Oxygen demand, delivery, and consumption

.apter 22

OXYGEN DEMAND, DELIVERY, AND CONSUMPTION

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Transport of oxygen (O_2) from the environment to the cells of the body tissues depends on the integrated functioning of three organ systems: the lungs, the blood, and the circulation. In normal infants and children under resting conditions, th vstems not only supply an "adequate" amount of O_2 t issues but also provide O_2 in great excess of the tissue de..ands. The integration and reserve capacity of the body's O_2 .sport system are often assessed by the ability of an individual to respond to increasing demands for O_2, as with exercise. Similarly, pathological stresses such as fever, which also increases metabolic demands, test the integrity of these three systems. Disease processes that lead to critical illness (e.g., hypoxia or shock) often seem to be insidious in their onset; they reduce the reserve capacity first and impair the ability to respond appropriately to superimposed stresses. As the disease process progresses, not only is reserve depleted but even resting O_2 demands cannot be met; organ dysfunction ensues, and signs become readily apparent. There is, however, no good measure of reserve capacity of most organs.

Therapeutic interventions in critically ill infants and children have two basic goals: (1) to improve a perceived imbalance between nutrient (particularly O_2) delivery and the metabolic demands of an organ and (2) to treat the underlying disease process. When successful, these maneuvers improve or restore organ function and replenish systemic reserve so that the patient can tolerate superimposed demands dictated by healing and rehabilitation.

DETERMINANTS OF O_2 SUPPLY

he rate at which O_2 is supplied to the body tissues is ıtified as the systemic O_2 transport (commonly abbreviated as $\dot{D}o_2$), which is the product of cardiac output or systemic blood flow ($\dot{Q}$) and arterial O_2 content (Cao_2):

$$\dot{D}o_2 = \dot{Q} \times Cao_2 \times 0.01 \quad (1)$$

where $\dot{D}o_2$ is in ml O_2/min, $\dot{Q}$ is in ml blood/min, and Cao_2 is in ml O_2/dl blood.

Arterial O_2 content is a function of arterial hemoglobin concentration (Hb); hemoglobin O_2 saturation (Sao_2) and the pressure of O_2 (Pao_2):

$$Cao_2 = (1.34 \times Hb \times Sao_2) + (Pao_2 \times 0.003) \quad (2)$$

where Hb is in g/dl blood, Sao_2 is expressed as a fraction, Pao_2 is in mm Hg, 1.34 is the O_2 carrying capacity of Hb in ml O_2/g, and 0.003 is the Bunsen solubility coefficients for O_2 in plasma at 37° C.

Substituting equation (2) into equation (1) yields:

$$\dot{D}o_2 = \dot{Q} \times [(1.34 \times Hb \times Sao_2) + (0.003 \times Pao_2)] \times 0.01 \quad (3)$$

This equation again demonstrates the dependence of systemic O_2 transport on the lungs (Sao_2, Pao_2), blood (Hb), and circulatory system ($\dot{Q}$). These three systems act together in an integrated fashion to adapt both acutely and chronically to changes in tissue O_2 demands by altering O_2 delivery. In addition, each organ system can respond individually to overcome deficiencies in O_2 delivery, should either of the other systems fail. However, as is discussed later, these systems differ greatly in their ability to compensate for acute or chronic deficiencies in the other systems and thereby in their ability to restore O_2 delivery.

Examination of equation 3 shows that $\dot{D}o_2$ may be compromised by severe decreases in (1) O_2 carrying capacity (anemic hypoxia), (2) arterial hemoglobin O_2 saturation (hypoxic hypoxia), or (3) cardiac output (stagnant hypoxia) (Fig. 22-1). A subject who becomes acutely *hypoxemic* (low Pa_{O_2} or hemoglobin O_2 saturation) will compensate initially by an increasing cardiac output to maintain $\dot{D}o_2$ close to normal levels.[54] In relatively stable patients with chronic hypoxemia, erythropoietin stimulates increased hemoglobin concentration so that $\dot{D}o_2$ can be maintained at a lower cardiac output than during the acute stage of the process.[76] Although the increased viscosity with polycythemia can potentially further reduce cardiac output and $\dot{D}o_2$, this is uncommon in critically ill patients because hemoglobin production is depressed and there is usually increased blood loss (e.g., blood withdrawal). A subject who becomes acutely *anemic* will compensate rapidly by an increase in cardiac output to maintain $\dot{D}o_2$.[71] Initially, the heart rate and stroke volume increase because of chemoreceptor stimulation and decreased blood viscosity. Should the anemia persist, there is an expansion of the blood volume, augmenting stroke volume further, so that the higher level of cardiac output can be maintained at a lower heart rate.[84] The subject with decreased cardiac output has little or no compensatory adaptations to restore $\dot{D}o_2$. Hyperventilation can raise Pa_{O_2} only slightly and therefore would not significantly raise hemoglobin O_2 saturation. Low cardiac output is not a stimulus for erythropoietin release. Therefore subjects with decreased cardiac output cannot restore $\dot{D}o_2$. Because hemoglobin concentration and O_2 saturation remain relatively constant, $\dot{D}o_2$ falls in direct portion to cardiac output, as in equation 3.

Obviously, in combined O_2 deficiencies it will also be difficult to compensate and maintain $\dot{D}o_2$. For example, patients with cyanotic heart disease and hypoxemia poorly tolerate anemia or dehydration, whereas infants with ventricular septal defects and compromised cardiac output can decompensate rapidly with superimposed anemia or hypoxemia.[48]

If these compensations to restore $\dot{D}o_2$ are inadequate, the organism must then rely on other mechanisms to improve the uptake and distribution of the limited O_2 delivered to the tissues. The "adequacy" of systemic O_2 delivery must be viewed as the ability to meet the O_2 demands of the tissues and avoid tissue hypoxia and organ dysfunction.

DETERMINANTS OF O_2 DEMANDS

Many factors can alter tissue O_2 demands both at rest and during stress. Although there is no method to determine O_2 demands a priori, it is presumed that the increase in O_2 consumption ($\dot{V}o_2$) that occurs when a work (e.g., exercise) or a metabolic (e.g., fever) load is imposed, in the absence of signs of tissue hypoxia (e.g., increase in lactate), provides a reasonable estimate. However, when O_2 transport is low enough to cause tissue hypoxia, $\dot{V}o_2$ reflects not only metabolic demands for O_2 but the limitation in supply as well.

Homeostatic factors

Whole-body $\dot{V}o_2$ varies in proportion to body temperature over the physiological range[10]; there is a 10% to 13% increase in $\dot{V}o_2$ per degree centigrade elevation above normal body temperature (so-called Q_{10} effect). An extreme example of this is malignant hyperthermia, which can raise demands well beyond the capacity to eliminate metabolic by-products (see Chapter III). However, lowering body temperature below 37° C may not reduce demands unless homeostatic responses to maintain body temperature, such as shivering, are blocked. For this reason, maintaining a normal body temperature in a cool environment imposes a large O_2 cost.[75] This is an issue in some common clinical settings; e.g., infants or small children with a large surface area-to-mass ratio can have large convective heat losses (especially when uncovered); patients rewarming from surgically-induced hypothermia, as after cardiac surgery, have large increase in O_2 demands, especially if shivering occurs[61]; and patients with burns over a large surface area dissipate heat readily, which raises their metabolic demands substantially (see Chapter 97).

Growth rate is also an important determinant of metabolic demands. Healthy infants and young children have higher metabolic rates ($\dot{V}o_2$) than adults when indexed to body weight or surface area.[49] Infants and young children generally exhibit $\dot{V}o_2$ in the range of 175 ml/min/m^2, whereas

$\dot{D}o_2 = \dot{Q} \times [(1.34 \times Hb \times O_2\ sat) + (.003 \times PaO_2)] \times 0.01$

A. Hypoxic hypoxia

Disturbance:	$\downarrow O_2$ sat, $\downarrow PaO_2 \rightarrow \downarrow \dot{D}O_2$
Acute compensation:	$\uparrow \dot{Q} \rightarrow \uparrow \dot{D}O_2$ (NL)
Chronic compensation:	$\uparrow$ Hb $\rightarrow \downarrow \dot{Q}, \leftrightarrow \dot{D}O_2$ (NL)

B. Anemic hypoxia

Disturbance:	$\downarrow$ Hb $\rightarrow \downarrow \dot{D}O_2$
Acute and chronic compensation:	$\uparrow \dot{Q}, \leftrightarrow$ O_2 sat $\rightarrow \uparrow \dot{D}O_2$

C. Stagnant hypoxia

Disturbance:	$\downarrow \dot{Q} \rightarrow \downarrow \dot{D}O_2$
Compensation:	None ($\leftrightarrow$ Hb, $\leftrightarrow O_2$ sat $\rightarrow \downarrow \dot{D}O_2$)

$\downarrow$ – decreased, $\uparrow$ – increased, $\leftrightarrow$ no change,
(NL) - SOT returned to normal value

Fig. 22-1. The potential disturbances in systemic O_2 transport ($\dot{D}o_2$). Both hypoxic hypoxia and anemic hypoxia have compensations available to restore $\dot{D}o_2$ to near normal values. Stagnant hypoxia has no compensation.

adults are in the range of 140 ml/min/m^2. A significant proportion of the O_2 demands in infants is required for growth.

Effects of illness, injury, and therapy

The stress of injury, infection, or repair has also been associated with large increases in metabolic demands. For example, skeletal injuries may increase $\dot{V}o_2$ by up to 30%, infection may increase $\dot{V}o_2$ by 60%, and burns may increase $\dot{V}o_2$ by more than 100% (see Chapter 68). Other more specific clinical conditions (such as convulsions and hyperthyroidism) can greatly increase tissue O_2 demands.

In addition, O_2 requirements may be raised or lowered by medications. Infusion of catecholamines (e.g., isoproterenol, dopamine, epinephrine) can increase metabolic rate by more than 10%.[14] Sedatives and anesthetic agents can lower O_2 demands by reducing movement, agitation, or pain.[80] Muscle relaxants will decrease resting muscle tone and alleviate the work of breathing, thereby decreasing O_2 demands. In addition, hyperventilation that causes alkalemia can raise whole body $\dot{V}o_2$ by as much as 15% to 20%, an effect that is independent of the increase in respiratory work.[45]

Effects of severely lowered $\dot{D}o_2$

Multiple factors influence $\dot{V}o_2$ in the critically ill child. However, when the clinical condition also involves impairment of $\dot{D}o_2$, $\dot{V}o_2$ may be altered further and may no longer reflect metabolic demands. The rate of whole-body $\dot{V}o_2$ and $\dot{D}o_2$ are related by the Fick O_2 balance as follows:

$$\dot{V}o_2 = \dot{Q} \times (Cao_2 - C\bar{v}o_2) \times 0.01 \quad (4)$$

where $\dot{V}o_2$ is expressed in ml O_2/min and $C\bar{v}o_2$ is the mixed systemic venous O_2 content in ml O_2/dl blood. Multiplying by Cao_2/Cao_2 and regrouping terms:

$$\dot{V}o_2 = (\dot{Q} \times Cao_2 \times 0.01)\ (Cao_2 - C\bar{v}o_2)/Cao_2 \quad (5)$$

Substituting equation 1 into equation 5 yields

$$\dot{V}o_2 = \dot{D}o_2\ (Cao_2 - C\bar{v}o_2)/Cao_2 \quad (6)$$

or

$$\dot{V}o_2 = \dot{D}o_2 \times O_2 \text{ extraction} \quad (7)$$

where $(Cao_2 - C\bar{v}o_2)/Cao_2$ is the fractional O_2 extraction.

In the normal subject at rest, $\dot{D}o_2$ is in great excess of $\dot{V}o_2$. For example, in the unstressed human newborn, the $\dot{V}o_2$ is in the range of 7 ml O_2/min/kg, $\dot{D}o_2$ is approximately 30 ml O_2/min/kg, and resting O_2 extraction is approximately 0.23. Thus at rest the tissues consume only about one quarter of the available O_2. With this large reserve in supply, $\dot{V}o_2$ is generally a reflection of metabolic demands and does not depend on O_2 supply. Accordingly, mild to moderate reductions in $\dot{D}o_2$ are well tolerated and do not compromise $\dot{V}o_2$; that is, $\dot{V}o_2$ is independent of a wide range of changes in $\dot{D}o_2$.

The relationship of $\dot{V}o_2$ and $\dot{D}o_2$ is shown in a stylized schema in Fig. 22-2. There is a biphasic response, assuming O_2 demands remain constant.[3,28] Initially, as $\dot{D}o_2$ is decreased from baseline or resting values, $\dot{V}o_2$ remains constant (flat portion of the curve). Over this range, reductions in $\dot{D}o_2$ must be balanced by proportional increases in whole-body O_2 extraction (equation 7). With larger decreases in $\dot{D}o_2$, there is a critical level of $\dot{D}o_2$ below which increased O_2 extraction can no longer fully compensate to maintain $\dot{V}o_2$ constant. Reserve has been depleted at this point, and $\dot{V}o_2$ falls with any further decreases in $\dot{D}o_2$ below this critical level. $\dot{V}o_2$ no longer reflects only metabolic demands but reflects $\dot{D}o_2$ as well. Similar relationships $\dot{V}o_2$ of to $\dot{D}o_2$ as in Fig. 22-2 have been demonstrated in variety of animal models, using both young and older animals, whether $\dot{D}o_2$ was acutely lowered by anemia,[71] hypoxemia, low cardiac output,[28,71] or combinations. It is assumed that similar responses to O_2 supply limitation occur in patients, but this is difficult to prove. Moreover, there are pathological conditions in which the relationship between $\dot{V}o_2$ and $\dot{D}o_2$ may not be similar to that just described.

Below the critical $\dot{D}o_2$, tissue O_2 metabolism is limited by $\dot{D}o_2$. Unless tissue metabolic demands are simultaneously decreased, the decreasing $\dot{V}o_2$ means demands are not being met and at least some tissues will become hypoxic. Under such circumstances, it has been proposed that consumption may decline in the face of inadequate $\dot{D}o_2$ owing to a decline in "nonessential" or "facultative" metabolism. Metabolism utilized for growth, other cellular anabolic and reparative processes, thermoregulation, and neurotransmitter synthesis are potential examples of nonessential metabolism. Elimination of such nonessential metabolism during critical limitations in $\dot{D}o_2$ would allow intracellular redistribution of O_2 to the mitochondria to sustain most vital functions. How these processes are regulated, the time course of such regulation, or how important such alterations in intracellular O_2 metabolism are during periods of O_2 limitation is uncertain. However, it would be expected that young and growing humans and animals would have higher proportions of facultative metabolism and that this would be a more important mechanism for compensation in these subjects.[31,79] These processes may represent an additional O_2 reserve capacity available to young subjects and may explain part of the reported "tolerance" to acute hypoxia of young subjects when compared to the adult. By lowering demands, the supply-demand match would be improved, even with no further increase in O_2 extraction.

Changes in demands when $\dot{D}o_2$ is reduced can be of critical importance for organ function and can even influence whether injury results. For example, when renal blood flow is diminished, the potential for ischemic damage may be tempered somewhat by the simultaneous reduction in demands caused by reduced glomerular filtration and resultant

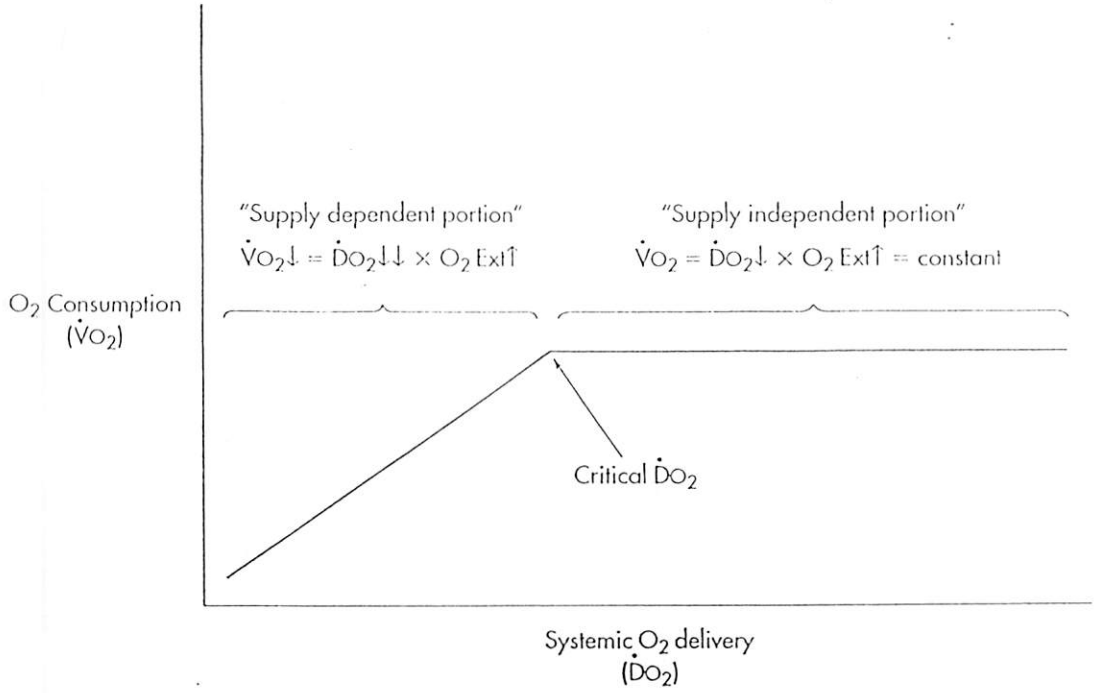

Fig. 22-2. Stylized schema showing the normal relationship of whole-body O_2 consumption ($\dot{V}o_2$) to systemic O_2 transport ($\dot{D}o_2$). The curve is biphasic, showing a range where $\dot{V}o_2$ is independent of $\dot{D}o_2$ and a range at lower levels of $\dot{D}o_2$ where $\dot{V}o_2$ is dependent upon $\dot{D}o_2$. The intersection of these two curves marks the critical $\dot{D}o_2$.

decreased ion transport.[36] Although azotemia may result with the renal hypoperfusion, injury may be avoided (see Chapter 63). By contrast, if the demands of the kidney are increased when O_2 is in short supply, the onset or degree of damage can be amplified. This has been shown in studies in which ischemic or hypoxic injury was increased by agents that raised Na-K pump activity and was reduced by ouabain, a drug that blocks Na-K ATPase.[12] Although it may not be possible to rest organs, it is worth reducing stresses that elevate demands. Interestingly, when there is a diminution of metabolic demands by processes that limit O_2 supply, it may be virtually impossible to determine whether the diminished $\dot{V}o_2$ is a result of or contributor to the decreased $\dot{D}o_2$ without some independent assessment of tissue oxygenation.

RESPONSE TO INADEQUATE $\dot{D}o_2$

Systemic responses

At any given level of Cao_2, the circulatory system affects tissue O_2 delivery through variations in either the cardiac output, proportionately altering $\dot{D}o_2$ (equation 1), or in the distribution of cardiac output, altering individual organ blood flow and O_2 delivery. In most tissues, blood flow, and therefore $\dot{D}o_2$, is controlled in proportion to the tissue metabolic demands.[38] For example, skeletal muscle blood flow increases with exercise; gastrointestinal blood flow increases following feeding[25]; and respiratory muscle blood flow increases with increased work of breathing.[31] Thus, in general, blood flow through an organ matches the metabolic needs. Some organs are exceptions to this general concept. For example, kidney blood flow and O_2 delivery are very high, well in excess of the metabolic needs (see Chapter 59). The "excess" blood flow is necessary for the kidney to act as a filter, and the majority of its blood flow is nonnutrient. Similarly, the skin receives blood flow out of proportion to its O_2 demands owing to its role in heat transfer for body temperature regulation. The resting distribution of blood flow compared to organ metabolic demands ($\dot{V}o_2$) is shown for a resting man in Table 22-1. Blood flow to the brain, heart, and muscle is mainly nutrient and reflects high resting metabolic demands. This is also apparent in the wide resting arteriovenous O_2 content differences. Blood flow to the kidney and skin is high and not in proportion to the O_2 requirements. This is reflected in the very narrow arteriovenous O_2 content differences. Thus, at rest, there are large differences in organ O_2 reserve capacity. This becomes important when $\dot{D}o_2$ becomes inadequate.

When $\dot{D}o_2$ is reduced, there are a variety of systemic neurohumoral mechanisms that are activated in order to redistribute the blood and O_2 flow in order to increase O_2 extraction.[1] These mechanisms are mediated predominantly by the sympathetic nervous system. Activation of the sympathetic nervous system leads to differential peripheral vasoconstriction.[52] Degree of organ vasoconstriction depends upon the density of sympathetic innervation. Whereas the skin, kidneys, and gastrointestinal tract have the greatest sympathetic innervation, the coronary arteries and brain

Table 22-1. Distribution of Cardiac Output and O_2 Consumption in a Healthy Resting Normal Subject

...an	% of total cardiac output	Arteriovenous O_2 difference (vol %)	% of total O_2 consumption
G...t and	24	4.1	25
Skeletal muscle	21	8.0	30
Kidney	19	1.3	7
Brain	13	6.3	20
Skin	9	1.0	2
Heart	4	11.4	11
Other organs	10	3.0	5

Adapted from Wade OL, Bishop JM: *Cardiac output and regional blood flow*, Oxford, 1962, Blackwell.

have little or none and skeletal muscle is intermediate. Thus sympathetic activation leads to vasoconstriction of the skin, kidneys, gastrointestinal tract, and skeletal muscles, and resistance to blood flow through these organs is acutely increased. There is no significant vasoconstriction in the heart and brain blood vessels.[7] Interestingly, blood flow redistribution may also be directly controlled by arterial Po_2, which, in some vascular beds, may cause vasodilation. Although it is well recognized that some tissues sense O_2 (e.g., the kidney and aortic bodies), it has long been suggested and more recently confirmed that systemic vascular smooth muscle al... has the capacity to sense changes in O_2.[44] The precise ...anism(s) by which vascular smooth muscle relaxes in ...onse to decreases in O_2 tension has not been resolved, b... here is evidence for O_2-sensitive, voltage-dependent C... channels that may regulate regional flow, for a cytochrome a,a_3 sensor that transduces its response via changes in inorganic phosphate, and for an ATP-dependent potassium channel.[33,44,82] Although this direct control appears to be a fundamental mechanism, the physiological range over which changes in arterial Po_2 effect vasodilation and contribute to overall blood flow redistribution is not yet certain.

Differential organ vasoconstriction (and vasodilation) leads to redistribution of blood flow because of the parallel arrangement of the organ circulations; that is, most organs receive blood from a common arterial source and drain to a common venous system (the major exceptions to this are the liver and the lungs) (see Chapter 21). In addition, each regional organ circulation is exposed to the same pressure head for perfusion (mean arterial pressure). In such a parallel arrangement, organ blood flows are additive, and cardiac output is the sum of the individual organ blood flows.

Blood flow redistribution decreases the proportion of blood flow to the organs with the largest O_2 reserve. The skin, kidney, and splanchnic circulations can tolerate relatively large decreases in blood flow and $\dot{D}o_2$ by increasing O_2 extraction. Increasing O_2 extraction can maintain the organ O_2 demands, avoiding early tissue hypoxia in these organs. Redistribution forces closer matching of the O_2 supply to the O_2 demands of these three organ systems, and the nonnutrient portion of their blood flows is available for redistribution. Although the O_2 supply to these organs is adequate (to meet O_2 demands), the blood flows will no longer be adequate to subserve their specialized functions: decreased skin blood flow leads to poor temperature regulation, decreased renal blood flow can cause a reduced glomerular filtration rate and prerenal azotemia, decreased gastrointestinal blood flow leads to impaired nutrient uptake, and reduced hepatic blood flow interferes with both synthetic and degradative functions. These account for many of the clinical symptoms in patients with low $\dot{D}o_2$.

In addition to sympathetic vasoconstriction, activation of the sympathetic nervous system stimulates the adrenal medulla to release norepinephrine and epinephrine to the circulation.[1] Increased circulating levels of these catecholamines have similar effects on the peripheral vascular system as direct sympathetic nerve stimulation; however, the effects are more prolonged because norepinephrine and epinephrine are removed from the blood slowly.[13] In addition, decreased renal perfusion will lead to renin release from the kidney. Renin catalyzes the formation of angiotensin II, which is a potent vasoconstrictor, potentiates neural (sympathetic) vasoconstriction, stimulates release of aldosterone from the adrenal medulla, and crosses the blood-brain barrier, where it stimulates the release of arginine vasopressin[14] (see Chapters 59 and 63). Arginine vasopressin is also a potent vasoconstrictor and potentiates neural-mediated vasoconstriction. Aldosterone and arginine vasopressin stimulate increased sodium and water retention by the kidney to expand circulating blood volume, particularly when cardiac output is decreased. Overall, increases in the circulating vasoactive hormones (epinephrine, norepinephrine, angiotensin II, aldosterone, and arginine vasopressin) aid in the response to decreased $\dot{D}o_2$ by: (1) direct vasoconstriction, facilitating blood flow redistribution and blood pressure maintenance; (2) potentiation of neural differential vasoconstriction; (3) augmentation of circulating blood volume; and (4) direct myocardial stimulation (catecholamines), increasing heart rate and contractility.

Thus systemic neural and humoral mechanisms act in a complementary fashion to maintain perfusion pressure and redistribute a limited systemic O_2 supply. These coordinated responses maintain O_2 delivery to the heart, brain, and other metabolically active tissues that have limited O_2 reserve by diverting blood flow from tissues with "luxurious" O_2 supply.

Local organ responses

At any level of organ blood flow, all organs can normally increase O_2 extraction to very high levels by microcirculatory redistribution of capillary perfusion.[38,47] Oxygen is unloaded predominantly at the capillary level and diffuses

down a Po_2 gradient from blood to tissue cells and mitochondria. This transcapillary O_2 flux is a function of the affinity of hemoglobin for O_2, capillary blood Po_2, tissue cell Po_2, and diffusion parameters, which include the capillary wall surface area available for diffusion, the capillary-to-cell diffusion distance, membrane conductance, and the residence time of the blood in the capillaries.

Precapillary sphincters are proposed to be located at the arterial end of each capillary, maintaining the capillary either closed or open to blood flow. As organ O_2 delivery is diminished, previously closed capillaries are opened, probably by sphincter dilation, which seems to be under local metabolic control.[37] This capillary recruitment increases perfused capillary density and allows the tissues to extract more of the available O_2 by at least three mechanisms (Fig. 22-3). First, this increases the lateral surface area of capillaries available for diffusion. Second, opening previously closed capillaries brings the blood closer to the tissue cells, decreasing the diffusion distance. Third, increasing the capillary density increases the cross-sectional area of capillaries available for blood flow, resulting in a decreased velocity of blood in each capillary (flow = velocity × cross-sectional area). Slower passage of the blood cells through the capillaries (increased transit time) allows more time for the diffusion of O_2 out of the blood. Together, these three mechanisms allow extraordinarily high levels of tissue O_2 extraction by affecting three variables important in optimizing the diffusion of O_2: surface area, distance, and time.

In addition to changes in the diffusion parameters, local metabolic changes also increase regional O_2 extraction by producing a rightward shift of the hemoglobin O_2 dissociation curve, facilitating unloading of O_2 from hemoglobin[67] at any given capillary Po_2. This takes place acutely by two related mechanisms: local pH decreases due to lactic acid production, and local increases in Pco_2.[14]

Increases in red blood cell 2,3-diphosphoglycerate (which shift the O_2 dissociation curve to the right) occur if the impairment in $\dot{D}o_2$ has been prolonged.[67]

ESTIMATING ADEQUACY OF O_2 DELIVERY

With severe decreases in organ blood flow and $\dot{D}o_2$, a point is reached at which the local compensations to increase O_2 extraction are not adequate to maintain mitochondrial metabolism, oxidative phosphorylation is diminished, and hypoxia ensues. Cellular energy transduction in the form of ATP formation is reduced, and the cells must rely on anaerobic metabolism[19] (see Chapter 66). The end product of anaerobic metabolism, lactic acid, accumulates within the cells and eventually is released to the capillary blood and carried systemically. Anaerobic metabolism is inefficient at

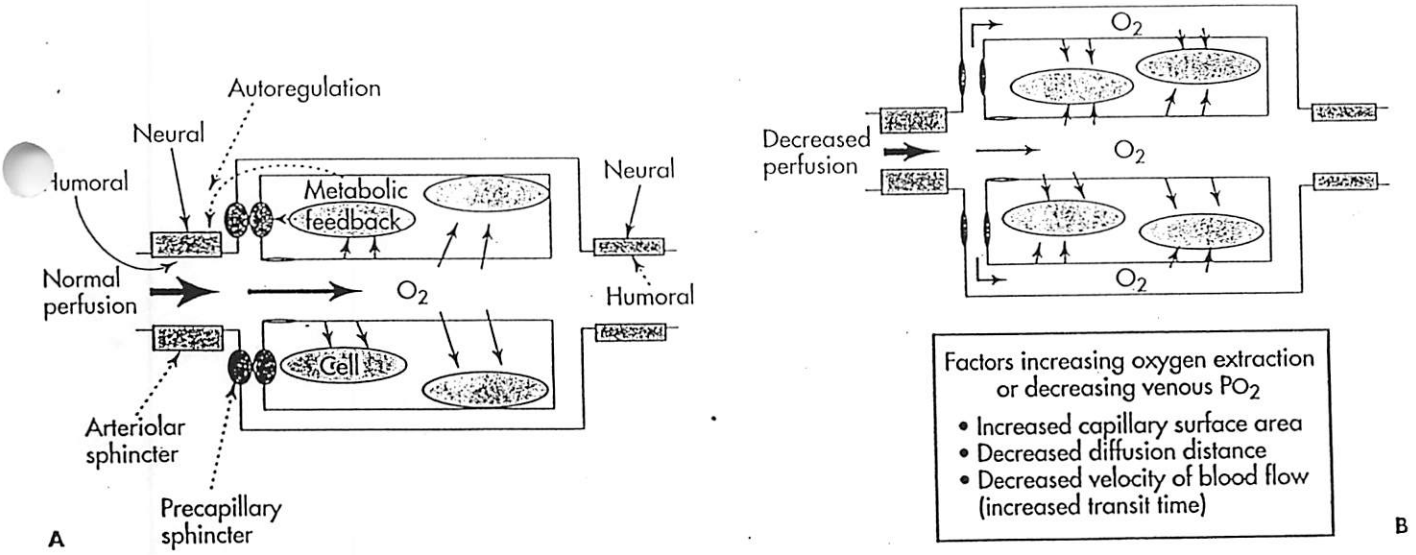

Fig. 22-3. Schematic diagram of metabolism in the microcirculation during conditions of (A) normal perfusion and (B) decreased perfusion. As shown, arteriolar sphincters control perfusion of the microcirculation, and precapillary sphincters control the distribution of microcirculatory blood flow. Arteriolar tone is controlled by neural and humoral influences, autoregulation, and feedback from local metabolic factors. Venular tone is also under the influence of neural and humoral control. A, With normal perfusion, some capillaries are closed. This limits the capillary surface area available for diffusion of O_2, and increases the diffusion distance for O_2 to supply the more remote cells. B, When perfusion is markedly decreased, previously closed capillaries are opened (recruited) predominantly by local metabolic factors. This increases the surface area for O_2 diffusion, decreases the diffusion distance as blood flow is closer to the remote cells, and slows the velocity of flow in individual capillaries (increased transit time) allowing more time for O_2 to diffuse from the blood to the cells. These three factors allow marked increases in microcirculatory extraction of O_2 from the blood, resulting in severe decreases in the Po_2 of the blood exiting the capillaries (fall in $P\bar{v}o_2$).

maintaining cellular energy charge; as energy stores are depleted, impairment of cellular function ensues and organ dysfunction follows.

Adequacy of tissue O_2 delivery cannot be assessed from measurement of $\dot{D}o_2$ alone, but must be evaluated in relation to metabolic demands.[16] If the relationship of supply to demand as described in Fig. 22-2 holds, then "adequacy" means O_2 transport is in the range where O_2 consumption is "normal," that is, on the flat part of the curve. If the O_2 transport is "inadequate," it falls below the critical level as defined in Fig. 22-2, and any or all of the following responses would be expected: (1) an abnormally low systemic $\dot{V}o_2$, (2) greatly increased O_2 extraction, (3) tissue hypoxia and anaerobic metabolism, or (4) organ dysfunction. Strategies for determining the adequacy of $\dot{D}o_2$ in patients take advantage of the above four responses and fall into three general categories: (1) determining normality or abnormality of organ function, (2) manipulating systemic O_2 transport without changing metabolic demands and measuring the response of whole-body $\dot{V}o_2$, and (3) measuring metabolic markers of tissue oxygenation.

Organ function

Organ function can be assessed by clinical examination (skin perfusion, level of consciousness, urine output) and laboratory testing (measure of hepatocellular integrity, creatinine clearance). Normal function of all organs assessed indicates sufficient and adequately distributed systemic O_2 transport. However, normal function implies nothing about reserve capacity or the ability to respond to superimposed stresses.

Dysfunction of multiple organ systems implies global inadequacy of O_2 transport. Dysfunction of a single organ system is much more difficult to interpret. The organ may have been selectively damaged by the underlying disease process, and the O_2 supply to that organ may be normal. Alternatively, single organ dysfunction may be an early manifestation of mildly insufficient systemic O_2 transport and organ blood flow; the function of other organs may be normal or the dysfunction subtle enough to escape casual physical examination or routine laboratory testing.

Thus the extremes of normal organ function at one end of the spectrum and gross dysfunction of multiple organ systems at the other are obvious, and no further assessment of "adequacy" is usually indicated. However, when oxygen transport is close to the critical level assessment of the adequacy of O_2 delivery is most crucial because these borderline patients may appear relatively stable but can deteriorate rapidly with small changes in O_2 delivery or O_2 demands.

It is useful to evaluate each major organ system in an orderly fashion with particular attention to physical findings at rest and during stress. In addition, the routine observations and laboratory data should be closely scrutinized for subtle hints of organ hypoperfusion or dysfunction. For example: enteral feedings tolerated? Does perfusion deteriorate when the patient becomes febrile? Does the patient maintain temperature normally? Is the patient restless, particularly when sitting upright? Is the elimination normal for drugs that depend on renal or hepatic clearance (e.g., aminoglycosides, barbiturates)?

Measurement of O_2 consumption

Measurement of O_2 consumption while O_2 transport is increased or decreased has been used extensively in experimental animal studies to detect the critical O_2 transport.[54] In these studies, a decrease in $\dot{V}o_2$ as O_2 transport is decreased indicates supply dependency and inadequate O_2 delivery, assuming O_2 demands are kept constant; O_2 transport is usually manipulated over a wide range. To determine the critical O_2 transport, two intersecting lines can be constructed.[68] As in Fig. 22-2, one line defines the points where $\dot{V}o_2$ is decreasing and the other defines the points where the $\dot{V}o_2$ is relatively constant. The lines are chosen by minimizing the total residual sum of squares, and the intersection of the lines is the critical point.

Similar manipulations of O_2 transport in patients, especially critically ill patients, are usually neither practical nor ethical, especially if $\dot{D}o_2$ is below the critical level. The approach in most clinical studies has been to measure $\dot{V}o_2$ while O_2 transport is altered from baseline to one or two new levels. Oxygen transport has been manipulated most commonly by changing positive end-expiratory pressure (PEEP)[22,59] or infusing fluid[35,41] or inotropic[35] or vasodilating[18] medications.

There are problems with this approach both in the measurement of $\dot{V}o_2$ and in the interpretation of any changes in $\dot{V}o_2$. Oxygen consumption may be measured directly using either of two methods.[6] Using a "closed circuit" with the patient breathing 100% O_2 through a respiratory circuit in which carbon dioxide is absorbed, O_2 consumption can be calculated from the rate of change of gas volume in the system.

Alternatively, in a subject breathing an inspired gas mixture that contains some nitrogen, O_2 consumption can be calculated from knowledge of expired gas volume and measurement of O_2, carbon dioxide, and nitrogen concentrations in inspired and expired gas. This "open circuit" technique has technical difficulties that interfere with the validity and predictability of data under certain conditions: (1) there is a large potential error as the inspired O_2 concentration approaches 1.0; (2) the calculations assume steady-state conditions regarding gas exchange, and this assumption may not be valid over time; and (3) there may be loss of expired gas from the circuit in children who are intubated when there is high positive-pressure breathing or when an uncuffed endotracheal tube is used causing O_2 consumption to be underestimated.[20] Owing to these limitations in direct measurement of $\dot{V}o_2$, $\dot{V}o_2$ may be calculated indirectly, using the Fick O_2 balance, as the product of cardiac output and arteriovenous O_2 content difference.[2]

letabolic markers of tissue oxygenation

A variety of markers have been proposed for clinical use oth t edict the onset of tissue hypoxia and to estimate its v n general, these markers take advantage of two asic rocesses that occur as $\dot{D}o_2$ is reduced to critically low vel rst, there is increased whole-body and individual gan O_2 extraction, as previously discussed in detail, with concomitant fall in mixed venous O_2 saturation and Po_2 ig. 22-4, *B*). In addition, as the fall in $\dot{D}o_2$ progresses, ssues become progressively more dependent on anaerobic metabolism to maintain cellular energy, and local and systemic lactic acidosis ensues (see Fig. 22-4, *A* and *B*).

Mixed venous Po_2. Mixed venous Po_2 has received much recent attention as the single most reliable indicator currently available for adults and children to detect imbalances between O_2 supply and demand and therefore signal the onset of tissue hypoxia.[24,83] The reasoning for this assumption is based on the knowledge that O_2 diffusion from blood to tissue cells is directly proportional to the difference between capillary Po_2 and the intracellular Po_2. Capillary

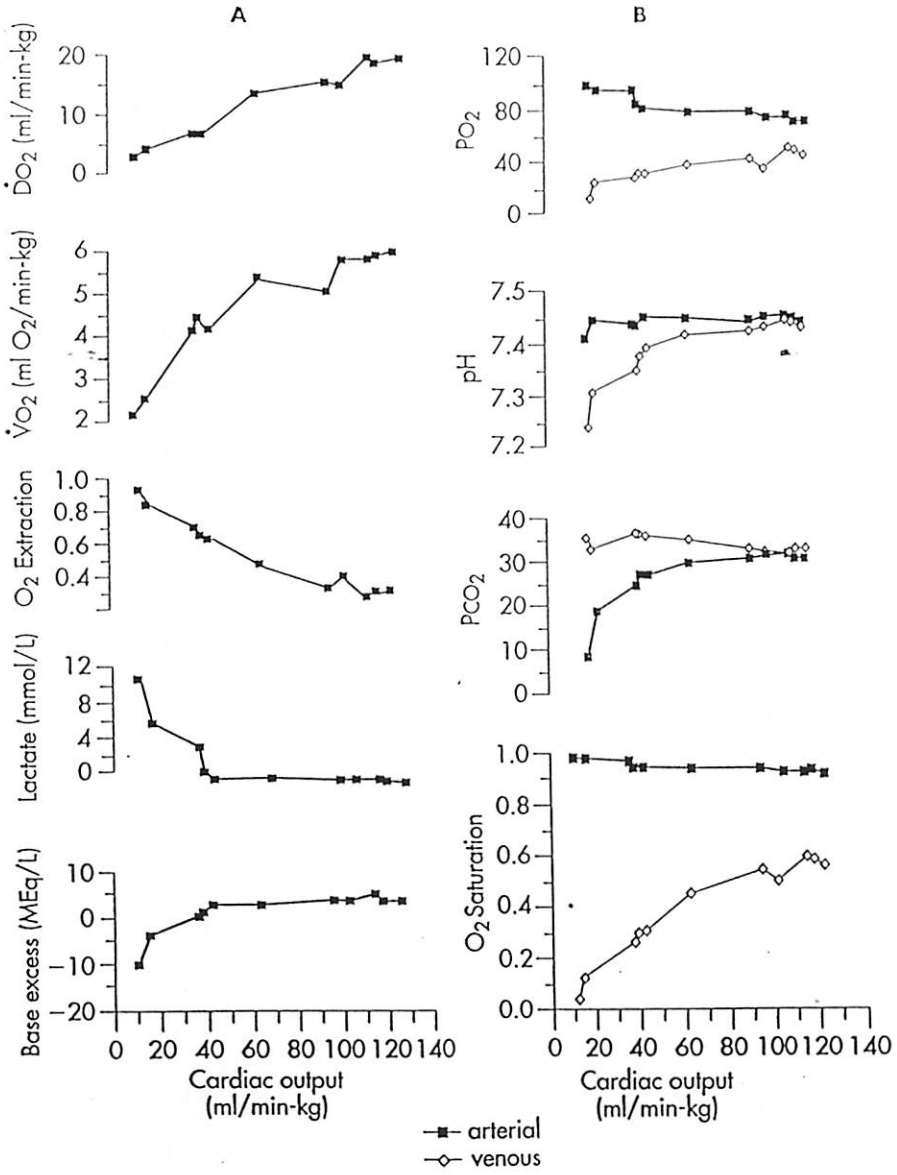

Fig. 22-4. **A,** Changes in systemic O_2 transport, O_2 consumption, fractional O_2 extraction, arterial lactate, and base excess as a function of cardiac output. Data are from a conscious, spontaneously breathing lamb with cardiac output progressively lowered by incremental inflation of a right atrial balloon. **B,** Comparative changes in arterial and venous blood gas (Po_2, pH, Pco_2) and O_2 saturation. Data are from the same lamb study as in **A.** Note the increasing disparity between arterial and mixed venous values at the lower levels of cardiac output.

Po_2 reflects arterial O_2 content, organ blood flow, capillary geometry, and organ O_2 consumption, as has already been discussed in detail. The Po_2 of the blood exiting an organ, "end-capillary" Po_2, reflects the balance between these factors. The assumption is then made that there is a critical driving pressure for diffusion, capillary Po_2 minus tissue Po_2, below which local O_2 uptake cannot keep pace with demands and tissue hypoxia ensues. If this assumption is correct, then the critical end-capillary Po_2 will be the same whether O_2 delivery is impaired by anemia, hypoxemia, or low cardiac output. Whole-body mixed venous Po_2 (usually sampled in the pulmonary artery) reflects the flow-weighted average of the end-capillary Po_2 from each individual organ. Therefore monitoring of mixed venous Po_2 has been advocated as both an indicator of inadequate tissue perfusion and as a means to follow response to therapy.

However, careful examination of equations 5 and 6 would suggest that use of a critical $P\bar{v}o_2$ value may be valid only for anemia or low cardiac output.[43] If, for a given subject with constant O_2 demands (constant $\dot{V}o_2$), there is a single, critical systemic O_2 transport regardless of whether the impairment in $\dot{D}o_2$ is due to anemia, hypoxemia, low cardiac output, or combinations of these, then equation 7 would demand that this occur at a single, critical fractional O_2 extraction. The fractional O_2 extraction is by definition:

$$O_2 \text{ Extraction} = (Cao_2 - C\bar{v}o_2)/Cao_2 = 1 - (C\bar{v}o_2/Cao_2) \quad (8)$$

Furthermore, when dissolved O_2 is small,

$$O_2 \text{ Extraction} = 1 - (S\bar{v}o_2/Sao_2) \quad (9)$$

and

$$S\bar{v}o_2 = (1 - O_2 \text{ Extraction})\ Sao_2 \quad (10)$$

With both anemia and low cardiac output, Sao_2 remains normal and constant and there is a single $S\bar{v}o_2$ at the critical O_2 extraction. With hypoxemia, Sao_2 obviously must decrease from normal, and $S\bar{v}o_2$ will fall proportionally at the critical O_2 extraction. Because $P\bar{v}o_2$ depends on $S\bar{v}o_2$, one would predict a single critical $P\bar{v}o_2$ for anemia, low cardiac output, and combinations (as long as Sao_2 remains normal), whereas the critical $P\bar{v}o_2$ would be lower with hypoxemia.[14] Furthermore, when $\dot{D}o_2$ is reduced by hypoxemia in combination with anemia or low cardiac output, $P\bar{v}o_2$ at the critical $\dot{D}o_2$ should be an intermediate value.

Although not reported for children, a critical mixed venous Po_2 (28 mmHg) has been reported in adult human studies.[46] Thus, if the patient remains fully saturated, a $P\bar{v}o_2$ value less than 28 mmHg is probably a reliable indicator of hypoxia. However, when arterial Po_2 is decreased or changing, $P\bar{v}o_2$ can be misleading as a marker for hypoxia because values less than 28 mmHg may reflect arterial hypoxemia not tissue hypoxia.[14]

Fractional O_2 extraction. As outlined previously (equation 7), whole-body O_2 extraction increases in compensation for decreases in $\dot{D}o_2$. Studies using experimental animals have suggested that the fractional O_2 extraction at the critical O_2 delivery is relatively consistent and in the 0.6 to 0.7 range. Recalling that O_2 extraction = $\dot{V}o_2/\dot{D}o_2$, this would suggest $\dot{V}o_2$ declines only when it becomes a critical fraction of the available O_2 transport. In the animal studies, $\dot{D}o_2$ was progressively lowered by anemia, hypoxemia, low cardiac output, or combinations of these. Moreover, it is important to recognize from equation 7 that, in contrast to $P\bar{v}o_2$, critical values of O_2 extraction should be comparable for all these types of disturbances in O_2 transport.[43]

To define a critical value of O_2 extraction in a given human subject, data points must be obtained both above and below the critical level, which is usually neither practical nor ethical. However, critical values of O_2 extraction in critically ill human subjects were obtained by making repeated measurements in patients being withdrawn from inotropic, oxygen, and then ventilatory support.[62] Interestingly, these findings indicated the critical values of O_2 extraction to range from 0.48 to 0.78, in the range of values obtained from animal studies.

In some forms of critical illness, an O_2 extraction defect may exist. The abnormality is in peripheral O_2 extraction independent of $\dot{D}o_2$. Tissue hypoxia may become manifest in these disease states even at relatively high levels of $\dot{D}o_2$ and O_2 extraction.

Therefore even a single measurement of fractional O_2 extraction is practical and very useful in detecting the patient at risk for tissue hypoxia. If the O_2 extraction is high (>0.5), one should suspect that $\dot{D}o_2$ might be critically low and it is worth pursuing further evidence of tissue hypoxia and lactic acidosis. Furthermore, if the O_2 extraction is abnormally low with evidence of hypoxia and acidosis, a pathological defect in O_2 extraction must be suspected.

Arterial blood lactate concentration. With tissue hypoxia, cellular levels of lactic acid increase, and lactate begins to appear in venous blood. Whether this results in the systemic accumulation of lactate, measured as an increase in arterial lactate concentration above normal levels, depends upon the balance of the increased lactate production and lactate clearance.[21] The liver accounts for the largest fraction of lactate removal by the body, and it is capable of increasing lactate metabolism twofold to threefold.[55] The heart and kidneys are also capable of removing lactate from arterial blood and metabolizing it. In hypoxic states, where liver blood flow is often reduced as cardiac output is redistributed, lactate probably accumulates as the result of both increased production and decreased clearance. In animal studies, it appears that lactate accumulation is not a gradual process but accumulates abruptly at or just below the critical systemic O_2 transport[43] (see Fig. 22-4). Further, at sustained low levels of $\dot{D}o_2$ below the critical level, lactate increases progressively with time and with the accumulating O_2 deficit.[29] Therefore

the lactate concentration reflects not only the severity of the decrease in $\dot{D}o_2$, but also the time at any given level of critically low O_2 delivery.

Clinical studies lactate has been found to be a sensitive indicator of tissue hypoxia.[8,35,40,79] For example, in patients with shock,[35] increasing $\dot{D}o_2$ by either blood transfusion or fluid loading led to increases in $\dot{V}o_2$ only in those patients with elevated lactate concentrations (>2.2 mM). Presumably, patients with elevated lactate levels were below the critical $\dot{D}o_2$ (dependent part of the curve, See Fig. 22-2) and responded to increasing $\dot{D}o_2$ by raising their $\dot{V}o_2$.

Lactate levels may also have prognostic significance.[8] In various forms of shock, mortality increased greatly when the initial arterial blood lactate concentration was above 4.5 mM.[60] However, there was a good deal of overlap between the survivor and nonsurvivor groups. Accordingly, any prediction of outcome from an isolated value is necessarily hazardous.

It is important to note that other clinical conditions besides hypoxia may elevate blood lactate levels. Lactate levels are elevated in patients with liver dysfunction or liver failure. Shivering or seizures elevate blood lactate levels. Hyperventilation, hyperglycemia, and catecholamine infusion may also account for modest increases in arterial blood lactate concentrations.[27,58] Although these factors should be considered in patients with elevated lactate levels, elevation of arterial blood lactate concentration often provides a sensitive indicator of an inadequate O_2 supply in infants, children, and adults.

Base excess. Base excess (or base deficit) is a theoretical construct devised to differentiate respiratory from metabolic changes in a patient's acid-base balance. It is a readily calculated value based on accurate measurement of arterial pH (or H^+ concentration), Pco_2, and hemoglobin and, as such, should be able to detect acute changes (see Fig. 22-4). Base excess has wide clinical use and is frequently reported along with arterial blood gas values.

A poor correlation was reported between base deficit and lactate concentration in 84 patients undergoing therapy for shock (including hypovolemic, cardiogenic, and septic shock).[60] It is speculated that this discrepancy was due to many factors, including: (1) the presence of acid-base disorders prior to the onset of hypoxia (shock); (2) potentially different fates of protons and lactate in the body fluids; and (3) the release by tissues of acids other than lactic acid. Thus, as a single value, base deficit is difficult to interpret without knowledge of the patient's prior acid-base status.

Arterial blood pH. As expected with tissue hypoxia and lactic acidemia, blood pH will eventually fall. However, the fall in arterial blood pH with hypoxia is a relatively late phenomenon[71] (see Fig. 22-4, *B*). This is due to the large capacity of the blood to buffer hydrogen ions. In addition, as long as patients are able to increase ventilation, a reduction in arterial Pco_2 (respiratory compensation) will delay the fall in arterial pH. Therefore a fall in arterial pH occurs so late in the course of a declining systemic O_2 delivery that it is not useful in detecting the onset of inadequate oxygenation and tissue hypoxia. Its presence, however, is a sign of severe hypoxia, especially if Pco_2 is low.

Examination of Fig. 22-4, *B*, shows a progressive widening in the difference between arterial and mixed venous pH as cardiac output (and therefore $\dot{D}o_2$) is decreased. Under hypoxic conditions, venous pH is much lower than arterial pH, reflecting both a metabolic acidosis and a much higher venous Pco_2. Therefore when O_2 transport is critically low, the difference between arterial and mixed venous Po_2, pH, and Pco_2 progressively increases (see Fig. 22-4, *B*), and venous blood gases cannot be used to estimate arterial blood gases.[81]

CURRENT CONTROVERSIES

Pathological supply-demand matching and impaired O_2 extraction

Under certain pathological conditions, the biphasic relationship of $\dot{V}o_2$ to $\dot{D}o_2$ (see Figure 22-2) may be disturbed. The independent portion of the curve depends on increases in O_2 extraction proportional to any fall in $\dot{D}o_2$. If O_2 extraction does not increase in direct proportion to the decrease in $\dot{D}o_2$, $\dot{V}o_2$ must decline and there would be no independent portion of the curve. $\dot{V}o_2$ would decline whenever $\dot{D}o_2$ fell and the relationship would appear to be supply dependent at all levels of $\dot{D}o_2$. Such a relationship of $\dot{V}o_2$ to $\dot{D}o_2$ has been termed "pathological supply dependency."[15,47] As first reported in patients with ARDS,[22] when cardiac output (and $\dot{D}o_2$) was acutely decreased by raising levels of PEEP, $\dot{V}o_2$ decreased even at levels of $\dot{D}o_2$ well above what would have been considered "critical". The response of mixed venous Po_2 and O_2 extraction was variable (i.e., either increased, decreased, or stayed the same) and had no relation to the fall in cardiac output. It was postulated that these patients were unable to increase peripheral O_2 extraction in response to the decrease in cardiac output, leading to the pathological supply dependency. Pathological supply dependency has also been reported in other human studies of sepsis[35,39,41,51] and ARDS.[9,30,39] In addition, there are well controlled laboratory-based studies in which impairments in O_2 extraction have been demonstrated in organ systems or for the whole body during endotoxin infusion or bacteremia or with hyperoxia[50,56,57,69]

Caution must be exercised when interpreting the above mentioned studies or applying them to clinical situations. First, these studies deal with critically ill and therefore frequently unstable patients. Spontaneous changes in the metabolic state of these patients may occur even if no intervention is made. If $\dot{V}o_2$ is changing, $\dot{D}o_2$ will also change in proportion to keep pace with the altered demands, in a manner similar to exercise.[23] In these situations, $\dot{V}o_2$ is the independent variable and $\dot{D}o_2$ is the dependent variable. Villar

et al[78a] made repeated calculations of $\dot{V}o_2$ and $\dot{D}o_2$ in critically ill patients during periods of apparent stability with no experimental intervention (3 to 5 measurements separated by 20 to 30 minutes were made in each patient). Variation of $\dot{V}o_2$ within each study, expressed as a percent of the mean value, was 7% to 147% (mean 38%). Variation of $\dot{D}o_2$ calculated in a similar manner was 9% to 189% (mean 42%). Plots of $\dot{V}o_2$ vs. $\dot{D}o_2$ showed a linear and apparent dependent relationship in 18 of the 28 patients studied. Obviously, interpretation of these graphs as showing "pathological" supply dependence is erroneous, since $\dot{D}o_2$ is not the independent variable.

A similar situation exists if the intervention used to manipulate $\dot{D}o_2$ also changes metabolic demands. If $\dot{V}o_2$ and $\dot{D}o_2$ both change as a result of the intervention, then neither variable can be considered as dependent; it is incorrect to plot $\dot{V}o_2$ vs. $\dot{D}o_2$ and erroneous to interpret the apparent relationship as showing pathological supply dependency (Fig. 22-5). This is especially concerning in studies where $\dot{D}o_2$ was manipulated by inotropic-infusions, which are known to alter $\dot{V}o_2$, and in studies using peripheral vosodilation, which is known to lead to reflex elevations in catecholamines. In addition, it is impossible to interpret such clinical studies if lactate levels are not also reported. If lactic acidosis exists, then $\dot{D}o_2$ is presumably below the critical level (as in Fig. 22-4). If $\dot{D}o_2$ were increased in these clinical situations, then $\dot{V}o_2$ would be expected to increase normally in a dependent fashion (see Fig 22-2). This is not "pathological" dependence but represents physiological dependence.

Studies identifying pathological supply dependency have recently come under additional scrutiny and criticism,[63-65,85] relative to the manner in which $\dot{V}o_2$ was measured. In the studies that found a pathological supply dependence, $\dot{V}o_2$ was not directly measured but was calculated from the Fick equation (see equation 4). Measured variables were cardiac output (from thermodilution) and arterial and mixed venous oxygen content. To demonstrate pathological dependence of $\dot{V}o_2$ on $\dot{D}o_2$, calculated $\dot{V}o_2$ and calculated $\dot{D}o_2$ were the dependent and independent variables of the relationship, respectively, and both variables share cardiac output and arterial oxygen content. An artifactual correlation of $\dot{V}o_2$ and $\dot{D}o_2$ could occur because of mathematical coupling of errors in the measurement of shared variables used to calculate $\dot{V}o_2$ and $\dot{D}o_2$.[53,65] Since both $\dot{D}o_2$ and $\dot{V}o_2$ include cardiac output in the calculation, any increase in cardiac output will cause a comparable change in both $\dot{D}o_2$ and $\dot{V}o_2$ and may produce an apparent correlation. Importantly, in every study of patients who had ARDS or sepsis in which $\dot{V}o_2$ and $\dot{D}o_2$ were determined independently to avoid mathematical coupling, $\dot{V}o_2$ was found to be independent of $\dot{D}o_2$.[4,17,63,64,79] Further, in studies of patients with ARDS and sepsis in which $\dot{V}o_2$ was determined both by calculation and by analysis of respiratory gases, pathological dependence of $\dot{V}o_2$ on $\dot{D}o_2$ is associated with calculated $\dot{V}o_2$ but not with measured $\dot{V}o_2$.[64,85] Also, in the studies where $\dot{V}o_2$ was measured by indirect calorimetry and not calculated, O_2 extraction was not impaired and appeared to respond in the predicted direction whether cardiac output and $\dot{D}o_2$ were decreased (by PEEP) or increased (by transfusion or dobutamine infusion) in patients with sepsis and/or ARDS.[64,65,85] Therefore the

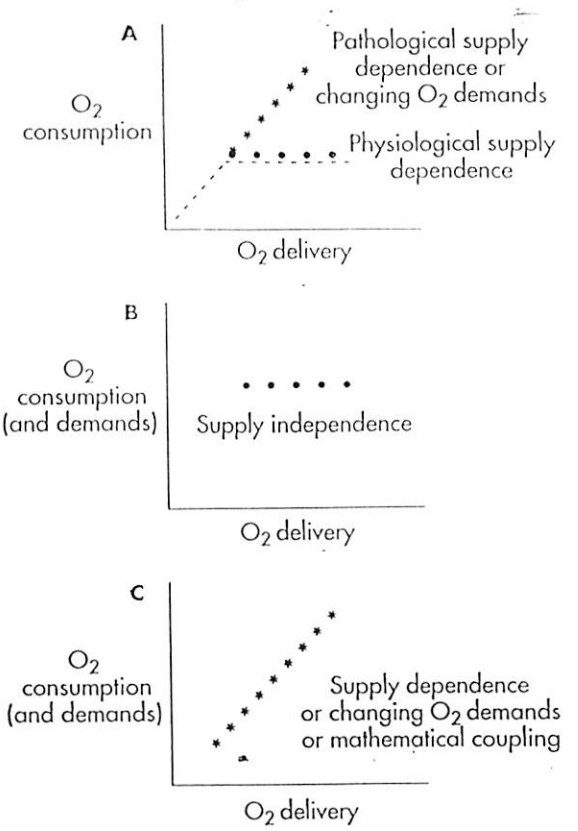

Fig. 22-5. Stylized schema of the relationship between O_2 consumption, O_2 delivery, and O_2 demands. A, The two patterns of response in O_2 consumption when O_2 delivery is manipulated. The biphasic (physiological) response as outlined in Fig. 22-2 with supply independent and supply dependent portions is compared to the linear (pathological) response, which appears to be supply dependent at all levels of O_2 delivery. B, If O_2 delivery is manipulated above the critical level without changing demands, O_2 consumption will remain constant through a wide range of delivery. C, Apparent "pathological" responses could be generated under four very different circumstances: (1) There may be true pathological supply dependence caused by O_2 extraction defects; (2) Supply dependence can also be artifactual if the manipulation in O_2 delivery also produces a change in the O_2 demands; as delivery is decreased, demands also decline, producing an apparent dependence of O_2 consumption on O_2 delivery; (3) Apparent supply dependence will occur when demands are altered primarily, as with exercise or fever, in which case O_2 delivery varies as O_2 consumption changes; and (4) Alternatively, an erroneous relation will be produced if there is mathematical coupling of errors due to shared variables. (Modified from Lister G: Metabolic demands during hypoxia. In Haddad G, Lister G, editors: *Lung biology in health and disease. Vol 95 Tissue oxygen deprivation,* New York, 1996, Marcel Dekkar.)

:ept of a defect in the peripheral tissue extraction of O_2 in :is, ARDS, and related conditions may also be in doubt.

nt' e of supranormal values of $\dot{D}o_2$ in critically at. , to improve mortality and survival

nva hemodynamic monitoring in critically ill pa- s, using arterial, central venous, and pulmonary artery eters, has allowed serial measurements of cardiac output repeated sampling of arterial and mixed venous blood ples. With these measurements, $\dot{D}o_2$, O_2 extraction, and may be calculated and tracked. $\dot{V}o_2$ may also be mea- d by indirect calorimetry in a serial fashion. By monitor- these variables in patients with a wide variety of clinical dromes associated with shock (including ARDS, sepsis, ma, and high-risk surgery), several interesting observa- s have been made[10,65,66,77,78]: (1) The values of $\dot{D}o_2$ $\dot{V}o_2$ were significantly higher in survivors than non- ivors both on admission and during therapy and may be dictive of outcome; (2) the values of $\dot{V}o_2$ and $\dot{D}o_2$ were uently above accepted normal values. Many of the pa- ts studied may have been hypermetabolic with very high requirements as a result of the disease process itself sis, ARDS), fever, or superimposed stresses (increased k of breathing, wound healing). Alternatively, it has been gested that the $\dot{V}o_2$ may be elevated in these patients ause they are "paying back" a previously accumulated debt in a manner similar to the persistent elevation of $\dot{V}o_2$ ng recovery from exercise[72]; and (3) elevation of $\dot{V}o_2$ $\dot{D}$ these disease states, even to supranormal levels, s ndicate adequacy of O_2 delivery. Although el- ed, $\dot{D}o_2$ may not be sufficient to meet the increased $\dot{V}o_2$, tiss ypoxia with lactic acidosis may still be present. Based on the above findings, many subsequent studies e set their therapeutic goals to maintain supranormal ues of cardiac output and $\dot{D}o_2$ (cardiac output >4.5 min/M^2 and $\dot{D}o_2$ >600 ml/min/M^2) in an attempt to match values of the above mentioned survival group and better ch the anticipated elevated metabolic demands and O_2 uirements. Increased levels of $\dot{D}o_2$ were achieved by fluid apy, blood transfusion, and inotropic support if fluid ascitation alone was inadequate. This approach was cessful in improving survival in studies and generated ch initial enthusiasm.

Increased survival in high risk surgical patients managed toperatively with supranormal values of $\dot{D}o_2$ as com- ed to standard therapy was demonstrated.[73] Other studies wed increased survival, in ARDS, septic shock, and ma[26,32,77,86] using this approach. This concept was ex- ded by establishing supranormal values of $\dot{D}o_2$, prior to icipated high risk surgery and maintained during recov- . Mortality and complication rate were reduced by 75% l 50% respectively.[11]

However, two large recent studies using the same ap- ach showed no benefit to establishing supranormal values of $\dot{D}o_2$ and cardiac output.[34,42] In fact, such intervention appeared to be detrimental. Based on these latter larger studies in which treatment was randomized in patients with shock associated with sepsis, ARDS, trauma, or high risk surgery, it appears that goal-oriented hemodynamic therapy to achieve supranormal values of cardiac output and $\dot{D}o_2$ is not necessary and potentially detrimental.

THERAPEUTIC IMPLICATIONS AND CLINICAL USEFULNESS

Measurements of O_2 transport and consumption are not meant to replace the clinical assessments of perfusion and oxygenation but to complement them. Global organ perfusion is best assessed clinically by physical examination with repeated evaluation of specific components such as capillary refill, skin temperature, level of consciousness, urine output and any other findings that are perceived as abnormal or marginal (see Chapter 29). Organ perfusion parallels organ oxygenation when arterial blood is fully saturated, but when arterial blood is significantly desaturated, clinical assessment of perfusion alone may be misleading.

In general, $\dot{D}o_2$ is inadequate in two broad clinical situations: (1) $\dot{D}o_2$ has decreased below a "critical" value, O_2 extraction can no longer fully compensate, $\dot{V}o_2$ falls (see Fig. 22-4), and hypoxia ensues, and (2) The metabolic demands of the organs are excessively high (supranormal $\dot{V}o_2$), and $\dot{D}o_2$ cannot increase to meet the excessive demands. This latter condition was previously thought to be rare and to occur only in unusual situations like thyrotoxicosis and malignant hyperthermia. However, as mentioned in the previous section, supranormal levels of $\dot{V}o_2$ may be seen in sepsis, trauma, burns, and ARDS. $\dot{D}o_2$ may be higher than normal and still inadequate.

Many measurements of O_2 transport variables require invasive monitoring, using an arterial catheter in conjunction with either a pulmonary artery or central venous catheter. Pulmonary arterial catheters provide the most information in terms of O_2 transport variables (cardiac output-using thermodilution as well as sampling of the mixed venous blood for $P\bar{v}o_2$, $S\bar{v}o_2$ and O_2 content), which can be used in combination with simultaneous measurement of arterial blood (for Sao_2 and Cao_2) to determine $\dot{D}o_2$ and O_2 extraction and derive $\dot{V}o_2$. However, placement of a pulmonary catheter in the intensive care setting may be technically difficult or impart unnecessary risks with limited benefit. Alternatively, a central venous catheter, depending upon the location of the distal lumen, may allow estimation of the best available mixed venous blood sample for measurement of $S\bar{v}o_2$ and calculation of $C\bar{v}o_2$. Used in conjunction with arterial O_2 saturation determined simultaneously (pulse oximetry or from an arterial blood gas sample), O_2 extraction can be readily calculated. Measurement of $\dot{V}o_2$ by indirect calorimetry is currently not routinely available nor practical in most clinical settings.

Accordingly, the most useful O_2 transport variables in ıost clinical situations requiring intensive care may be ɔrial calculation of O_2 extraction in conjunction with ıea' ent of lactate concentration. This requires si- ıu. ous sampling of arterial blood and the best mixed eno blood available. For the calculated O_2 extraction ɔ be aningful, much care and thought must go into the ɔcation of sampling for the mixed venous blood.[5] In the bsence of intracardiac shunting, the best mixed venous ample is obtained from the pulmonary artery. If this is ot available, blood should be sampled from a central enous catheter placed either in the superior vena cava or ıe superior portion of the right atrium. If the catheter tip ; in the inferior-portion of the right atrium, blood may ɔe sampled from the coronary sinus and would have a very ɔw saturation even with normal hemodynamics and O_2 ransport (see Table 22-1). In general, blood should not ɔe sampled from the inferior vena cava to obtain a mixed enous sample for calculation of O_2 extraction. The aturation will be dependent on catheter location. If the ample is obtained from the level of the renal veins, the aturation will be high and not reflective of a whole body nixed sample. Similarly, if the saturation is obtained from he hepatic veins, which drain into the diaphragmatic ɔortion of the inferior vena cava, the saturation will be ow and not reflective of the whole body.

Calculated O_2 extraction should be viewed in the ɔontext of the clinical state. If the clinically assessed ɔerf n is fair or poor, the O_2 extraction is high (>0.6), ınd ate is elevated (>2.0 mmole/L), then the $\dot{D}o_2$ is na uate and below the critical level.

If rfusion is adequate but not excellent, the O_2 extract is higher than normal (0.3 to 0.6), and the lactate is normal (<2.0 mmole/L), then $\dot{D}o_2$ is compromised but not critical. This patient should not be considered "stable" and deserves very close monitoring, since there may be no reserve to increase $\dot{D}o_2$.

If the perfusion is adequate or diminished and the O_2 extraction is abnormally low (<0.3), then further investigations are needed to determine whether the patient has a defect in O_2 extraction. Only if there is associated lactic acidosis or signs of disturbed organ function does it seem reasonable to augment $\dot{D}o_2$ further, and with caution. Rather, management should be aimed at minimizing metabolic demands, treating the underlying disease state, and preventing any compromise in $\dot{D}o_2$.

SUMMARY

It should be clear from this discussion that there is not a universally applicable measure of hypoxia, O_2 adequacy, or O_2 reserve. Therefore both the usefulness and limitations of the variety of approaches available for estimating the adequacy of O_2 supply have been indicated. Comments on specific therapies have purposely been omitted, since these must be individualized to the specific disease states and are detailed elsewhere in this textbook.

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