen transport requires both keeping the capillary P_{O_2} high enough,

and keeping the intercapillary spacing close enough [3]. For the normal circulation, the maintenance of an adequate P_{O_2} depends largely on convective oxygen transport accomplished by the heart, lungs and blood [4].

The tissue P_{O_2} , and even the capillary P_{O_2} , cannot easily be measured in clinical settings, and measurements that can be made (e.g. venous P_{O_2}) bear an indirect relationship to the actual driving forces for diffusive oxygen transport and for mitochondrial oxygen availability. The interpretation of the available measurements relies instead on what they tell us about the oxygen economics of the body, based on the principle of mass conservation. We will explore these relationships below.

The oxygen delivery (\dot{Q}_{O_2}) is defined as the total oxygen carried (convected) by blood to tissue, and is calculated as the product of cardiac output (\dot{Q}_t) and arterial oxygen content (C_{aO_2}):

$$\dot{Q}_{O_2} = \dot{Q}_t \cdot C_{aO_2}$$

Many other names have been applied to this variable, including systemic O_2 transport (SOT), total O_2 transport (TOT), transport of O_2 (T_{O_2}), and delivery of O_2 (D_{O_2}), but the concept is the same.

The oxygen consumption (\dot{V}_{O_2}) is defined as the product of the cardiac output and the arteriovenous oxygen difference ($C_{aO_2} - C_{vO_2}$), where C_{vO_2} is the oxygen content in mixed venous blood:

$$\dot{V}_{O_2} = \dot{Q}_t \cdot (C_{aO_2} - C_{vO_2})$$

The ratio of oxygen consumption to delivery is the oxygen extraction ratio (ER):

$$ER = \dot{V}_{O_2} / \dot{Q}_{O_2} = (C_{aO_2} - C_{vO_2}) / C_{aO_2}$$

If oxygen delivery is high enough to ensure that cell respiration is not supply-dependent, then oxygen consumption remains fairly constant. The constant level of oxygen consumption present when the delivery is high is the tissue oxygen demand. Below a critical level of delivery (the critical \dot{Q}_{O_2}), oxygen uptake falls in a roughly linear fashion (fig. 1 top panel). In this case, when oxygen delivery fell below 8 $ml \cdot kg^{-1} \cdot min$ the oxygen consumption fell off. As oxygen delivery falls in the supply-independent region, extraction ratio must increase to maintain a constant oxygen delivery (fig. 1 bottom panel). However, at the critical point, this animal extracted about 70% of the oxygen from the delivered blood. The rise in oxygen extraction continued even when the oxygen delivery fell below the critical point. However, below the critical \dot{Q}_{O_2} increases in oxygen delivery are no longer enough to maintain a normal oxygen consumption.

In the research laboratory, normal anaesthetized animals generally extract between 60 and 75% of the delivered oxygen before becoming supply-dependent [5-17]. The critical delivery level, unlike the critical extraction ratio, increases in proportion to metabolic

demand. For example, rats have a high metabolic rate (15-17 $ml \cdot kg^{-1} \cdot min$) compared to dogs (5-7 $ml \cdot kg^{-1} \cdot min$) and a correspondingly higher critical delivery (22-23 $ml \cdot kg^{-1} \cdot min$), but have the same critical extraction ratio (68-74% [13, 14]) as dogs [5-10]. The variation in \dot{V}_{O_2} may be due to the larger amount of metabolically inactive connective tissue and fat in larger animals or to intrinsic tissue differences; whatever the reason, the critical extraction ratio (ER_c) effectively normalizes the critical oxygen delivery (\dot{Q}_{O_2c}) for variations in O_2 demand.

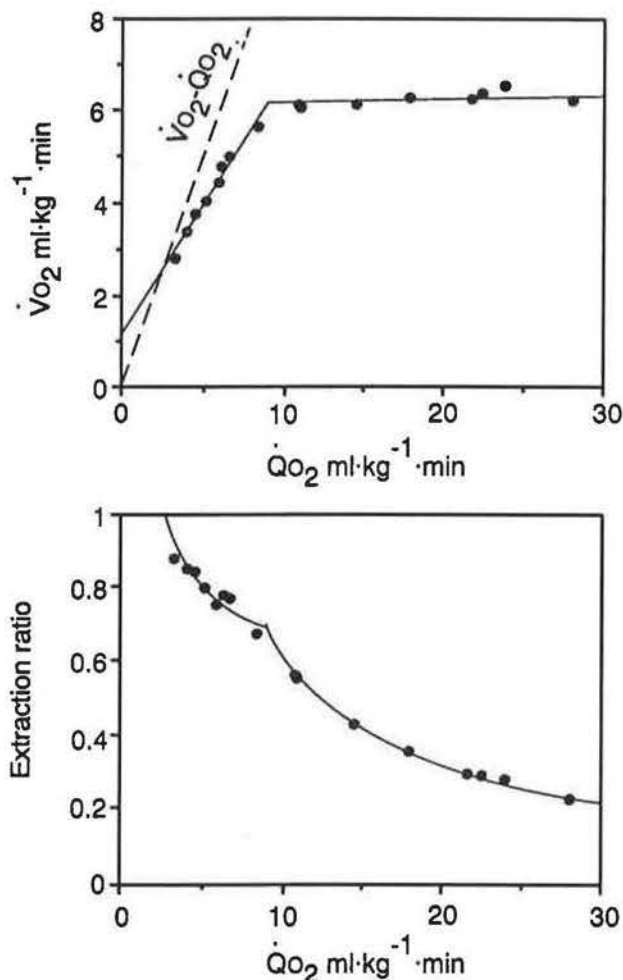


Fig. 1. - Top panel: The relationship between systemic oxygen uptake (\dot{V}_{O_2}) and delivery (\dot{Q}_{O_2}) in a typical anaesthetized dog. Bottom Panel: The relationship between the systemic oxygen extraction ratio and oxygen delivery in the same dog. From reference [8], with permission.

When O_2 delivery falls below the \dot{Q}_{O_2c} , a variety of other changes occur, reminiscent of clinical shock. Blood lactic acid levels rise, bicarbonate is driven off as carbon dioxide while pH falls, and blood pressure becomes unstable and falls. One can detect the fall in \dot{V}_{O_2} or the increase in the respiratory exchange ratio ($R = \dot{V}_{CO_2} / \dot{V}_{O_2}$) from measurement of expired gases [18]. However, in critically ill patients ventilated with high inspired fractions, the accurate

measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ by expired gases is a major undertaking. In contrast, arterial and pulmonary artery catheters are easily introduced, and allow the arteriovenous content difference and cardiac output to be easily measured, so that $\dot{V}O_2$, $\dot{Q}O_2$ and extraction ratios may be calculated. Blood or plasma lactates can be easily measured, and offer additional information on the level of tissue hypoxia.

Forms of hypoxia

About seven decades ago, BARCROFT [19] introduced a classification of the forms of hypoxia; with modifications and minor name changes it remains in use today [20]. Hypoxic hypoxia refers to falling arterial PO_2 , anaemic hypoxia to falling haemoglobin concentration, and stagnant hypoxia to falling blood flow. We will focus largely on these three "physiological" forms of hypoxia, but other forms of hypoxia also exist.

These other forms of hypoxia include "affinity hypoxia", referring to what happens if haemoglobin binds oxygen too tightly, or "histotoxic hypoxia", referring to the effects of mitochondrial poisons such as cyanide [20]. Carbon monoxide hypoxia is a curious case: it binds and inactivates some haemoglobin, increases the affinity of the rest, and binds myoglobin, cytochromes and oxidases in tissue. How these effects participate in the pathophysiology of carbon monoxide toxicity is still open to argument, and the interested reader is referred to other sources [21].

The three physiological forms of hypoxia correspond to changes in the terms of the extended equation for oxygen delivery:

$$\dot{Q}O_2 = \dot{Q}t(\alpha \text{ Hgb} \cdot \text{Sao}_2 + \beta \text{ Pao}_2)$$

where Hgb is the haemoglobin concentration, Sao_2 is the fractional arterial haemoglobin saturation, Pao_2 is the arterial PO_2 , and α and β are constants (α is the haemoglobin oxygen carrying capacity = 1.39 ml $O_2 \cdot g^{-1}$ Hgb, β is the solubility of oxygen in plasma = 0.003 ml $O_2 \cdot \text{torr}^{-1}$). Any of the three terms ($\dot{Q}t$, Sao_2 , and Hgb) can fall, and they can fall in any combination.

The utility of oxygen delivery comes from the observation that the $\dot{V}O_2$ depends only on the $\dot{Q}O_2$, and falls in $\dot{V}O_2$ appear similar whether the fall in $\dot{Q}O_2$ arose through a falling Pao_2 , Hgb, or $\dot{Q}t$. This observation is based on Cain's landmark studies comparing anaemic and stagnant hypoxia in anaesthetized dogs [11], and from the observations that different laboratories studying different forms of hypoxia have reported similar values for critical deliveries and oxygen extractions. While subtle differences between forms of hypoxia probably exist [22], to first order the approximation appears to remain valid.

The experimental basis for these statements, together with a physical interpretation of the evidence is discussed elsewhere [23, 24]. In this paper we will

concentrate on what they tell us about interpreting oxygen transport parameters in critically ill patients.

Mixed venous oxygenation

Since $\dot{V}O_2$ appears experimentally to depend primarily on $\dot{Q}O_2$, and not independently on $\dot{Q}t$, Hgb, or Sao_2 , it follows that the extraction ratio, the ratio of $\dot{V}O_2$ to $\dot{Q}O_2$, should also depend on the $\dot{Q}O_2$. In anaemic and hypoxic hypoxia, however, the arteriovenous oxygen difference remains low, while in stagnant hypoxia, the arteriovenous oxygen difference grows large. Thus, the increase in extraction ratio happens in a different way in the anaemic or hypoxic case and in the stagnant case. In stagnant hypoxia, the CaO_2 remains constant while the arteriovenous O_2 difference grows large, while in anaemic or hypoxic hypoxia, the arteriovenous oxygen difference is small, but the denominator of $(\text{CaO}_2 - \text{CvO}_2)/\text{CaO}_2$ becomes progressively lower.

For purposes of illustration, we have assumed a relationship between O_2 delivery and uptake based on the data in figure 1, and calculated the relationships between the constituent variables. These are plotted for stagnant and hypoxic hypoxia in figure 2. For the stagnant case, arterial oxygen content remains constant, while the mixed venous content falls faster and faster. At the critical point, the rate of decline of CvO_2 slows as $\dot{V}O_2$ falls, but the rate of decline again appears to increase as extraction ratios continue to rise. For the hypoxic case, the contents fall together until they reach the critical point; at this point the lines begin to converge. The oxygen partial pressures represent a nonlinear transformation of the contents, but obey qualitatively similar rules.

The critical point in humans

The curves drawn in figures 1 and 2 are based on data from studies of anaesthetized animals, where accurate measurements and tightly controlled physiological changes are possible. Measuring the critical point requires forcing animals into tissue hypoxia, with consequent tissue damage. Obviously, one cannot perform such a measurement in normal patients.

Several studies have been done in patients, and are frequently cited as sources for information in normal humans. Firstly, studies have varied the flow rate in cardiopulmonary bypass circuits in extremely hypothermic patients, to examine the resulting changes in oxygen extraction [25]. These patients did experience falls in $\dot{V}O_2$, but their tissues were protected by their low body temperature. However, even mild hypothermia impairs oxygen extraction in animals [10], and little information about normothermic humans can be extrapolated from these severely hypothermic patients on cardiopulmonary bypass.

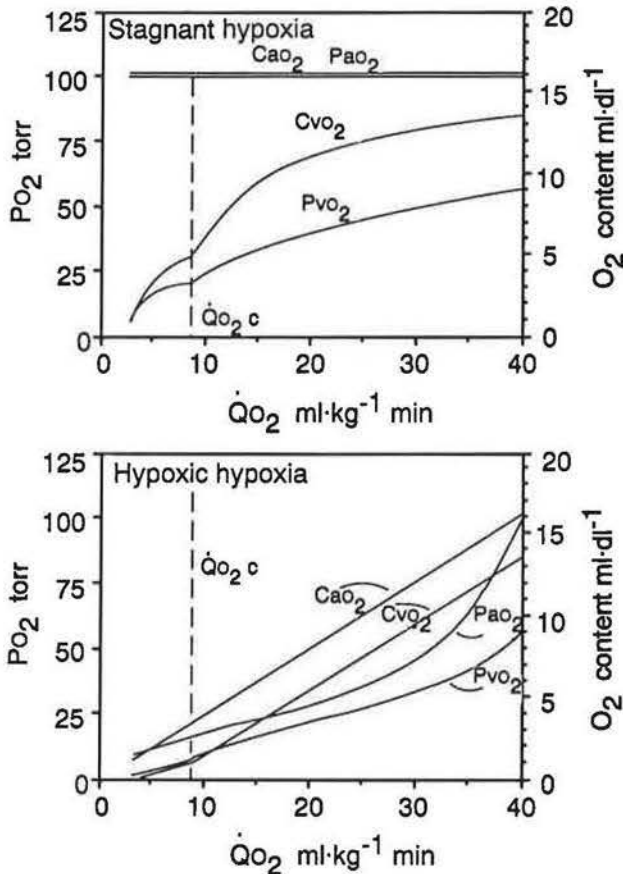


Fig. 2. - Top panel: Arterial (P_{aO_2}) and venous (P_{vO_2}) oxygen pressures (P_{O_2}) and contents (C_{aO_2} , C_{vO_2}) are plotted against oxygen delivery (\dot{Q}_{O_2}) for stagnant hypoxia, assuming the theoretical \dot{V}_{O_2} vs \dot{Q}_{O_2} behaviour shown for the dog in figure 1. Bottom panel: Arterial and venous oxygen pressures and contents are plotted against \dot{Q}_{O_2} for hypoxic hypoxia, assuming the theoretical \dot{V}_{O_2} vs \dot{Q}_{O_2} behaviour shown for the dog in figure 1.

Secondly, one group measured oxygen consumption and delivery in patients undergoing cardiac surgery, just before [26] or just after [27] cardiopulmonary bypass. No specific intervention was used to change O_2 delivery. These investigators made a single measurement on each patient, and plotted all of the composite data on a single pair of axes.

Patients with \dot{Q}_{O_2} values below $8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}$ (or $300\text{--}330 \text{ ml}\cdot\text{m}^{-2}\cdot\text{min}$) appeared to have lower values of \dot{V}_{O_2} . From the \dot{V}_{O_2} values on the plots, one can estimate a critical extraction ratio of about 33%, or about half of the corresponding value in animals. For comparison, if the critical extraction ratio for normal resting humans were 70% as in animals, then a person with a metabolic oxygen demand of $3.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}$ would have a critical oxygen delivery threshold of $3.5/0.7=5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}$.

From the disparity in these estimates, either: a) O_2 extraction is substantially worse in man than in other animals; b) poor extraction may have resulted from cardiac anaesthesia; or c) lumping single measurements from many patients yields a poor

representation of the O_2 uptake-delivery relationship for a single patient. Distinguishing between these possibilities ultimately must await definitive measurements of critical limits of O_2 delivery in humans.

Physiologic determinants of tissue oxygen extraction

Maintaining a constant oxygen uptake in the face of dwindling supply probably involves both passive and active processes. Passive processes may include increased capillary O_2 extraction fraction as delivery falls and O_2 uptake remains stable, until end-capillary P_{O_2} falls too low to support the tissue it nourishes. Active processes may include blood flow redistribution to ensure that no regional bed is overperfused at the expense of others that are hypoxic. It thus seems reasonable that all tissues might reach their own delivery thresholds at the same time. In fact, studies of isolated intestine suggest that it reaches its local critical point just prior to the body as a whole [6].

A theoretical picture of how this regulation occurs is beginning to emerge. In anaesthetized dogs, interfering with sympathetic tone by alpha blockade reduced systemic oxygen extraction during hypoxia, suggesting a role for sympathetic vasoconstriction [28]. Thus, neurohumoral tone may increase as hypoxia threatens, and local autoregulatory vasodilation could maintain each tissue in optimal oxygen balance [29]. Capillary recruitment has been demonstrated in tissues perfused with hypoxic blood [30]. Such capillary recruitment would be expected to minimize the diffusion distance for oxygen to move from capillary to cell. Interfering with any of the normal physiological mechanisms that serve to properly distribute blood among and within tissues might therefore impair extraction, and cause an increase in the $\dot{Q}_{O_2,c}$.

Impairment of oxygen extraction in ARDS and sepsis

Almost two decades ago, POWERS *et al.* [31] were studying the physiological consequences of positive end-expiratory pressure (PEEP) ventilation, and found that an increase in the level of PEEP often changed the oxygen delivery, either by improving oxygenation or by reducing cardiac output. When they plotted the change in oxygen consumption against the change in oxygen delivery, a strong positive correlation was seen, despite a starting delivery that was in the normal range.

The patients should not have been physiologically supply-dependent, as are animals below the $\dot{Q}_{O_2,c}$, and oxygen consumption should not have depended on oxygen delivery. However, it appeared that they were.

Attention to the phenomenon, later termed pathological supply dependence, remained mostly in the surgical literature in the 1970s, with subsequent studies

confirming the finding [32]. The patients studied suffered mostly from post-traumatic or septic respiratory failure. Investigations into the effect of PEEP ventilation suggested that PEEP might redistribute organ blood flow [33], but PEEP itself does not seem to reproduce the finding of pathological supply dependence in animals [34, 35]. It seemed likely that the supply dependence seen in these patients was a consequence of ARDS.

At the same time, it was becoming evident that ARDS patients who died often succumbed not to intractable pulmonary failure, but to failure in one or another unrelated organ [36, 37]. It has been suggested that pathological supply dependence is evidence for undisclosed tissue hypoxia that could play a role in the genesis of multiple organ failure [24]. Multiple organ failure syndrome is intimately associated with sepsis [36], and a large fraction of patients who die from ARDS have either occult or obvious infections at autopsy [38]. Extraction defects in patients with ARDS reflect the systemic nature of the disease, and sepsis may be the underlying cause for these extraction defects. Since the pioneering studies of POWERS *et al.* [31], a large number of studies have redemonstrated the findings of pathological supply dependence of oxygen consumption in ARDS and sepsis [39–47]. Methodological problems have plagued the studies and their interpretations, and some sceptics have argued that the findings may be artifactual [48, 49]. Moreover, two recent studies have directly questioned the existence of pathological supply dependence in patients [50, 51].

Among the studies of oxygen delivery and uptake in critical illness, there has been little or no evidence that patients ever reach the supply-independent plateau seen in normal animals. Thus, even at the highest level of oxygen delivery found in these patients, oxygen uptake continued to rise. One study reported such a plateau, but only two patients appeared to reach it [41]. Although it seems plausible that a plateau phase may exist; the high O_2 demand and poor extraction seen in these patients could preclude its demonstration. Observations of lactate elevations in these patients lend further support to the notion that pathological supply dependence reflects occult tissue hypoxia [40, 42]

Insights from animal studies

In human studies it is difficult to get enough data to identify mechanisms for an extraction defect. Accordingly, a series of studies sought animal models for extraction impairment. The simplest attempts involved injuring the lung with oleic acid infusion, but failed to find oxygen extraction defects [34, 35]. Thus, lung injury with non-cardiogenic pulmonary oedema does not produce an extraction defect, and neither does PEEP ventilation. Hyperoxia from high inspired oxygen fractions (F_{iO_2}) was found to impair extraction efficacy, but only minimally [35].

Moreover, most patients are treated with the minimal satisfactory F_{iO_2} , and do not experience severe arterial hyperoxia.

Because of the association of ARDS and extraction defects with sepsis, NELSON and co-workers [5, 7] infused *Pseudomonas aeruginosa* bacteria or *Escherichia coli* endotoxin into anaesthetized dogs, and demonstrated an extraction defect. Figure 3 summarizes the change in the systemic O_2 delivery-uptake relationship found after endotoxin administration. The salient features are a 30% decline in the critical extraction ratio, a 21% increase in O_2 uptake at high oxygen delivery, and an 88% increase in the critical oxygen delivery. Furthermore, these investigators reported that endotoxin induced the same oxygen extraction defect in the isolated autoperfused intestine as it did in the body as a whole [7], but that endotoxin had less effect on skeletal muscle oxygen extraction [8, 52]. In these studies, vascular reactivity in the isolated tissues was assessed by measuring the reactive hyperaemia following release of transiently occluded arteries. This reactive hyperaemia is a normal response in both the skeletal muscle and the intestinal beds. The hyperaemia disappeared following endotoxin in the gut but not the hindlimb, suggesting that the differential effects of the endotoxin on vascular reactivity correlated with oxygen extraction defects. Such studies identify important differences among tissues in models of sepsis.

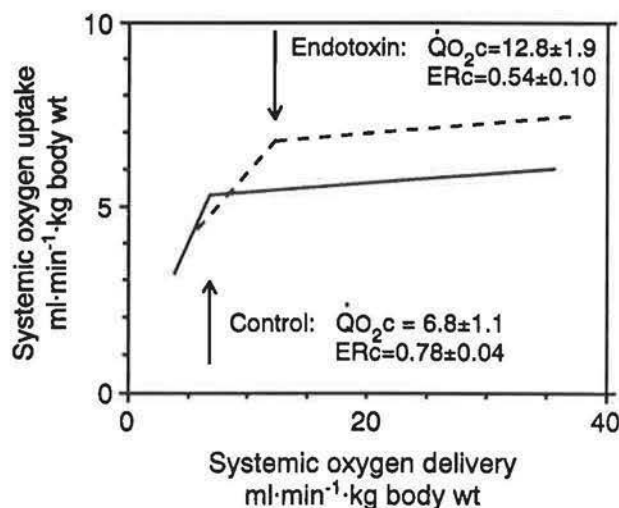


Fig. 3. — Summary plot of the relationship between systemic oxygen uptake and delivery in endotoxin treated and control dogs. The dashed line represents summary data from endotoxin-treated dogs, the solid line from controls. $\dot{Q}O_{2c}$: critical oxygen delivery; ERC: critical extraction ratio. From reference [7], with permission.

Possible mechanisms for an extraction defect

The possible mechanisms for extraction defects are determined by the physiology of oxygen transport. Plausible possibilities include cellular oxygen uptake defects, anatomical or diffusional arteriovenous

shunting, decreases in perfused capillary density, and heterogeneity of blood flow distribution. We will discuss these in turn.

A variety of studies have sought evidence for direct mitochondrial effects of sepsis or endotoxin. While some of these studies have shown changes in respiratory function of mitochondria [53], most investigators have concluded that the effects of sepsis on mitochondria were due to changes in cellular oxygen delivery, rather than due to direct cellular effects of sepsis [54–57]. The only cellular defect likely to account for pathological supply dependence is a change in the relationship between O_2 consumption and cell PO_2 , such as an increase in the critical PO_2 . While many studies have sought mitochondrial changes, none have (to our knowledge) specifically addressed the PO_2 dependence of cell oxygenation.

Anatomical shunting of blood flow directly from artery to vein could easily account for the extraction defects that have been seen, but shunting of blood requires an anatomical substrate: arteriovenous anastomoses. A variety of studies have measured shunt fraction by looking for arteriovenous passage of microspheres that are too large to pass through capillaries [58–61]. Shunt fractions by these studies are too small (<10%) to offer an explanation for the extraction defects seen either in animal models or in patients.

Diffusional shunting is the countercurrent exchange of oxygen from paired arterioles and venules [62, 63], as in the vasa recta of the kidney or the vascular architecture of intestinal villi [64]. While it is likely that diffusional shunting is important in these specialized circulations, most tissues probably do not transfer much oxygen through countercurrent diffusional shunt [65].

TENNEY [3] emphasized the importance of maintaining a high perfused capillary density, to keep diffusion distances small. If the density of perfused capillaries falls, then the average distance oxygen must diffuse increases. Larger distances from capillary to cell means larger partial pressures of oxygen, and results in greater loss of oxygen back into the veins at the critical point [4]. Accordingly, loss of perfused capillaries might be expected to lower the extraction ratio at the critical point. Activation of neutrophils and other formed elements has been cited as a likely participant in ARDS, and is a natural response to sepsis [66, 67]. It seems likely that neutrophils that may lodge in the lung might also be marginating in the peripheral circulation [68]. Such neutrophils may act to plug capillaries in a fashion similar to microemboli.

A variety of studies have explored the effect of microembolization on oxygen consumption [69]. Embolization presumably blocks capillaries or even arterioles. Based on available studies, it seems likely that infusion of microspheres lowers tissue oxygen extraction capacity. However, the interpretation is difficult, since on mathematical grounds one must occlude 75% of previously open capillaries even to double the average intercapillary distance.

Heterogeneity of blood flow distribution is the last likely mechanism for extraction defects. Any mismatch of local oxygen delivery to local oxygen demand may impair oxygen extraction capability. This might be termed $\dot{V}O_2/QO_2$ mismatching, in rough analogy with $\dot{V}A/Q$ mismatching in the lung. One can conceive of heterogeneity at several levels [4]. One might have too much blood going to one organ, leaving other organ systems relatively hypoperfused. Some studies have suggested that skeletal muscle is overperfused in sepsis [70, 71], while others have reported that skeletal muscle is underperfused in sepsis [72]. While variation in regional flow may be important, other reports [7, 8] suggest that defects within single organs, rather than maldistribution of flow among organs, play a dominant role in acute endotoxaemia.

Heterogeneity on a microvascular scale is much harder to assess than interorgan redistribution of blood flow, however, it seems likely that microvascular heterogeneity is responsible for extraction defects seen in the experiments of NELSON and co-workers [7, 8]. The correlation of extraction defects with the loss of reactive hyperaemia suggests that vascular reactivity is critical to normal tissue extraction.

Determinants of vascular reactivity

Optimal oxygen extraction during reductions of oxygen delivery requires autoregulatory vasodilation coupled with maintenance of vascular tone systemically. GRANGER and SHEPHERD [29] have emphasized a difference between flow-controlling vessels (medium sized arterioles) and distribution vessels (small arterioles and precapillary sphincters). In this schema, most of the arteriovenous pressure drop occurs in the flow-controlling vessels, which determine systemic vascular resistance. According to this model, capillary recruitment is controlled at the level of the distribution vessels. Systemic influences, such as sympathetic tone, presumably have their greatest effect on flow controlling vessels, whereas local autoregulation would play the greater role in regulating distribution vessels.

Since the 1950s it has been recognized that endotoxin and sepsis can alter the responsiveness of vessels to topically applied catecholamines [73]. In some reports, the responses were biphasic, with increases in reactivity followed by declining responsiveness [74]. In whole dogs given endotoxin, an acute drop in blood pressure (due to splanchnic pooling) can cause reflex vasoconstriction, but this is presumably a response to lowered blood flow. After adequate volume resuscitation restores blood flow to normal, blood pressure is lower at every flow rate, reflecting a systemic vasodilation [7].

A primary target for sepsis may be the endothelial cell; endothelial damage could therefore be the link between pulmonary manifestations of ARDS and peripheral manifestations of pathological supply

dependence. Endothelial disruption in the pulmonary vasculature increases permeability of the alveolar-capillary barrier, with oedemagenesis and respiratory failure. In the peripheral circulation, a comparable insult might cause failure of normal endothelial function. A growing body of evidence has suggested that the endothelial cell may play a pivotal role in regulation of local vascular tone [75]. Endothelial cells release endothelin, endothelium-derived relaxation factor (EDRF), prostacyclin (PGI_2), and possibly other paracrine mediators in response to various endogenous or exogenous stimuli. These paracrine mediators exert local effects on the subjacent smooth muscle, and account for many of the responses seen *in vivo* and *in vitro*. It follows that alteration in endothelial functions may have a profound effect on the regulation of overall vascular resistance and blood flow distribution. We hypothesize that impairment of vascular endothelial function in sepsis may prevent the optimal distribution of blood flow during progressive hypoxia.

Identifying and monitoring O_2 extraction in patients

Determining whether a particular patient is exhibiting supply dependence is difficult. The simplest approach is to measure oxygen delivery and consumption before and after a manoeuvre designed to increase cardiac output. If the oxygen consumption and delivery both increase, then the patient's O_2 consumption is by definition supply-dependent. Unfortunately, most oxygen delivery and consumption measurements both rely on the cardiac output, and so error in the cardiac output measurement will appear as a coordinated change in both delivery and consumption, leading falsely to the conclusion that the patient's O_2 consumption is supply-dependent. If measured cardiac output increases, then the arteriovenous O_2 content difference should narrow. If it does not narrow, one may conclude that the patient's O_2 consumption is supply-dependent. However, if the arteriovenous O_2 content difference narrows, but less than is expected, the patient may still be supply-dependent. Comparing arteriovenous O_2 difference changes to cardiac output might thus lead one to falsely conclude that the patient's oxygen uptake is not supply-dependent.

These problems plague not only the routine interpretation of patient data in the Intensive Care Unit (ICU), but also research studies designed to address the presence or absence of pathological supply dependence. The difficulty can be avoided altogether if accurate measurements of oxygen consumption could be made using expired gas, and compared to thermodynamic cardiac output measurements. Unfortunately, this technique remains impractical in routine care. In our view, it is reasonable to suppose that patients who are septic and have elevated lactic acid levels despite a normal O_2 delivery are probably exhibiting an

extraction defect, even if corroborating measurements are not practical.

Improving oxygen delivery

It is a truism that supportive therapy can at best keep the body alive while definitive therapy of the underlying disease is undertaken. In many cases, the success of temporizing supportive therapy is crucial in determining survival. The implication of tissue hypoxia in sepsis and ARDS is that patients may benefit from maximizing oxygen delivery even if oxygen delivery is in the normal range. One can improve oxygen delivery by manipulating its constituent variables: cardiac output, Pao_2 , and blood oxygen carrying capacity.

Optimizing each of the accessible physiological variables carries its own problems. Increasing cardiac output by increasing preload is sensible if preload is low; maximizing filling pressures are often limited by oedema formation. Blood transfusion to increase oxygen carrying capacity seems sensible, but carries the usual risks of transfusion-associated diseases. Another objection to the use of transfusions in patients without severe anaemia concerns the effect of haematocrit on blood rheology. The viscosity of whole blood and of red cell suspensions is a rapidly increasing function of haematocrit, and a weaker function of red cell deformability, plasma viscosity, and red cell aggregability [76, 77]. The increase in viscosity occurs over the entire range of haematocrit, and there is no specific critical point where viscosity suddenly jumps. There is a distinct trade-off between viscosity and oxygen carrying capacity, but the optimum haematocrit may depend on the specific clinical circumstances. We know of no specific evidence that blood viscosity is a problem in ARDS or sepsis.

Reducing oxygen demand

The alternative approach to improving tissue oxygenation is to reduce oxygen uptake by reducing demand. Manoeuvres to reduce oxygen demand form a mainstay of standard intensive care, and include mechanical ventilation, sedation, and paralysis. The increased oxygen demand associated with elevations in body temperature has two mechanisms: an increased metabolic rate that accompanies the higher tissue temperatures, and active thermogenesis by patients trying to increase their body temperature. Maintaining normal temperature whenever possible seems appropriate, insofar as it can be accomplished with conventional means. Shivering and possibly also nonshivering thermogenesis can presumably increase O_2 substantially, so use of cooling blankets may have mixed effects.

The use of catecholamines to stimulate cardiac output, and to support cardiac output raises the

spectre of increased O_2 demand, owing to the specific calorogenic effect of catecholamines. While intraperitoneal bolus injections of catecholamines in awake rats do increase oxygen consumption, the same does not seem as obvious in anaesthetized dogs infused with clinically relevant doses of norepinephrine or dobutamine. It seems likely that use of inotropes or pressors in ICU settings more closely resembles the latter than the former setting, and the specific calorogenic effect of catecholamines may be of more theoretical than practical concern.

The use of halothane to lower oxygen demand has been suggested, but is (like profound hypothermia) associated with impairment in tissue oxygen extraction [16]. Thus, these more extreme manoeuvres are probably excessive, and it seems prudent to use moderate sedation rather than general anaesthesia, and reasonable temperature control rather than profound hypothermia, to limit oxygen demand.

Expectations for future developments

Future work in clinical settings should address several unanswered questions. Are extraction defects real, and is optimizing oxygen delivery appropriate? After reviewing the evidence currently available, we concluded that affirmative answers are likely, but far from certain. If optimizing oxygen delivery is appropriate, then what end-point should be used for therapy? The inability to demonstrate a plateau level for oxygen uptake in patients renders this question difficult to answer. Better measurement techniques for human oxygen delivery will offer substantial information on this topic.

Correcting extraction defects in patients is further away. Progress is being made in identifying the pathophysiology of extraction defects in the animal laboratory, and further understanding may identify a target for therapeutic intervention. For example, the appropriate drug might improve oxygen distribution among microvessels, alleviating the oxygen distribution problem. Carefully testing such interventions in animal models may establish whether any interventions are safe and effective in reversing extraction defects. Until a firmer understanding of the pathophysiology of extraction defects becomes available, human studies of drugs seem premature.

References

1. Fisher AB, Forman HJ. - Oxygen utilization and toxicity in the lungs. *In: Handbook of Physiology, The Respiratory System, Sec. 3, Vol. 1.* A.P. Fishman, A.B. Fisher eds, Williams and Wilkins, Baltimore, 1985, pp. 231-254.
2. Longmuir IS. - Respiration rate of rat liver cells at low oxygen concentration. *Biochem J*, 1957, 65, 378-382.
3. Tenney SM. - A theoretical analysis of the relationship between venous blood and mean tissue oxygen pressures. *Respir Physiol*, 1974, 20, 280-296.
4. Schumacker PT, Samsel RW. - Analysis of oxygen delivery and uptake relationships in the Krogh tissue model. *J Appl Physiol*, 1989, 67(3), 1234-1244.
5. Nelson DP, Beyer C, Samsel RW, Wood LDH, Schumacker PT. - Pathological supply dependence of O_2 uptake during bacteremia in dogs. *J Appl Physiol*, 1987, 63(4), 1487-1492.
6. Nelson DP, King CE, Dodd SL, Schumacker PT, Cain SM. - Systemic and intestinal limits of O_2 extraction in the dog. *J Appl Physiol*, 1987, 63(1), 387-394.
7. Nelson DP, Samsel RW, Wood LDH, Schumacker PT. - Pathologic supply dependence of systemic and intestinal O_2 uptake during endotoxemia in dogs. *J Appl Physiol*, 1988, 64(6), 2410-2419.
8. Samsel RW, Nelson DP, Sanders WM, Wood LDH, Schumacker PT. - The effect of endotoxin on systemic and skeletal muscle oxygen extraction. *J Appl Physiol*, 1988, 65(3), 1377-1382.
9. Schumacker PT, Long GR, Wood LDH. - Tissue oxygen extraction during hypovolemia: role of hemoglobin P_{50} . *J Appl Physiol*, 1987, 62(5), 1801-1807.
10. Schumacker PT, Rowland J, Saltz S, Nelson DP, Wood LDH. - Effects of hyperthermia and hypothermia on oxygen extraction by tissues during hypovolemia. *J Appl Physiol*, 1987, 63, 1246-1252.
11. Cain SM. - Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *J Appl Physiol*, 1977, 42(2), 228-234.
12. Gutierrez G, Warley AR, Dantzker DR. - Oxygen delivery and utilization in hypothermic dogs. *J Appl Physiol*, 1986, 60(3), 751-757.
13. Adams RP, Dieleman LA, Cain SM. - A critical value for O_2 transport in the rat. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1982, 53(3), 660-664.
14. Cain SM, Bradley WE. - Critical O_2 transport values at lowered body temperatures in rats. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1983, 55(6), 1713-1717.
15. Willford DC, Hill EP, White FC, Moores WC. - Decreased critical mixed oxygen tension and critical oxygen transport during induced hypothermia in pigs. *J Clin Monit*, 1986, 2, 155-168.
16. Hershenson MB, O'Rourke PP, Schena JA, Crone RA. - Effect of halothane on critical levels of oxygen transport in the anesthetized newborn lamb. *Anesthesiology*, 1988, 64, 174-179.
17. Fahey JT, Lister G. - Postnatal changes in critical cardiac output and oxygen transport in conscious lambs. *Am J Physiol*, 1987, 253, H100-H106.
18. Wasserman K. - Determinants and detection of the anaerobic threshold and consequences of exercise above it. *Circulation*, 1987, 76(6), V129-139.
19. Barcroft J. - Physiological effects of insufficient oxygen supply. *Nature*, 1920, 106, 125-129.
20. West JB. - *In: Respiratory Physiology - the Essentials.* Williams and Wilkins, Baltimore, 1979, p. 85.
21. Coburn RF, Forman HJ. - Carbon monoxide toxicity. *In: Handbook of Physiology, Sec. 3, Vol. IV.* L.E. Farhi, S.M. Tenney eds, Williams and Wilkins, Baltimore, 1987, pp. 439-456.
22. Gutierrez G, Pohil RJ, Strong R. - Effect of flow on O_2 consumption during progressive hypoxemia. *J Appl Physiol*, 1988, 65(2), 601-607.
23. Cain SM. - Gas exchange in hypoxia, apnea, and hyperoxia. *In: Handbook of Physiology, Sec 3, Vol. IV.* L.E. Farhi, S.M. Tenney eds, Williams and Wilkins, Baltimore, 1987, pp. 403-420.
24. Schumacker PT, Cain SM. - The concept of a

- critical oxygen delivery. *Intensive Care Med*, 1987, 13, 223-229.
25. Fox LS, Blackstone EH, Kirklin AW, Stewart RW, Samuelson N. - Relationship of whole body oxygen consumption to perfusion flow rates during hypothermic cardiopulmonary bypass. *J Thorac Cardiovasc Surg*, 1982, 83, 239-248.
26. Shibutani K, Komatsu T, Kubal K, Sanchala V, Kumar V, Bizzari DV. - Critical level of oxygen delivery in anesthetized man. *Crit Care Med*, 1984, 11(8), 640-643.
27. Komatsu T, Shibutani K, Okamoto K, Kumar V, Kubal K, Sanchala V, Lees DE. - Critical level of oxygen delivery after cardiopulmonary bypass. *Crit Care Med*, 1987, 15(3), 194-197.
28. Cain SM. - Effects of time and vasoconstrictor tone on O_2 extraction during hypoxic hypoxia. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1978, 45, 219-224.
29. Granger HJ, Shepherd AP. - Dynamics and control of the microcirculation. *Adv Biomed Eng*, 1979, 7, 1-63.
30. Shepherd AP. - Intestinal O_2 consumption and ^{86}Rb extraction during arterial hypoxia. *Am J Physiol*, 1978, 234(3), E248-E251.
31. Powers SR, Mannal R, Neclerio M, English M, Marr C, Leather R, Ueda H, Williams G, Custead W, Dutton R. - Physiologic consequences of positive end-expiratory pressure (PEEP) ventilation. *Ann Surg*, 1973, 178, 265-272.
32. Rhodes GR, Newell JC, Shah D, Scovill W, Tauber J, Dutton RE, Powers SR. - Increased oxygen consumption accompanying increased oxygen delivery with hypertonic mannitol in adult respiratory distress syndrome. *Surgery*, 1978, 84, 490-497.
33. Manny J, Justice R, Hechtman B. - Abnormalities in organ blood flow and its distribution during positive end-expiratory pressure. *Surgery*, 1979, 85(4), 425-432.
34. Pepe PE, Culver BH. - Independently measured oxygen consumption during reduction of oxygen delivery by positive end-expiratory pressure. *Am Rev Respir Dis*, 1985, 132, 788-792.
35. Long GR, Nelson DP, Sznajder JJ, Wood LDH, Schumacker PT. - Systemic oxygen delivery and consumption during acute lung injury in dogs. *J Crit Care*, 1988, 3(4), 249-255.
36. Bell RC, Coalson JJ, Smith JD, Johanson WD. - Multiple organ failure and infection in adult respiratory distress syndrome. *Ann Intern Med*, 1983, 99, 293-298.
37. Peters JI, Seidenfeld JJ. - Coping with multiple organ failure: key to survival in ARDS. *J Crit Illness*, 1988, 3(2), 96-105.
38. Montgomery AB, Stager MA, Carrico CJ, Hudson LD. - Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis*, 1985, 132, 485-489.
39. Danek SJ, Lynch JP, Weg JG, Dantzker DR. - The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. *Am Rev Respir Dis*, 1980, 122, 387-395.
40. Gilbert EM, Haupt MT, Mandanas RY, Huaranga AJ, Carlson RW. - The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. *Am Rev Respir Dis*, 1986, 134(5) 873-878.
41. Mohsenifar Z, Goldbach P, Tashkin DP, Campisi DJ. - Relation between O_2 delivery and O_2 consumption in the adult respiratory distress syndrome. *Chest*, 1984, 84, 267-271.
42. Haupt MT, Gilbert EM, Carlson RW. - Fluid loading increases oxygen consumption in septic patients with lactic acidosis. *Am Rev Respir Dis*, 1985, 131, 912-916.
43. Kariman K, Burns SR. - Regulation of tissue oxygen extraction is disturbed in adult respiratory distress syndrome. *Am Rev Respir Dis*, 1985, 132(1), 109-114.
44. Kaufman BS, Rackow EC, Falk JC. - The relationship between oxygen delivery and consumption during fluid resuscitation of hypovolemic and septic shock. *Chest*, 1984, 85, 336-340.
45. Astiz ME, Rackow EC, Falk JL, Kaufman BS, Weil MH. - Oxygen delivery and consumption in patients with hyperdynamic septic shock. *Crit Care Med*, 1987, 15(1), 26-28.
46. Bihari D, Smithies M, Gimson A, Tinker J. - The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. *N Engl J Med*, 1987, 317, 397-403.
47. Abraham E, Shoemaker WC, Cheng PH. - Cardiorespiratory responses to fluid administration in peritonitis. *Crit Care Med*, 1984, 12, 664-667.
48. Archie JP. - Mathematical coupling of data. A common source of error. *Ann Surg*, 1981, 193(3), 296-303.
49. Snyder JV, Carroll GC. - Tissue oxygenation: a physiological approach to a clinical problem. *Curr Probl Surg*, 1982, 19(11), 652-719.
50. Annat G, Viale J-P, Percival C, Froment M, Motin J. - Oxygen delivery and uptake in the adult respiratory distress syndrome. *Am Rev Respir Dis*, 1986, 133, 999-1001.
51. Carlile PV, Gray BA. - Effect of opposite changes in cardiac output and arterial Po_2 on the relationship between mixed venous Po_2 and oxygen transport. *Am Rev Respir Dis*, 1989, 140, 891-896.
52. Bredle DL, Samsel RW, Schumacker PT, Cain SM. - Critical O_2 delivery to skeletal muscle at high and low Po_2 in endotoxemic dogs. *J Appl Physiol*, 1989, 66(6), 2553-2558.
53. Mela L, Bacalzo LV Jr, Miller LD. - Defective oxidative metabolism of rat liver mitochondria in hemorrhagic and endotoxin shock. *Am J Physiol*, 1971, 220(2), 571-577.
54. Rehnrona S, Mela L, Siesjo BK. - Recovery of brain mitochondrial function in the rat after complete and incomplete cerebral ischemia. *Stroke*, 1979, 10, 437.
55. Dawson KL, Geller ER, Kirpatrick JR. - Enhancement of mitochondrial function in sepsis. *Arch Surg*, 1988, 123(2), 241-244.
56. Clemens M, Chaudry IH, Baue AE. - Oxidative capability in hepatic tissue in late sepsis. *Adv Shock Res*, 1981, 6, 55-64.
57. Fry DE, Kaelin CR, Giammara BL, Rink RD. - Alterations of oxygen metabolism in experimental bacteremia. *Adv Shock Res*, 1981, 6, 45-54.
58. Delaney JP. - Arteriovenous anastomotic blood flow in the mesenteric organs. *Am J Physiol*, 1969, 216(6), 1556-1561.
59. Cronenwett JL, Lindenauer MS. - Direct measurement of arteriovenous anastomotic blood flow in the septic canine hind limb. *Surgery*, 1979, 85, 275-282.
60. Archie JP. - Anatomic arterial-venous shunting in endotoxic and septic shock in dogs. *Ann Surg*, 1977, 186, 171-176.
61. Maxwell LC, Shepherd AP, McMahan CA. - Microsphere passage through intestinal circulation: through shunts or capillaries? *Am J Physiol*, 1985, 248, H217-224.
62. Sharan M, Popel AS. - A mathematical model of

countercurrent exchange of oxygen between paired arterioles and venules. *Math Biosci*, 1989, 91, 17-34.

63. Piiper J, Meyer M, Scheid P. - Dual role of diffusion in tissue gas exchange: blood-tissue equilibration and diffusion shunt. *Respir Physiol*, 1984, 56, 131.

64. Lundgren O, Haglund U. - The pathophysiology of the intestinal countercurrent exchanger. *Life Sciences*, 1978, 23, 1411-1422.

65. Rose CP, Goresky CA. - Limitation of tracer oxygen uptake in the canine coronary circulation. *Circ Res*, 1985, 56, 57-71.

66. Rinaldo JE, Rogers RM. - Adult respiratory distress syndrome: changing concepts of lung injury and response. *N Engl J Med*, 1982, 306, 900-909.

67. Rinaldo JE, Rogers RM. - Adult respiratory distress syndrome. *N Engl J Med*, 1986, 315, 578-580.

68. Dorinsky PM, Costello JL, Gadek JE. - Oxygen distribution and utilization after phorbol myristate acetate-induced lung injury. *Am Rev Respir Dis*, 1988, 138, 1454-1463.

69. Ellsworth ME, Goldfarb RD, Alexander RS. - Microembolization induced oxygen utilization impairment in the canine gracilis muscle. *Adv Shock Res*, 1981, 5, 89-99.

70. Finley RJ, Duff JH, Holiday RL, Hones D, Marchuk JB. - Capillary blood flow in human sepsis. *Surgery*, 1975, 78(1), 87-94.

71. Wright CJ, Duff JH, McLean APH, MacLean LD. - Regional capillary blood flow and oxygen uptake in severe sepsis. *Surg Gynecol Obstet*, 1971, 132, 637-644.

72. Lang CH, Bagby GJ, Ferguson JL, Spitzer JJ. - Cardiac output and redistribution of organ blood flow in hypermetabolic sepsis. *Am J Physiol*, 1984, 246, R331-R337.

73. Zweifach BW, Thomas L. - The role of epinephrine in the reactions produced by the endotoxins of gram negative bacteria. The changes produced by endotoxin in the vascular reactivity of epinephrine of the rat mesoappendix and the isolated perfused rabbit ear. *J Exp Med*, 1956, 104, 881-896.

74. Baker CH, Wilmoth FH. - Microvascular responses to *E. coli* endotoxin with altered adrenergic activity. *Circ Shock*, 1984, 12, 165-176.

75. Furchgott RF. - The role of endothelium in the responses of vascular smooth muscle to drugs. *Ann Rev Pharmacol Toxicol*, 1984, 24, 175-197.

76. Chien S. - Hemorheology in disease: pathophysiological significance and therapeutic implications. *Clin Hemorheol*, 1981, 1, 419-442.

77. Usami S. - Physiologic significance of blood rheology. *Biorheology*, 1982, 19, 29-46.

Distribution d'oxygène dans les tissus. R. Samsel, P. Schumacker.

RÉSUMÉ: Dans les tissus sains et bien perfusés, la captation d'oxygène est déterminée principalement par les besoins métaboliques plutôt que par l'apport d'oxygène. L'hypoxie tissulaire survient lorsque la P_{O_2} tissulaire baisse en dessous d'une point critique, et le point où ceci se produit peut être prédit à partir de l'apport systémique d'oxygène ou du ratio d'extraction. Des faits en nombre croissant suggèrent que l'extraction tissulaire d'oxygène peut être diminuée dans le syndrome de détresse respiratoire aiguë et dans le septicémie. Dans ces syndromes, la délivrance minimale d'oxygène nécessaire pour maintenir une captation d'oxygène normale, est augmentée, puisque les tissus deviennent hypoxiques malgré de hauts degrés de délivrance d'oxygène. Une controverse entoure chacune des phases de cette observation, depuis sa base expérimentale jusqu'aux causes potentielle et à ses implications pour le traitement des patients. Dans cette revue générale, nous discutons la physiologie du transport d'oxygène, les déterminants de l'oxygénation tissulaire dans les états normaux et pathologiques, et les implications thérapeutiques du transport d'oxygène.

Eur Respir J, 1991, 4, 1258-1267.