CHAPTER 22

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Oxygen Content, Delivery, and Uptake

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the principal determinants of oxygen content and appreciate the concepts of oxygen delivery and consumption.
- Understand the normal physiologic relationship between oxygen delivery and consumption.
- Understand oxygen supply dependency in critically ill patients.
- Understand goal-directed therapy and the controversies that surround it.

Normal cellular function in the body is critically dependent on oxygen. Therefore, it is important for the body to be able to deliver oxygen to the cells and for the cells to utilize the oxygen once it has arrived. A change in either of these variables could lead to the development of cellular hypoxia and result in end-organ failure and possibly death. In many disease states, changes in oxygen delivery (DO_2) and oxygen consumption ($\dot{V}O_2$) are noted to occur and may be responsible for the clinical presentation of these patients. Meeting the metabolic demands of the cells is thus an important component of therapy in the critically ill patient.

A change in oxygen delivery or consumption can result in cellular hypoxia.

OXYGEN UTILIZATION

At the cellular level, the most efficient means of generating ATP is through oxidative phosphorylation, which is a series of oxidation–reduction reactions in which oxygen serves as the terminal electron acceptor (Figure 22-1). In the absence of oxygen the cell must depend on glycolosis, which is a very inefficient process to generate ATP, or depend on limited high-

G. J. Criner et al. (eds.), *Critical Care Study Guide*

CASE STUDY: PART 1

G.C. is a 47-year-old alcoholic college professor who complained of 2 days of shaking chills, fever, cough productive of yellow sputum, and left-sided chest pain. Initial examination in the emergency room revealed an acutely appearing man with a respiratory rate of 36, pulse of 122, and blood pressure of 90/42. His initial chest radiograph showed a left lower lobe infiltrate; arterial blood gas analysis demonstrated a metabolic acidosis and a respiratory alkalosis. His CBC was significant for a WBC of 22.0 with 24% bands and hemoglobin of 10. The patient was treated empirically for community-acquired pneumonia with a third-generation cephalosporin and given 2 liters of normal saline intravenously.

The critical level of oxygen in normal humans is P_aO_2 of 20 mmHg.

In disease states, cellular hypoxia occurs at higher values of P_aO_2.

energy stores in the body such as creatine phosphate. The critical level of oxygen required by the cells for oxidative phosphorylation is unknown, yet it has been shown that mitochondria can continue to function normally so long as the partial pressure of oxygen (PO_2) is maintained at greater than 0.5 mmHg. In intact animals and in humans, the critical level of oxygen appears to be an arterial PO_2 (P_aO_2) of 20 mmHg, as evidenced by changes in end-organ function and changes in the level of ATP. Such findings suggest that humans are able to tolerate severe hypoxia before cellular and end-organ dysfunction develop. In disease states such as sepsis or in the acute respiratory distress syndrome (ARDS), however, cellular hypoxia and end-organ dysfunction can occur at much higher levels of P_aO_2, possibly because of the changes in DO_2 and oxygen utilization at a mitochondrial level that occur with these disorders.

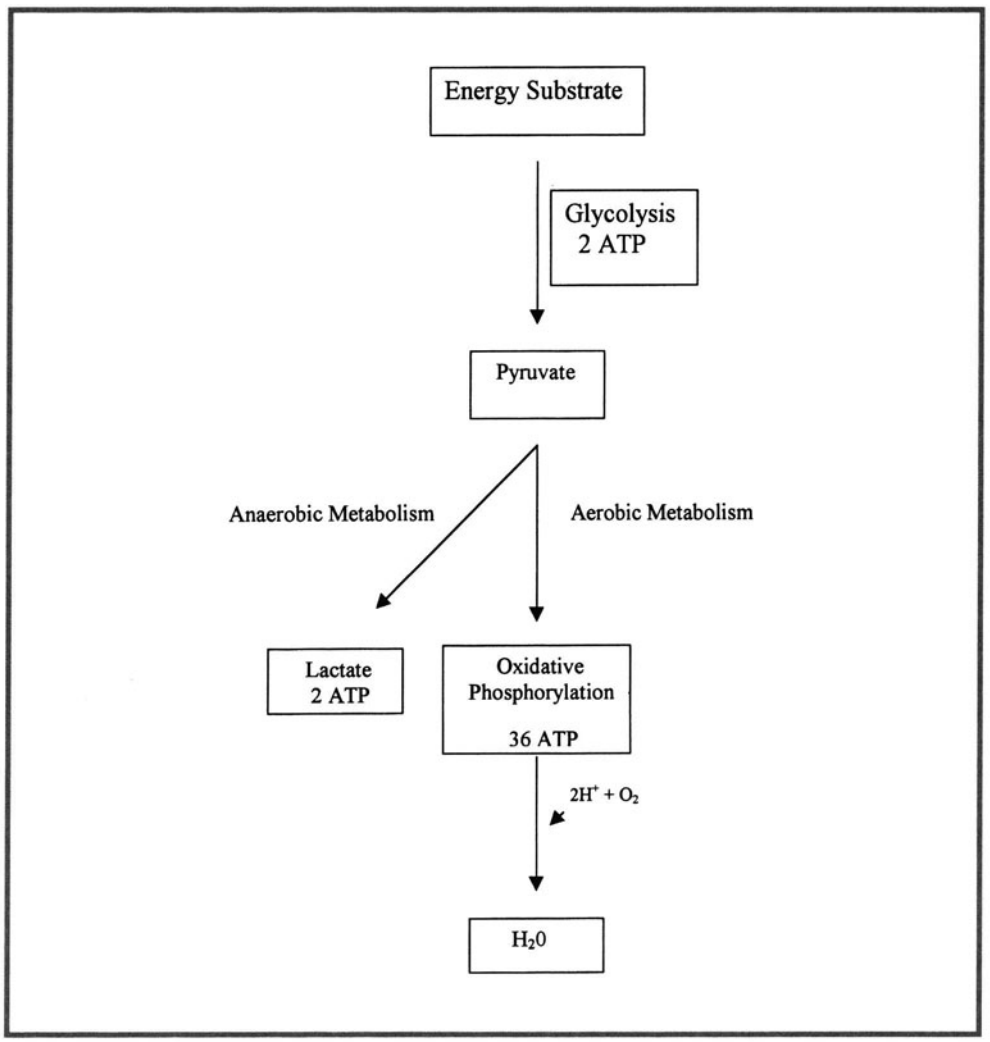

FIGURE 22-1

At the cellular level, the most efficient means of generating ATP is through oxidative phosphorylation, which is a series of oxidation–reduction reactions in which oxygen serves as the terminal electron acceptor. Under anaerobic conditions, pyruvate is converted to lactate, which is a very inefficient mechanism for ATP production.

TABLE 22-1

DISTRIBUTION OF BLOOD FLOW AND OXYGEN UTILIZATION

ORGAN	CARDIAC OUTPUT (l/min)	OXYGEN DELIVERY (ml/min)	OXYGEN UPTAKE (ml/min)	RESISTANCE (mmHg/min)
Brain	14	840	52	7
Heart	5	300	34	20
Splanchnic bed	28	1680	83	3.6
Kidney	23	1380	19	4.4
Skeletal Muscle	16	960	57	6.3
Skin	8	480	12	12.4

OXYGEN REQUIREMENTS OF THE VARIOUS TISSUES

Each organ system in the body has different oxygen requirements that must be met to function properly and maintain normal homeostasis (Table 22-1). To meet the oxygen demands of the different organ systems, changes occur in cardiac output and microcirculatory flow. The microcirculatory system consists of the arterioles, capillaries, and the venous system. Although 80% of the blood in circulation is stored in the venous system, local control of DO_2 to the organ systems occurs at two levels: (1) the small muscular arterioles, which are the major resistance vessels in the body and dilate in response to tissue hypoxia; and (2) the precapillary sphincters, which regulate the number of capillaries that are available for gas diffusion into the tissue cells. It would be ideal if we could directly measure the DO_2 to each organ system to ensure that it is adequate. Unfortunately, this is not possible, and at present we can only obtain measurements of total body DO_2 and $\dot{V}O_2$ and thereby indirectly assess overall body oxygen requirements from these less sensitive and specific values.

Local control of DO_2 occurs at the arterioles and precapillary sphincters.

OXYGEN CONTENT

The oxygen content of arterial blood (CaO_2) is the sum of two components, the oxygen bound to hemoglobin and the oxygen dissolved in blood:

$$CaO_2 = (1.3 \times Hb \times SaO_2) + (0.003 \times PaO_2)$$

where Hb is hemoglobin, SaO_2 is the arterial oxygen saturation, and PaO_2 is the arterial partial pressure of oxygen. The first part of the equation states that each 1 g of hemoglobin binds 1.3 ml of oxygen when the hemoglobin is completely saturated (SaO_2 = 100%). The second part of the equation measures the amount of oxygen that is actually dissolved in the blood, which is of the order of 0.003 (ml/dl/mmHg). As can be seen, under normal physiologic conditions the oxygen that is dissolved in the blood contributes little to CaO_2. Most of the oxygen in the blood is bound to hemoglobin, and thus SaO_2 is the most important blood gas variable for assessing the CaO_2 of arterial blood. Assuming a Hb of 14 g/dl, SaO_2 of 98%, and a PaO_2 of 100 mmHg, CaO_2 (Table 22-2) can be calculated as:

Most of the oxygen in the blood is bound to hemoglobin.

$$CaO_2 = (1.3 \text{ ml/g} \times 14 \text{ g/dl} \times 0.98) + [0.003 \text{ (ml/dl)/mmHg} \times 100 \text{ mmHg}]$$

$$CaO_2 = 18.1 \text{ ml/dl}$$

OXYGEN DELIVERY

Global oxygen delivery is calculated as the product of the cardiac output (Q) and the CaO_2:

$$DO_2 = Q \times CaO_2 \quad \text{or} \quad DO_2 = Q \times (1.3 \times Hb \times SaO_2) \times 10$$

where DO_2 is oxygen delivery and Q is cardiac output. The equation is multiplied by 10 to convert volumes percent to ml/min. A DO_2 index (DO_2I) can be calculated by substituting

TABLE 22-2

OXYGEN DELIVERY AND CONSUMPTION VARIABLES

VARIABLES	EQUATION	NORMAL VALUE
Oxygen content (CaO_2)	$CaO_2 = (1.3xHbxSaO_2) \times (0.003xPaO_2)$	16–22 ml/dl
Mixed venous content ($C\bar{v}o_2$)	$M\bar{v}O_2 = (1.3xHbxSvO_2) \times (0.003xP\bar{v}O_2)$	12–17 ml/dl
Oxygen delivery (DO_2)	$DO_2 = QxCaO_2$	460–650 ml/min
Oxygen uptake ($\dot{V}O_2$)	$\dot{V}O_2 = Qx(CaO_2 - C\bar{v}O_2)$	96–170 ml/min
Oxygen extraction ratio (O_2ER)	$O_2ER = \dot{V}O_2/DO_2$ $O_2ER = CaO_2 - C\bar{v}O_2/CaO_2$	22%–32%
Arterial oxygen tension (PaO_2)	Measured	95 ± 5 mmHg
Arterial saturation (SaO_2)	Measured	97% ± 2%
Mixed venous oxygen tension ($P\bar{v}O_2$)	Measured	40 ± 5 mmHg
Mixed venous saturation ($M\bar{v}O_2$)	Measured	75% ± 5%
Systemic vascular resistance (SVR)	(Mean arterial pressure − central venous pressure)/Qx80	800–1200 dyne/s/cm^{-5}
Pulmonary vascular resistance (PVR)	(Mean pulmonary artery pressure − pulmonary wedge pressure)/Qx80	150–250 dyne/s/m^{-5}

the cardiac index (CI) for the cardiac output, which is simply the cardiac output divided by the body surface area (BSA):

$$DO_2I = Q/BSA \times (1.3 \times Hb \times SaO_2) \times 10$$

Assuming a cardiac output of 5 l/min, hemoglobin of 14 g/dl, and SaO_2 of 98%, a normal DO_2 (see Table 22-2) can be calculated as:

$$DO_2 = 5 \text{ l/min} \times (1.3 \text{ ml/g} \times 14 \text{ g/dl} \times 0.98\%) \times 10 \text{ (scaling factor)}$$

$$DO_2 = 900 \text{ ml/min}$$

Using a cardiac index of 3 l/min, a normal DO_2I (Table 22-2) can be calculated as:

$$DO_2I = 3 \text{ l/min/m}^2 \times (1.3 \text{ ml/g} \times 14 \text{ g/dl} \times 0.98\%) \times 10 \text{ (scaling factor)}$$

$$DO_2I = 540 \text{ ml/min} \cdot \text{m}^2$$

Thus, from the foregoing equation it can be seen that oxygen delivery is simply the product of three main variables: arterial oxygen saturation, hemoglobin, and cardiac output.

Oxygen delivery is the product of arterial oxygen saturation, hemoglobin, and cardiac output.

OXYGEN CONSUMPTION

Oxygen consumption is defined as the quantity of oxygen consumed per unit time. Total body $\dot{V}O_2$ can be measured by two different techniques: the reverse Fick equation or indirect calorimetry using a metabolic cart. $\dot{V}O_2$ can be affected by many variables, including fever, anxiety, pain, and shivering, and thus it is important for the patient to be relatively stable at the time the measurements are obtained.

$\dot{V}O_2$ can be measured by the reversed Fick equation or by indirect calorimetry.

The indirect Fick equation calculates $\dot{V}O_2$ by using the equation:

$$\dot{V}O_2 = Q \text{ l/min} \times (CaO_2 \text{ ml/dl} - C\bar{v}O_2 \text{ ml/dl})$$

where Q is cardiac output and $CaO_2 - C\bar{v}O_2$ is the arteriovenous difference in oxygen content. $C\bar{v}O_2$ is the venous oxygen content $[(1.3 \text{ ml/g} \times Hg \times S\bar{v}O_2\%)]$ and $S\bar{v}O_2$ is the saturation of venous blood. The indirect Fick method is usually employed in critically ill patients through the use of a pulmonary artery catheter. The cardiac output is determined by thermodilution technique. Mixed venous oxygen saturation ($S\bar{v}O_2$) is determined by a blood sample from the distal port of the pulmonary artery catheter; and SaO_2 is obtained by cooximetery. The equation can be rearranged as:

$$\dot{V}O_2 = Q \text{ l/min} \times (1.3 \text{ ml/g} \times Hb \text{ g/dl}) \times (SaO_2\% - S\bar{v}O_2\%)$$

Using a cardiac output of 5 l/min, hemoglobin of 14 g/dl, SaO_2 of 98%, and $S\bar{v}O_2$ of 75%, a normal $\dot{V}O_2$ (see Table 22-2) can be calculated as

$$\dot{V}O_2 = 5 \text{ l/min} \times (1.3 \text{ ml/g} \times 14 \text{ g/dl}) \times (0.98 - 0.75) \times 10 \text{ (scaling factor)}$$

$$\dot{V}O_2 = 244 \text{ ml/min}$$

The equation is again multiplied by 10 to convert volumes percent to ml/min.

Indirect calorimetry uses a metabolic cart to obtain measurements of expired gas volumes of both O_2 and CO_2 and then calculate $\dot{V}O_2$ according to the formula:

$$\dot{V}O_2 = (F_iO_2 \times V_I) - (F_EO_2 \times V_E)$$

where F_iO_2 is the fraction of inspired oxygen, V_I is the inspired minute volume, F_EO_2 is the mixed expired oxygen concentration, and V_E is the expired minute volume. As is discussed

later, this method has the advantage of actually measuring rather than calculating $\dot{V}O_2$ as is done using the indirect Fick method. Although indirect calorimetry may be more accurate in obtaining the $\dot{V}O_2$, it is also more cumbersome at the bedside and thus is not frequently done in the intensive care unit setting.

OXYGEN EXTRACTION RATIO

The oxygen extraction ratio reflects the tissue's avidity for oxygen.

The oxygen extraction ratio (O_2ER) is the fractional uptake of oxygen by the tissues from the capillary bed and thus reflects the tissue's avidity for oxygen. Under normal physiologic conditions, the tissues extract about 25% of the oxygen that is bound to hemoglobin in the circulation. A normal extraction ratio of 25% results in a $S\bar{v}O_2$ of 75%. The extraction ratio can be calculated as:

$$O_2ER = CaO_2 - C\bar{v}O_2/CaO_2 \times 100$$

$$0.25 = (20 \text{ ml/dl} - 15 \text{ ml/dl})/20 \text{ ml/dl}$$

where O_2ER is oxygen extraction ratio, CaO_2 is arterial oxygen content, and $C\bar{v}O_2$ is venous oxygen content. Another equation that can be used to calculate the oxygen extraction ratio is

$$O_2ER = \dot{V}O_2/DO_2 \times 100$$

If a normal $\dot{V}O_2$ of 250 (ml/min)/m^2 and DO_2 of 1000 (ml/min)/m^2 are assumed, a normal oxygen extraction ratio (Table 22-2) can be calculated as

$$O_2ER = 250 \text{ (ml/min)/m}^2/1000 \text{ (ml/min)/m}^2 \times 100$$

$$O_2ER = 0.25 \text{ (ml/min)/m}^2$$

NORMAL PHYSIOLOGIC RELATIONSHIP BETWEEN DO_2 AND $\dot{V}O_2$

Under normal conditions, DO_2 is determined by the oxygen requirements of the tissue cells and thus their $\dot{V}O_2$. Increases in cellular metabolic demand, as seen during exercise, are met by increases in both cardiac output and local perfusion to the associated organs. At maximal exercise, DO_2 can increase to 4 to 5 times the resting level. This increase in DO_2 may not be sufficient to meet the cellular demands for oxygen, however, with increases to as high as 10 fold during maximal exercise. The cells attempt to compensate for this inadequate DO_2 by increasing their oxygen extraction from a basal level of 25% to as high as 80% during maximal exercise, but at some point the oxygen demands of the cells can no longer be met and anaerobic metabolism begins. This point is referred to as the anaerobic threshold, and

CASE STUDY: PART 2

Despite volume resuscitation, the patient developed worsening hypotension with a blood pressure of 70/40 mm/Hg. The patient's urine output decreased, and his work of breathing increased requiring mechanical ventilation. A Swan–Ganz catheter was then placed, which showed right atrial pressure, 6 mmHg; pulmonary artery pressure, 16/10 mmHg; and pulmonary capillary wedge pressure (PCWP), 12 mmHg. Cardiac output was elevated at 8 l/min, systemic vascular resistance was decreased at 510 ml/kg/min, and mixed venous saturation was 68%; oxygen content was 12.8 ml/100 ml, oxygen delivery was 1024 ml/min, oxygen uptake was 300 ml/kg/min, and oxygen extraction ratio was 30%.

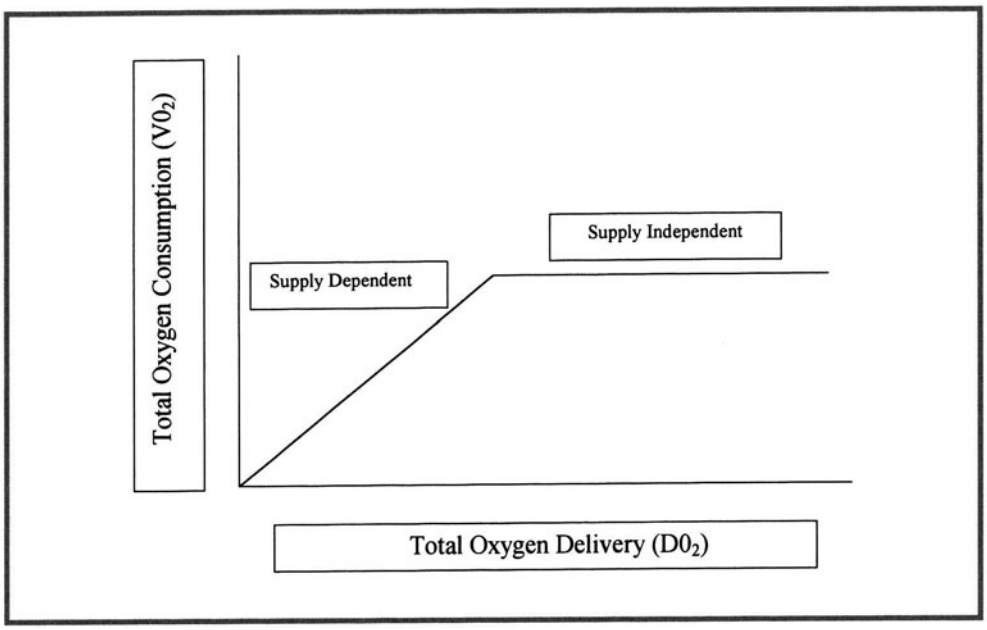

FIGURE 22-2

When DO_2 is the independent variable, $\dot{V}O_2$ remains unchanged in response to an increase in DO_2 (as with inotropic medications increasing cardiac output) for the oxygen supply to the cells is already adequate (supply independent). When DO_2 is decreased (as with anemia or a decreased cardiac output), however, a biphasic response in $\dot{V}O_2$ is observed. Initially, as DO_2 decreases the cells respond by increasing oxygen extraction to maintain $\dot{V}O_2$. A point is reached at which the cells can no longer increase their extraction of oxygen (critical DO_2), and $\dot{V}O_2$ becomes dependent on DO_2 (supply dependent).

in normal individuals it can occur when $\dot{V}O_2$ is as low as 40% of maximum. The inefficient use of anaerobic sources of ATP leads to the production of such by-products as lactate and the development of a metabolic acidosis. Thus, under normal conditions $\dot{V}O_2$ is the independent variable with changes in DO_2 occurring in response to the oxygen needs of the tissue.

The anaerobic threshold occurs when the oxygen demands of the cells are no longer being met.

A different relationship between DO_2 and $\dot{V}O_2$ can be observed in situations where DO_2 is the independent variable; this occurs when DO_2 is either decreased, as with anemia, hypoxemia, or decreased cardiac output, or increased, as when cardiac output is increased with inotropic medications. Under these conditions, a biphasic relationship between $\dot{V}O_2$ and DO_2 is observed (Figure 22-2). In normal individuals, increases in DO_2 do not result in a significant increase in $\dot{V}O_2$ because the cells do not require any additional oxygen. When DO_2 decreases, the cells initially are able to compensate by increasing oxygen extraction to meet their metabolic demands. Yet, as DO_2 decreases further a point is reached, referred to as the "critical point" (DO_2 crit), where maximal oxygen extraction can no longer meet cell oxygen demands and $\dot{V}O_2$ begins to decrease linearly with DO_2; this is referred to as supply dependency. In healthy animal models in which DO_2 was slowly decreased, values for DO_2 crit have been found to be 6–10 ml/kg/min.

OXYGEN SUPPLY DEPENDENCY IN THE CRITICALLY ILL

The normal biphasic relationship in DO_2 and $\dot{V}O_2$ is not observed in the critically ill.

In contrast to normal animals where supply dependency is noted only at very low values of DO_2, critically ill patients with sepsis and ARDS demonstrate supply dependency at much higher levels of DO_2. In addition, the normal biphasic relationship between DO_2 and $\dot{V}O_2$ is not observed (Figure 22-3). A number of mechanisms have been proposed to explain the linear relationship between DO_2 and $\dot{V}O_2$ observed in these patients. One such scheme suggests that the DO_2 crit is much higher than normal in these critically ill patients. Because of their disease state, these patients may not be able to increase DO_2 sufficiently to reach the supply-independent portion of the curve; a point where the increased oxygen demands of the cells can be met. Another explanation proposed for the observed supply dependency is the inability of cells to adequately increase extraction of oxygen to meet the increased demand. In other words, the extraction ratio remains unchanged whether DO_2 increases or decreases, and thus the relationship between DO_2 and $\dot{V}O_2$ remains linear (Figure 22-3). This

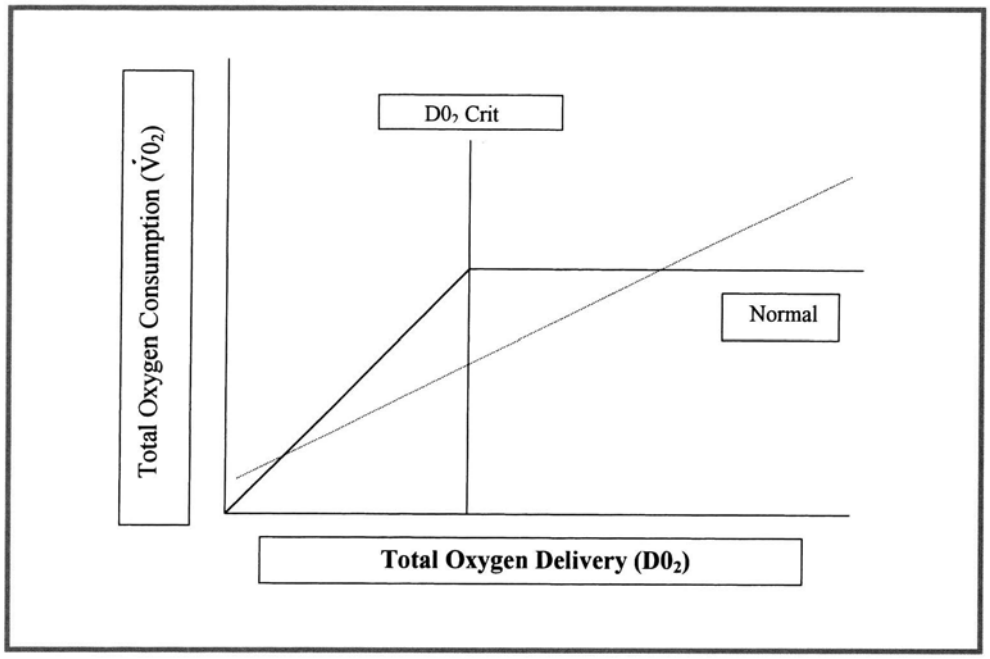

FIGURE 22-4

The *dotted line* represents pathologic supply dependency observed in patients with sepsis or the acute respiratory distress syndrome (ARDS). Oxygen consumption is observed to be continuously dependent on oxygen delivery with no evidence of a critical DO_2, above which a supply-independent state would exist.

Impaired O_2 extraction may result from direct endothelial or parenchymal cell injury.

inability to increase oxygen extraction can result from two main mechanisms: (1) alteration in organ blood flow distribution and (2) direct endothelial or parenchymal tissue injury.

Alteration in Blood Flow Distribution

An altered blood flow to the capillary beds could produce changes in the DO_2–$\dot{V}O_2$ relationship similar to that observed in sepsis by means of several mechanisms, including a redistribution of cardiac output to organs with low oxygen extraction ratios. This change can occur when there is loss of the normal microvascular tone and the major muscular arterioles are no longer able to control blood flow distribution to the organs with the highest oxygen requirements (Figure 22-4). Changes can also occur in the precapillary sphincters that control local organ blood flow. Despite compelling clinical evidence, neither of the proposed mechanisms for altered organ blood flow has been observed in animal models of septic shock.

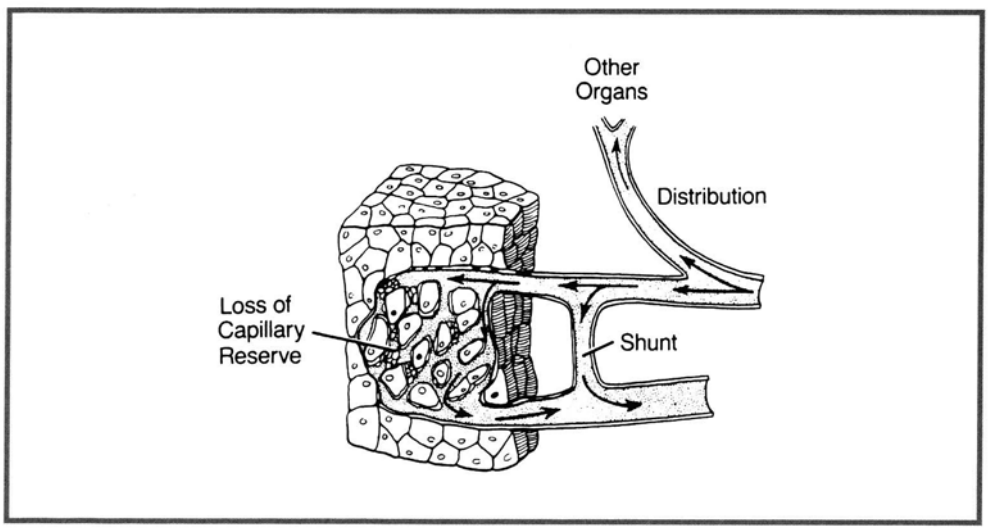

FIGURE 22-3

Alteration in blood flow distribution may lead to a decrease in blood flow to organs with increased oxygen demands, which may contribute to a state of supply dependency. (Reprinted with permission from Dorinsky PM, Gadek JE. Mechanisms of multiple nonpulmonary organ failure in ARDS. Chest 1989;96:885–892).

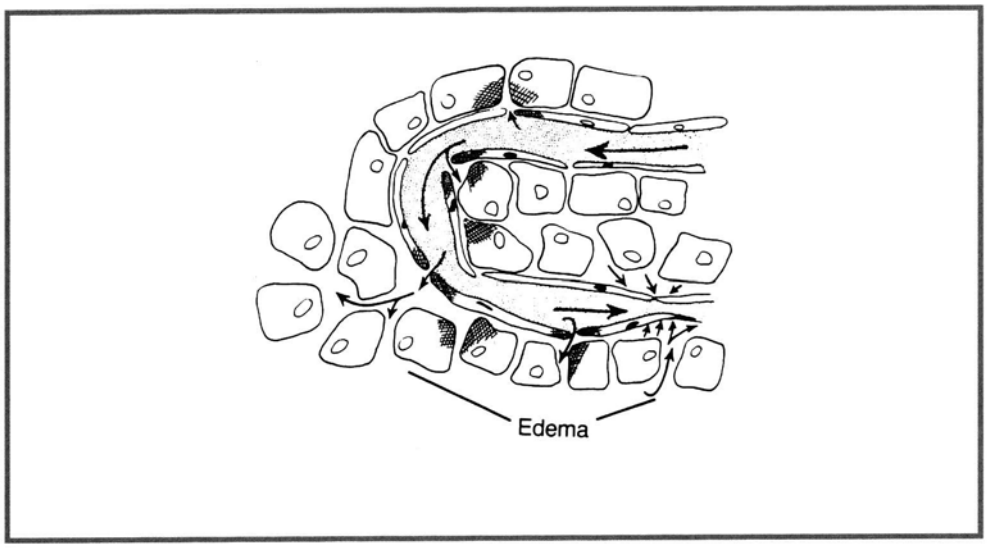

FIGURE 22-5

Oxygen extraction may be impaired secondary to endothelial or parenchymal cell injury, which may lead to a state of supply dependency. (Reprinted with permission from Dorinsky PM, Gadek JE. Mechanisms of multiple nonpulmonary organ failure in ARDS. Chest 1989;96:885–892).

Endothelial and Parenchymal Injury

Direct injury to the endothelium can impair the ability of the cells to directly extract oxygen from the blood (Figure 22-5). This impairment can occur in disease states that cause a systemic inflammatory response, such as sepsis and ARDS. The normal mixed venous oxygen levels observed in these disease states could be explained by this mechanism. Despite an apparently adequate DO_2, the injured endothelium cannot extract the amount of oxygen needed to meet cellular demand. Another proposed mechanism involves direct injury to the parenchymal cells themselves, which may impair oxygen utilization at any level of DO_2.

Studies Demonstrating Oxygen Supply Dependency

Earlier animal studies demonstrated that sepsis and not isolated lung injury was responsible for the apparent oxygen supply dependency. In dog models, it was shown that both bacteremia and endotoxemia, but not isolated lung injury, were responsible for the significantly increased DO_2 crit from 8 to 12 ml/kg/min. More important, the oxygen extraction ratio at the point where oxygen consumption became supply dependent fell from 70% to 51% in the bacteremic dogs. This result suggests a problem with end-organ tissue oxygen utilization rather than a primary respiratory process. Since these early animal experiments there have been numerous studies in patients with respiratory failure and sepsis demonstrating oxygen supply dependency.

Bahari et al. studied the effects of increasing DO_2 in 27 critically ill ARDS patients. In those patients who died, there was a significant increase in $\dot{V}O_2$ and O_2 ER in response to an increase in DO_2, whereas there was only a small increase in $\dot{V}O_2$ and an actual decrease in O_2ER in those who survived (Figure 22-6). This finding suggested an existing oxygen debt in those patients who died, with the tissue cells deprived of the required oxygen needed for optimum aerobic metabolism. In contrast, those patients who survived appeared to have adequate oxygen delivery to the cells for aerobic metabolism and thus remained on the supply-independent portion of the DO_2–$\dot{V}O_2$ curve. Other investigators have noted that additional markers suggesting an existing oxygen debt, such as the presence of a metabolic acidosis or increased serum lactate, predicted an oxygen supply-dependent state.

Thus, based on clinical studies suggesting the existence of an oxygen supply-dependent state in critically ill patients, treatment strategies were designed with the aim of increasing DO_2 to supranormal values. It was hoped that by correcting any existing oxygen debt, multisystem organ failure could be prevented and mortality decreased.

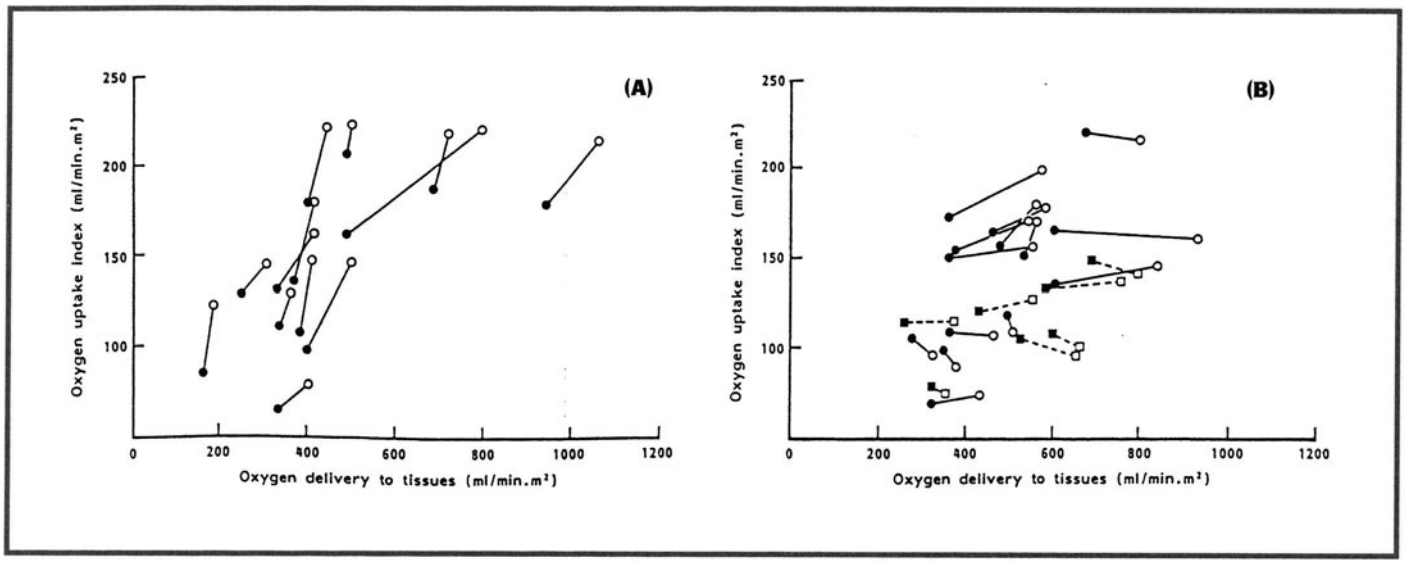

FIGURE 22-6

Effects of prostacyclin infusion on oxygen delivery and oxygen uptake in 27 patients with acute respiratory failure (*circles*) and 7 controls (*squares*). In the 13 patients who died **(A)**, there was a significant increase in oxygen uptake in response to an increase in oxygen delivery. A similar increase in oxygen uptake was not seen in those patients who survived, as well as the controls **(B)**. (Reprinted with permission from 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;317:397–405).

GOAL-DIRECTED THERAPY

In the early 1970s, Shoemaker et al. described a group of critically ill surgical patients with improved survival when supranormal values for DO_2 and $\dot{V}O_2$ were observed. Since then, studies have been designed for goal-directed therapy in which DO_2 and $\dot{V}O_2$ are increased to these previously noted supranormal values. This approach is based on three tenets: (1) that critically ill patients die of multisystem organ failure and that tissue hypoxia may be partially responsible for its development; (2) that tissue hypoxia may persist in critically ill patients despite early resuscitation to normal hemodynamic endpoints; and (3) that increasing oxygen delivery can reverse tissue hypoxia. Since this original observation by Shoemaker et al. there have been 13 randomized trials to evaluate goal-directed therapy. Six studies demonstrated favorable results, but most concerned trauma or surgical patients, and supranormal values for DO_2 and $\dot{V}O_2$ were obtained before hemodynamic compromise or the development of organ dysfunction. There is also concern in that improved outcome was based on a post hoc comparison of subgroups of patients who were able to reach supranormal values for DO_2 and $\dot{V}O_2$ regardless of whether they received goal-directed therapy to achieve these supranormal values.

There have also been seven studies in critically ill medical and surgical patients that failed to demonstrate improved survival with goal-directed therapy. In fact, in one study the control group actually had a lower mortality than the goal-directed group, in which dobutamine was used to increase DO_2 (Figure 22-7). Of note, in these studies only approximately 60% of the patients were able to reach these supranormal values for DO_2 and $\dot{V}O_2$ with therapy, while some of the control patients were able to meet these goals without intervention. In the largest study, Gattinoni et al. randomized 762 critically ill medical and surgical patients to three groups with different hemodynamic goals: (1) a normal cardiac index group (2.5–3.5 l/min/m^2), (2) a supranormal cardiac index (>4.5 l/min/m^2), and (3) a normal mixed ve-

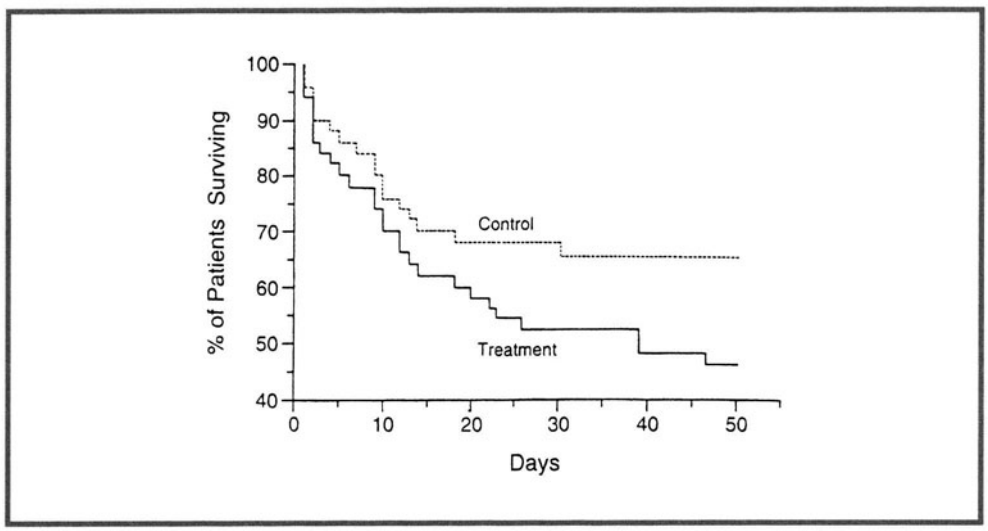

FIGURE 22-7

In-hospital survival was significantly better in the control group compared to the treatment group, which met certain hemodynamic goals in regards to oxygen delivery. (Reprinted with permission from Hayes MA, Timmins AC, Yau EHS, Palazzo M, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717–1722.

nous oxygen saturation group ($S\bar{v}O_2 \geq 70\%$); 94% of the normal cardiac index group, 45% of the supranormal cardiac index group, and 60% of the normal mixed venous saturation group were able to reach their goals. There was no difference in survival or the development of organ dysfunction among the groups, even when only those patients who were able to obtain their assigned goals were analyzed.

The relative lack of success with goal-directed therapy may be partially explained by the results of a recent study by Ronco et al. These investigators identified the DO_2 crit in nine septic and eight nonseptic patients by measuring DO_2 and $\dot{V}O_2$ as life support was being discontinued. They noted a significantly lower DO_2 crit than that previously found in animal experiments and in humans using pooled data. In addition, there was no difference in the DO_2 crit values for those patients with and without sepsis, at 3.8 and 4.5 ml/kg/min, respectively. Those studies that attempted goal-directed therapy had patients with baseline values for DO_2 that were much greater than the DO_2 crit noted in the Ronco et al. study. In addition, Ronco et al. noted no difference in the O_2ER at DO_2 crit in those with and without sepsis, at 0.61 and 0.59, respectively, which are values similar to those at maximal exercise. These findings suggest that DO_2 is most likely adequate in the majority of critically ill patients, even those with sepsis. In addition, sepsis does not appear to significantly impair the tissue's ability to extract oxygen. Therefore, attempting to increase DO_2 to supranormal levels in all or nonselected critically ill patients to increase $\dot{V}O_2$ may be without benefit.

Increasing DO_2 to supranormal values may be without benefit.

CONTROVERSIES REGARDING OXYGEN SUPPLY DEPENDENCY

The presence of oxygen supply dependency, which has been reported in a number of studies, should be interpreted with caution for the following reasons. First, concerns have been raised in regard to the methods used to determine $\dot{V}O_2$, which may produce an artifactual correlation between DO_2 and $\dot{V}O_2$. In many of these studies $\dot{V}O_2$ was calculated using the reverse Fick equation. Therefore, both DO_2 and $\dot{V}O_2$ were calculated using the shared variables of cardiac output and CaO_2. An increase or decrease in either variable could cause DO_2 and $\dot{V}O_2$ to change in the same direction, producing a linear relationship between the two variables and the appearance of a supply-dependent state. Since these initial studies, five investigations have directly compared the $\dot{V}O_2$ obtained with the reverse Fick equation to that measured using a metabolic cart. In all these studies, no correlation was found between the calculated $\dot{V}O_2$ values and those obtained using the metabolic cart. Also, although there appeared to be a supply-dependent state when $\dot{V}O_2$ was calculated using the reverse Fick equation, this was not evident when $\dot{V}O_2$ was measured using the metabolic cart.

Using the Fick equation, DO_2 and $\dot{V}O_2$ are calculated using shared variables.

CASE STUDY: PART 3

The diagnosis of pneumonia with systemic inflammatory response syndrome was made. At this point the patient was placed on maintenance IV fluids and started on dopamine. As a result, the patient's PCWP increased to 14 mm/Hg and his SVR increased to 876 dyne/s/m^5; cardiac output decreased to 5 l/min and oxygen content remained at 12 mm/Hg. These values resulted in oxygen delivery of 600 ml/kg/min and oxygen consumption of 120 ml/kg/min, with an extraction ratio of 20%.

The patient's mean arterial pressure stabilized and his urine output increased. Subsequently, his blood cultures grew *Pneumococcus* and the patient completed a 14-day course of antibiotics for bacteremia and sepsis. The patient was able to be weaned and extubated on the third ICU day and the dopamine eventually was weaned off with no significant changes in his oxygen delivery, oxygen consumption, or extraction ratio.

Another concern regarding the notion of supply dependency is that under normal conditions spontaneous changes in O_2 demand result in changes in DO_2, as seen with exercise. In a number of studies involving septic and ARDS patients, data had been collected over a period of time (hours to days) and appeared to demonstrate a supply-dependent state, but this finding may represent only appropriate changes in DO_2 occurring in response to changing O_2 demands. Finally, it should be noted that many of these studies, including those that attempted goal-directed therapy, were conducted without any knowledge of what is a normal DO_2 crit value in either healthy individuals or critically ill patients.

LACTIC ACIDOSIS

There has also been controversy regarding the significance of lactic acidosis in patients with sepsis. It has been assumed that the increased arterial lactate is the result of a decreased DO_2 and a tissue oxygen debt, resulting in anaerobic metabolism (see Figure 22-1). There is recent evidence, however, that arterial lactate increases as a result of an increase in glycolysis. Sepsis is characterized by a hypermetabolic state with increased glucose uptake by cells. This increased uptake appears to be mediated by the Glut-1 membrane transporter, which is not insulin dependent. Glut-1 production increases in sepsis, with increased mRNA production for the Glut-1 glucose transporter, a process thought to be mediated by cytokines. The increase in cellular glucose leads to an increase in the production of pyruvate. If the oxidative metabolic pathway is unable to metabolize the increased pyruvate, the cells will convert it to lactate. Thus, unlike an anaerobic state in which the lactate/pyruvate ratio is elevated, in sepsis, it remains unchanged, with lactate being produced solely because of an increase in the substrate pyruvate. A number of studies have reported this preserved lactate/pyruvate ratio in septic patients despite the presence of an elevated arterial lactate. These findings strongly suggest that arterial lactate is not an accurate marker for the presence of anaerobic metabolism in sepsis.

In sepsis, the lactate/pyruvate ratio remains unchanged.

Serum lactate is not an accurate marker for anaerobic metabolism in sepsis.

RECOMMENDATIONS

Initial management involves establishing hemodynamic stability.

The primary objective in the initial management of the critically ill patient is to establish hemodynamic stability and thus organ perfusion (Figure 22-8). Organ perfusion can be gauged by several clinical indexes such as mentation, urinary output, skin perfusion, and blood pressure. When perfusion is subnormal, treatment is targeted at the pathophysiologic cause (i.e., cardiac performance, vascular resistance, or inadequate filling pressure). The initial treatment for most patients is volume (crystalloid, colloid, or blood), and treatment is guided by the response to therapy, such as increased urine output, improved mentation, and increased mean arterial pressure. If there is no response to initial therapy, clinical assessment may be supplemented by invasive hemodynamic monitoring, which allows measurement of specific parameters that can be addressed with volume, if the pulmonary capillary artery pressure is

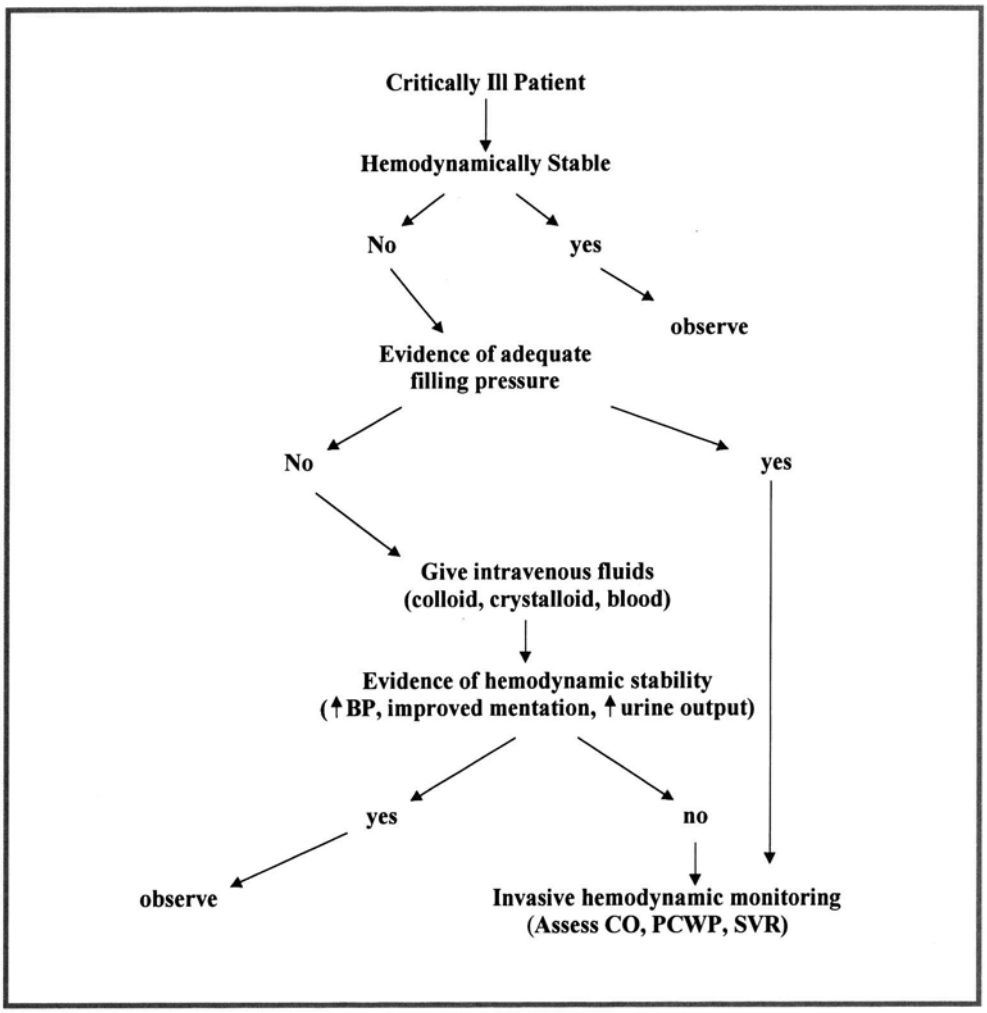

FIGURE 22-8

Algorithm for the treatment of the hemodynamically unstable critically ill patient.

low, or specific vasoactive therapy. DO_2 and $\dot{V}O_2$ are among the parameters that can be monitored in these patients during hemodynamic stabilization. Interventions aimed at optimizing DO_2 to values within the normal range should be the goal; this should result in adequate tissue oxygenation and metabolism as measured by O_2ER and $\dot{V}O_2$, respectively. The limitations of these measurements should be understood, because they are global measurements and because there are technical concerns in regard to shared variables. At the present time there are no data to support improved outcome in critically ill medical or surgical patients with the indiscriminate use of goal-directed therapy.

Interventions aimed at optimizing DO_2 to within the normal range should be the goal.

No data support the indiscriminate use of goal-directed therapy.

SUMMARY

Adequate oxygen delivery is crucial for normal cellular function. In critically ill patients, the normal relationship between DO_2 and $\dot{V}O_2$ is often disturbed and may be responsible for increased morbidity and mortality. Initial management should include efforts to normalize DO_2 to ensure that oxygen demands are met at the cellular level. Therapeutic interventions aimed at increasing DO_2 to supranormal levels in unselected patients have not been shown to improve survival. Maintaining hemodynamic stability and treatment of the underlying disease process thus remain the primary goals in the management of the critically ill patient.

REVIEW QUESTIONS

1. **What is the least important component of oxygen delivery?**
   - **A.** Hemoglobin
   - **B.** Oxygen saturation
   - **C.** Oxygen dissolved in blood
   - **D.** Cardiac output

2. **Which of the following has been associated with improved survival in septic patients?**
   - **A.** Increasing oxygen content
   - **B.** Increasing delivery
   - **C.** Decreasing oxygen consumption
   - **D.** None of the above

3. **The normal physiologic response to an increased oxygen uptake during exercise is to?**
   - **A.** Increase oxygen delivery by increasing cardiac output
   - **B.** Decrease oxygen extraction
   - **C.** Increase oxygen content of the blood by hyperventilating
   - **D.** All of the above

4. **A 47-year-old woman with toxic shock syndrome remains hypotensive despite volume resuscitation with 2 l normal saline. The house staff decides to place a Swan–Ganz catheter; the initial numbers are CVP = 5 mmHg, RAP = 12/7 mmHg, PAP = 13/8 mmHg, PCWP = 8 mmHg, MAP = 40 mmHg, CO = 5.5, and SVR = 509 dyne/s/m^5. The next intervention for hemodynamic support would be to:**
   - **A.** Add epinephrine to increase SVR.
   - **B.** Add dobutamine to increase cardiac output.
   - **C.** Administer more volume to increase the PCWP.
   - **D.** All of the above.

ANSWERS

1. The answer is C. The least effective way to increase oxygen delivery (DO_2) is by increasing PaO_2. Recalling the equation for oxygen content as [$CaO_2 = (1.3 \times Hgb \times SaO_2) + (0.003 \times PaO_2)$], note that PaO_2 contributes little to CaO_2. DO_2 is simply the cardiac output $\times$ CaO_2. Thus, SaO_2 and hemoglobin make up most of the CaO_2, and these two variables should be normalized in managing septic patients to ensure an adequate DO_2.
2. The answer is D. Large prospective randomized trials have shown no benefit of increasing DO_2 to supraphysiologic levels to improve outcome for septic patients. To the contrary, trying to achieve these levels has actually been shown to increase mortality. Optimizing DaO_2 by maintaining $SaO_2 > 90\%$ and hemoglobin at 7–10 g/dl, and decreasing oxygen consumption ($\dot{V}O_2$) by controlling hyperthermia and using sedation when indicated, is recommended. Even these measures have not been shown necessarily to affect survival.
3. The answer is A. The normal physiologic response to increasing $\dot{V}O_2$ during exercise is to increase DO_2 by increasing cardiac output up to 4–5 fold that seen at rest. Increased oxygen extraction occurs when cardiac output is unable to meet the increasing oxygen requirements, with $\dot{V}O_2$ noted to increase up to 10 fold at maximal exercise.
4. The answer is C. The following patient has toxic shock syndrome that can manifest with profound circulatory shock. Many of these patients have profound volume depletion secondary to capillary leak and vasculature dilatation and need large amounts of volume for hemodynamic support. In the following example, the initial 2 l of volume given was not sufficient to stabilize the patient. The numbers obtained from the Swan–Ganz catheter showed that the preload of the left ventricle was suboptimal and that the patient needed more volume. In this case, I recommend more volume until the PCWP is 12–14 mmHg, and a concomitant increase in the MAP and CO is desirable. If increasing the PCWP to normal values has no effect on organ perfusion (as evidenced by increases in the MAP, CO, and urine output), at this point I would add vasopressors.

   Initial treatment with epinephrine in this patient may be effective, but with the suboptimal PCWP, volume infusion would be the recommended first intervention. If there was hemodynamic instability after optimizing the PCWP, epinephrine may be added. The administration of dobutamine will increase cardiac output but may also decrease SVR, and for this reason this would not be the first intervention.

SUGGESTED READING

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