

JUAN A. GUTIERREZ AND ANDREAS A. THEODOROU

Oxygen Delivery and Oxygen Consumption in Pediatric Critical Care

CHAPTER OUTLINE

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 Arterial Oxygen Content
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 Interdependence of the Heart, Lungs and Blood on
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LEARNING OBJECTIVES

- Detail how to calculate oxygen delivery
- Demonstrate the interdependence of the lungs, heart, and blood on peripheral oxygen delivery
- Describe the mechanisms for measurement of oxygen consumption
- Describe the variables that can influence oxygen consumption in the PICU patient
- Define the use of and limitations of the Fick equation in the evaluation of the adequacy of oxygen delivery
- Define the oxygen extraction ratio; describe how it varies with regional demands and disease states
- Describe the difference between aerobic and anaerobic metabolism touching on relevant metabolic pathways (Kreb's Cycle, Glycolysis, Electron Transport, Oxidation of Fat, Synthetic Oxidative Pathways)
- Describe what ATP, NADP really do
- Describe the biochemical (laboratory) evaluation of the adequacy of circulatory function

INTRODUCTION

The maintenance of adequate oxygen delivery to meet the demands of tissues is the essence of critical care medicine. Inadequate oxygen delivery, which can occur on a global level as in cardiogenic shock, or on a regional level as in traumatic brain injury, must be recognized and treated in order to achieve a good clinical outcome. Therefore, an understanding of the determinants of oxygen delivery and oxygen consumption in the critically ill pediatric patient is essential for any pediatric critical care clinician.

The maintenance of adequate oxygen delivery to meet the demands of the tissues is the essence of critical care medicine.

The preceding chapters describe the process by which molecular oxygen moves down a concentration gradient from the atmosphere to the blood, and from there to the cell and into the mitochondria. Ultimately, this oxygen will be used not only in cellular respiration as the final step in the energy production from carbohydrates, fats, and protein, but also in a number of oxidative reactions unrelated to energy production throughout the body. This chapter will review those biochemical processes, their alterations in critical illness and their relationship to the various methods for measuring oxygen delivery and consumption.

BIOCHEMICAL BASIS

All tissues need energy to maintain their biological processes. This energy is provided by a series of biochemical oxidation/reduction reactions. In this case, oxidation refers to the process in which a molecule, not necessarily involving oxygen, loses electrons. Reduction is the reverse process in which a molecule gains electrons. In oxidation reactions, the electron moves down an energy gradient, releasing energy with every oxidation/reduction cycle. A portion of this energy is captured in reduction reactions by certain molecules, such as adenosine tri-phosphate (ATP), that then become reservoirs of energy. ATP is the most important energy storage/supply molecule because of two key properties. First, the two outer bonds between the three phosphate groups have a very high latent or intrinsic energy, many times more than that of most chemical bonds. This energy is liberated when the bond is broken. Second, these “high energy” bonds are very unstable and can easily break down, making such energy readily available. ATP is constantly being used and regenerated. It is the main energy carrier in the cellular system. The high energy molecule nicotinamide adenine dinucleotide (NADH) or its relative, nicotinamide adenine dinucleotide phosphate (NADPH) are also essential to the energy-generating processes of the cell because they can donate electrons to an electron transport system that produces many molecules of ATP. The phosphorylation of ATP and related molecules is a reduction reaction, with a net increase in stored energy. On the other hand, dephosphorylation, such as the transformation of ATP into ADP, releases energy. Although part of this released energy is dissipated as heat, much of it is used to generate the work needed for normal cellular function (e.g. maintaining a sodium gradient across a biological membrane).

Energy from nutrition is extracted and stored in ATP in three stages. The first step, glycolysis, is anaerobic. Under aerobic conditions, the second step is the conversion of pyruvate to acetyl-CoA that then enters the Krebs cycle. In the third stage of the process, molecules of NADH and FADH from the Krebs cycle enter the electron transport chain and through a cascade of electron donors in which molecular oxygen serves as the final electron donor, and via the process of oxidative phosphorylation, oxygen is reduced to water and an excess of 30 molecules of ATP are produced.

However, to maintain such a system, an external source of energy is always needed. In animals, this energy is provided indirectly by the oxidation of food. Cellular respiration is the process of oxidizing food molecules such as glucose into carbon dioxide and water. The energy from carbohydrates, fats and proteins is extracted and stored in ATP in three stages. The first step is glycolysis during which one molecule of glucose is converted into two molecules of pyruvate with the net production of two ATP molecules and two NADH molecules. This first step is anaerobic; it does not require oxygen. It occurs in the cytoplasm of the cells. Under aerobic conditions, the second step is the conversion of pyruvate into acetyl-CoA while NAD^+ is reduced to NADH. Acetyl-CoA enters the Krebs cycle where the oxidation process continues. Amino acids from protein breakdown enter the Krebs cycle by conversion to pyruvic acid or acetyl-CoA. Lipid metabolism generates glycerol and fatty acids that enter the Krebs cycle as metabolites of glycolysis or as acetyl-CoA. The Krebs cycle, which occurs in the mitochondria, is illustrated in a simplified form in Fig. 2-1. For the two molecules of acetyl-CoA that enter the Krebs cycle (from one molecule of glucose), two ATP molecules, 6 NADH molecules, and two FADH molecules are produced while four molecules of carbon dioxide are released. Although two ATP molecules are produced, the true energy gain from the Krebs cycle is generated from the NADH and FADH molecules. In the third stage of the process, these molecules of NADH and FADH enter the electron transport chain and through a cascade of electron donors in which molecular oxygen serves as the final electron donor, and via the process of oxidative phosphorylation, oxygen is reduced to water and an excess of 30 molecules of ATP are produced.

In the absence of oxygen, there is an elevation of plasma lactate levels and accumulation of H^+ with the development of a metabolic acidosis.

However, for the Krebs cycle, electron transport, and oxidative phosphorylation to occur with their efficient production of energy, oxygen must be present. Under anaerobic conditions, the final electron acceptor can be a metabolite such as pyruvate that will conserve

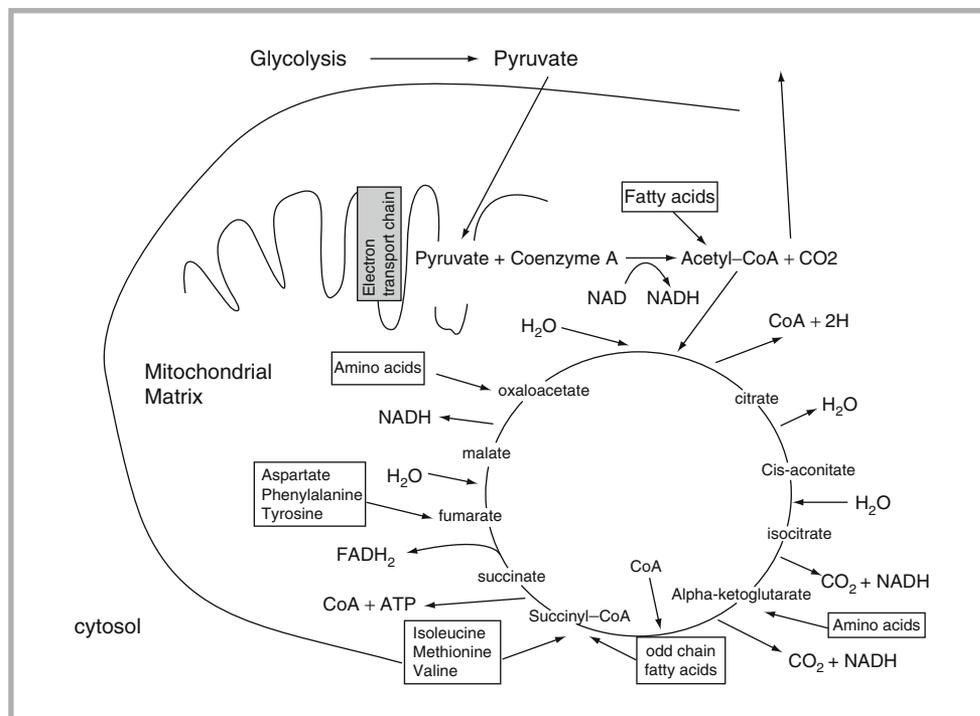


FIGURE 2-1

The Krebs cycle

some of the latent energy. Unfortunately, the anaerobic pathway is considerably less efficient than the aerobic process in producing energy and cannot support the functioning of most tissues for a very long time, particularly those with high energy demands such as the brain or the heart. In the absence of oxygen, two related events will happen: (1) the elevation of plasma levels of lactate, and (2) the development of metabolic acidosis. If oxygen is not present, pyruvate cannot enter the Krebs cycle, and instead, it is converted into lactate resulting in elevations of blood lactate levels. Allowing for the limitations described below, an elevated plasma lactate level can be used as an indicator of anaerobic metabolism and insufficient oxygen delivery. When oxygen becomes available, most of the lactate will rapidly be reconverted to pyruvate, and subsequently enter the Krebs cycle. Most of this reconversion occurs in the liver. Therefore, if liver dysfunction persists despite oxygen becoming abundantly available, the lactate may remain elevated because of impaired hepatic clearance.

The elevation of serum lactate is a marker of the metabolic stress response, and in some conditions, it has been associated with increased mortality. However, the mechanisms contributing to elevation of blood lactate are complex. Clearly, tissue hypoxia favors anaerobic glycolysis, and therefore, lactate production. However, it has been demonstrated that lactate production can also be stimulated in the absence of tissue hypoxia such as occurs in response to inflammatory mediators, catecholamines and other factors which may stimulate Na/K adenosine triphosphatase activity. This is commonly referred to as type B lactic acidosis. In addition, a decrease in lactate utilization can produce elevated blood lactate levels. This has been found to occur in the presence of acute hepatic failure as well as with severe sepsis. As such, simple measurements of blood lactate levels do not indicate the relative importance of the underlying processes, altered production and/or utilization.

The second event that transpires in the setting of hypoxia is that hydrogen ions begin to accumulate and diffuse out of the cell because oxygen is not available to be the final acceptor of hydrogen. This results in metabolic acidosis. In fact, the main mechanism of hypoxic acidosis is not the accumulation of lactate, but rather, the accumulation of these unused H⁺. This fact must be understood when using lactate as an indicator of oxygen delivery insufficiency, as that is not the main cause of the acidosis. It is for this reason that the distinction is made between elevated blood lactate levels with and without metabolic acidosis, the latter condition being less worrisome with regard to tissue oxygen delivery. It must also be understood that the acidosis of anaerobic metabolism is primarily intracellular. The intravenous

The use of sodium bicarbonate to correct hypoxic acidosis may be deleterious. The ideal treatment for acidosis associated with anaerobic metabolism is to improve oxygen delivery.

administration of sodium bicarbonate can correct the extracellular acidosis, but because it is not very diffusible, it only slowly corrects the intracellular acidosis. In fact, data suggest that the rapid infusion of bicarbonate may worsen intracellular acidosis. With rapid infusion of sodium bicarbonate there will be a significant increase in blood levels of carbon dioxide, liberated from the dissociation of carbonic acid formed when bicarbonate ion buffers extracellular hydrogen ion. Carbon dioxide readily diffuses into cells where it associates with water to re-form carbonic acid thereby worsening the intracellular acidosis. Therefore, the use of sodium bicarbonate to correct the hypoxic acidosis may actually be deleterious. As such, the ideal treatment for acidosis associated with anaerobic metabolism is to *improve oxygen delivery*. Consequently, a clear understanding of the factors that influence the delivery of oxygen to the tissues is core to the practice of critical care medicine.

In certain circumstances, the use of sodium bicarbonate may actually improve oxygen delivery. The extracellular acidosis adversely affects myocardial function and its response to catecholamines; therefore, sodium bicarbonate may improve cardiac function, increase the cardiac output, and thus, increase oxygen delivery. Sodium bicarbonate may also be useful when hypoxia is being caused by severe pulmonary hypertension, such as in the meconium aspiration syndrome and in many congenital heart defects. Acidosis increases pulmonary vascular resistance, so the administration of sodium bicarbonate may ameliorate pulmonary vasoconstriction, thus improving oxygenation.

OXYGEN DELIVERY

When oxygen demands are being met, further increases in oxygen delivery will have no effect on oxygen consumption.

In order to develop a clear understanding of the factors that influence the delivery and utilization of oxygen, it is necessary to have a clear understanding of the terms used to describe this process. These definitions include the following:

Oxygen delivery (DO_2): the supply of oxygen per unit of time to a tissue, organ or the entire body.

Oxygen consumption ($\dot{V}O_2$): the oxygen utilized per unit of time by a tissue, organ or the entire body.

Oxygen extraction (O_2ER): the fraction of the oxygen delivered in the blood that is actually utilized or consumed by a tissue, organ or entire patient.

Oxygen demand: a theoretical concept describing the amount of oxygen that a tissue, organ or entire patient would need to consume to meet all of its needs under a given set of circumstances. Oxygen demand cannot be measured, but it is a useful concept when reflecting upon the factors which affect oxygen delivery and consumption. For example, respiratory distress increases the oxygen demands of respiratory muscles. Therefore, we can estimate that assisted ventilation may improve the oxygen delivery/oxygen demands matching.

Oxygen debt: The difference between oxygen delivery and the estimated oxygen demand. Theoretically, when there is a significant oxygen debt, increases in oxygen delivery will increase oxygen consumption. On the other hand, when oxygen demands are being met (no oxygen debt), further increases in oxygen delivery will have no effect on oxygen consumption.

Although frequently discussed separately, these different factors are closely related.

The global delivery of oxygen throughout the body (DO_2) is defined as the product of the oxygen content of the arterial blood (CaO_2 ; in mL/dL) and the blood flow or cardiac output (CO; in L/min) as expressed in the following equation:

$$DO_2 = CO \times CaO_2$$

This equation is multiplied by 10 to convert the units into mL/min:

$$DO_2 (\text{mL} / \text{min}) = CO (\text{L} / \text{min}) \times CaO_2 (\text{mL} / \text{dL}) \times (10 \text{dL} / \text{L})$$

There are several determinants of the cardiac output (often abbreviated as Q) and CaO_2 and all of them can become deranged in critically ill patients. Therefore, careful monitoring and adjustment of these variables is required in order to achieve the best clinical outcome. Each of these variables is discussed below.

Arterial Oxygen Content

The arterial oxygen content is the sum of the oxygen bound to hemoglobin and the oxygen dissolved in the blood. Most of the oxygen in blood travels bound to hemoglobin; only a minimal amount travels as dissolved oxygen. Therefore, the oxygen content depends primarily on the oxyhemoglobin saturation and the hemoglobin concentration. The formula for the calculation of arterial oxygen content is:

$$\text{CaO}_2 = \text{Hgb} \times 1.34 \times \text{SaO}_2 + \text{PaO}_2 \times 0.003$$

where Hgb is the hemoglobin concentration in g/dL; 1.34 is the constant to define the maximum oxygen binding capacity of hemoglobin in mL O_2 /g at 100% oxyhemoglobin saturation (in other words, it is the amount of oxygen a fully saturated gram of hemoglobin can carry); SaO_2 is the percent of hemoglobin saturated with oxygen; PaO_2 is the partial pressure of oxygen in the arterial blood in mm Hg; 0.003 is the constant to define the solubility of oxygen in the blood in mL O_2 /dL/mm Hg. The units for CaO_2 are mL/dL. The formula demonstrates that a drop in oxygen saturation, as in acute respiratory failure, or a drop in the hemoglobin, as in acute hemorrhagic anemia, will significantly decrease the arterial oxygen content, and therefore, the oxygen delivery. The correction of the oxyhemoglobin desaturation and/or the transfusion of packed red blood cells will both increase oxygen delivery.

For example, a healthy child may have an arterial oxygen content of approximately 16.4 mL/dL (assuming a hemoglobin concentration of 12 g/dL, 100% oxyhemoglobin saturation and a PaO_2 of 105 mm Hg). Mathematically (rounding to the tenths digit),

$$\begin{aligned} \text{CaO}_2 &= [(12 \text{ g/dL}) \times (1.34 \text{ mL/g}) \times (1.00) + (105 \text{ mm Hg} \times 0.003 \text{ mL/dL/mm Hg})] \\ &= 16.1 \text{ mL/dL} + 0.3 \text{ mL/dL} = 16.4 \text{ mL/dL} \end{aligned}$$

In contrast, in a child with acute respiratory distress syndrome, hypoxemia ($\text{SaO}_2 = 88\%$, $\text{PaO}_2 = 60$) and anemia (Hgb 9 g/dL), the arterial oxygen content would be approximately 10.8 mL/dL.

Mathematically,

$$\begin{aligned} \text{CaO}_2 &= [(9 \text{ g/dL}) \times (1.34 \text{ mL/g}) \times (0.88) + (60 \text{ mm Hg} \times 0.003 \text{ mL/dL/mm Hg})] \\ &= 10.6 \text{ mL/dL} + 0.2 \text{ mL/dL} = 10.8 \text{ mL/dL} \end{aligned}$$

As such, transfusing the patient with packed red cells up to a hemoglobin of 12 g/dL would increase his CaO_2 to 14.3 mL/dL and thereby increase his arterial oxygen content by approximately one-third [e.g. $(14.3 - 10.8)/10.8 = (3.5/10.8) = 0.32$].

On the other hand, consider a patient with mild anemia with a hemoglobin of 9 g/dL and 100% oxyhemoglobin saturation and a PaO_2 of 105 mm Hg. Such a patient would have an arterial oxygen content of 12.4 mL/dL.

Mathematically,

$$\begin{aligned} \text{CaO}_2 &= [(9 \text{ g/dL}) \times (1.34 \text{ mL/g}) \times (1.0) + (105 \text{ mm Hg} \times 0.003 \text{ mL/dL/mm Hg})] \\ &= 12.1 \text{ mL/dL} + 0.3 \text{ mL/dL} = 12.4 \text{ mL/dL} \end{aligned}$$

An increase in the PaO_2 up to 500 mm Hg with supplemental oxygen would increase the arterial oxygen content to only 13.6 mL/dL. This would increase his CaO_2 by less than 10% [$(13.6 - 12.4)/12.4 = (1.2/12.4) = 0.097$]. Therefore, since hemoglobin cannot be more than

100% saturated, increasing the PaO_2 to high levels has minimal impact on CaO_2 with the exception of patients suffering from severe anemia where the dissolved oxygen represents a significant component of the total CaO_2 as illustrated below. A child with severe anemia and normal lungs presenting with a hemoglobin of 5 g/dL, an oxygen hemoglobin saturation of 100% and a PaO_2 of 105 mm Hg will have a CaO_2 of 7.0 mL/dL.

Mathematically,

$$\begin{aligned}\text{CaO}_2 &= [(5 \text{ g/dL}) \times (1.34 \text{ mL/g}) \times (1.00) + (105 \text{ mm Hg} \times 0.003 \text{ mL/dL/mm Hg})] \\ &= 6.7 \text{ mL/dL} + 0.3 \text{ mL/dL} = 7.0 \text{ mL/dL}\end{aligned}$$

Placing that child on a 100% non-rebreather mask and increasing his PaO_2 to 500 mm Hg would increase his CaO_2 to 8.2 mL/dL. Although that intervention would again only increase his CaO_2 by 1.2 mL/dL, in this scenario, that increase would represent a 17% increase in his CaO_2 $[(8.2 - 7.0)/7.0] = (1.2/7.0) = 0.17$.

Mathematically,

$$\begin{aligned}\text{CaO}_2 &= [(5 \text{ g/dL}) \times (1.34 \text{ mL/g}) \times (1.00) + (500 \text{ mm Hg} \times 0.003 \text{ mL/dL/mm Hg})] \\ &= 6.7 \text{ mL/dL} + 1.5 \text{ mL/dL} = 8.2 \text{ mL/dL}\end{aligned}$$

As such, increasing his dissolved oxygen can substantially improve his oxygen delivery until the more definitive therapy of a transfusion of packed red blood cells can be safely administered. Putting it into perspective, increasing the hemoglobin to even a level of only 8 g/dL with a transfusion of red cells would increase the CaO_2 by nearly 50% $[(12.2 - 8.2)/8.2] = (4.0/8.2) = 0.49$.

Mathematically,

$$\begin{aligned}\text{CaO}_2 &= [(8 \text{ g/dL}) \times (1.34 \text{ mL/g}) \times (1.00) + (500 \text{ mm Hg} \times 0.003 \text{ mL/dL/mm Hg})] \\ &= 10.7 \text{ mL/dL} + 1.5 \text{ mL/dL} = 12.2 \text{ mL/dL}\end{aligned}$$

The decision regarding blood transfusions to improve oxygen delivery is not necessarily straightforward, except in the case of acute severe anemia. Some studies suggest that in critically ill adult cardiac patients, a “liberal” transfusion policy may improve outcomes, presumably by maintaining adequate oxygen delivery in the coronary circulation. However, other studies suggest that a “liberal” policy of blood transfusions may be associated with increased mortality in non-selected critically ill patients. In a landmark study, stable, critically ill children randomized to a hemoglobin threshold of 7 g/dL performed as well as children randomized to a hemoglobin threshold level of 9.5 g/dL. In *post hoc* analyses, similar results were found among the subsets of general post-operative and post-operative cardiac patients. In fact, among the subset of general post-operative patients, the restrictive transfusion strategy was associated with a shorter length of PICU stay. Several factors have been invoked to explain the lack of benefit to the “liberal” transfusion policy including the relative impairment of oxygen dissociation from stored blood, transfusion reactions, and activation of inflammatory mediators and inflammatory cells that may be present in the transfused blood.

The CaO_2 alone does not necessarily describe how much oxygen is available at the tissue level. Certain factors may decrease oxyhemoglobin dissociation (unloading) in the capillary circulation thereby making less oxygen available. These factors include severe alkalosis (shifts oxygen/hemoglobin dissociation curve to the left), the depletion of 2,3-diphosphoglycerate (2,3 DPG) in stored blood, the presence of fetal hemoglobin, and certain hemoglobinopathies. On the other hand, factors that enhance oxyhemoglobin dissociation will make oxygen more readily available to the tissues. These factors include 2,3 DPG which may be increased by glycolysis, exercise, hypoxemia, fever and/or acidosis. In addition to these factors and the CaO_2 , the amount of oxygen available at the tissue level is influenced by the cardiac output.

Cardiac Output

The second component of the oxygen delivery is systemic cardiac output (CO), the amount of blood that is being pumped to the systemic circulation in liters per minute. In the absence of intracardiac or large systemic to pulmonary shunts, the systemic cardiac output is the product of the heart rate (HR) in beats per minute and the left ventricular stroke volume (SV) in milliliters:

$$\text{CO} = \text{HR} \times \text{SV}$$

and is frequently indexed (CI) to body surface area (BSA) (m^2).

$$\text{CI} = \text{CO} / \text{BSA}$$

Heart Rate

The normal heart rate varies with age. Newborns and small infants, or infants with congenital heart disease causing concentric hypertrophy, have relatively rigid ventricular walls limiting their distention. Consequently, they have a limited ability to increase stroke volume, and thus, may be more dependent on heart rate to increase cardiac output. On the other hand, pathologically fast heart rates, such as occurs in supraventricular tachycardia, may adversely affect cardiac output by limiting the time available for ventricular filling during diastole, thereby decreasing the stroke volume.

Stroke Volume

Stroke volume is the volume of blood pumped with each cardiac contraction, and is a reflection of three components: preload, contractility, and afterload. Data suggest that, even in neonates, stroke volume may vary in response to negative and positive inotropic influences. Preload is defined as the stretch of the cardiac myocytes just prior to contraction. As such, preload is related to the sarcomere length, and is difficult to assess clinically. According to the classic Frank Starling Relationship, the strength of the muscular contraction depends on the initial length (stretch) of the muscle. As the stretch of the cardiac myocyte is increased, the strength of the muscular contraction increases up to a point. The cardiac myocyte can be stretched to a point beyond which maximal contraction occurs, and the strength of the contraction begins to decrease as further stretching of the myocyte occurs (Fig. 2-2). As such, clinically determining preload is difficult. The left ventricular end diastolic volume, which is the volume of blood in the left ventricle just prior to contraction, is probably the best surrogate of systemic preload. Thermodilution techniques are available that can determine global end diastolic volume, but are not well established in pediatric critical care. Echocardiography and magnetic resonance imaging may also be used to estimate left ventricular end diastolic volume, but are technician dependent and do not allow for moment to moment monitoring. As such, other measures have been utilized to determine cardiac preload. Left ventricular end diastolic volume may be estimated by left ventricular end diastolic pressure. This estimation may be confounded by a change in the distensibility of the ventricular wall or pressure increases outside of the ventricle (increased intrathoracic pressure, pericardial tamponade, etc.). Moreover, left ventricular end diastolic pressure is also difficult to assess clinically. Consequently, more clinically relevant surrogates of preload are required. The next best indicator would be the left atrial pressure which is also difficult to assess. However, the pulmonary artery occlusion pressure can be used to reflect left atrial pressure, and as such, represents a clinically useful surrogate of left atrial pressure and of systemic preload. The pulmonary artery occlusion pressure is determined by inflating the balloon of a pulmonary artery catheter such that it floats out and wedges into a distal pulmonary artery. The distal lumen of the pulmonary artery catheter is distal to the balloon, and therefore, measures the downstream pressure without interference from proximal pressures as the inflated balloon isolates the distal pressures (Chap. 5). Unfortunately, pulmonary artery catheter monitoring is invasive,

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In the classic Law of Starling, the strength of the contraction depends on the initial length of the cardiac muscle up to a maximum point.

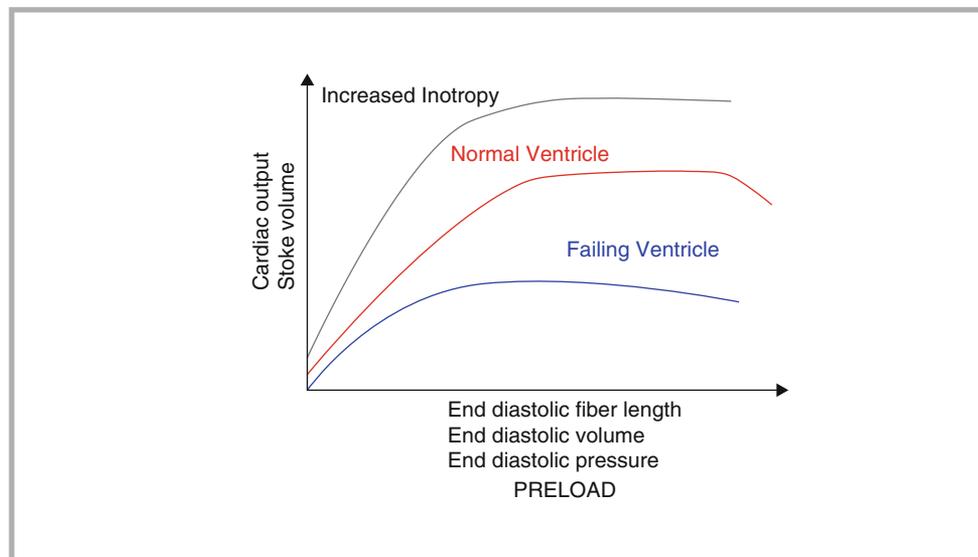


FIGURE 2-2

Frank Starling Relationship between preload and ventricular function. The middle curve represents a normal myocardium. As preload increases, markers of contractility increase as well. The lower curve represents a myocardium that is dysfunctional. The curve is shifted downward and to the right, such that for the same preload, there is decreased ventricular function. Finally, the upper curve represents the normal myocardium receiving inotropic support. Note that the curve is shifted upward and to the left, such that for the same preload, there is increased ventricular function

and adult studies have suggested that the routine use of such monitoring may be associated with worse outcomes. Therefore, pulmonary artery monitoring has become less common, and more routinely used surrogates of preload are needed. Following the flow of blood backwards, the next best clinically useful measure of preload is the central venous pressure as measured from the right atrium or a major vein within the thoracic compartment. Obviously, there are many factors that may affect central venous pressure independent of the true preload, and thus, it is not an optimal monitor of preload. However, because of its clinical availability, it is commonly used to assist in the assessment of preload.

Contractility depends on many factors including the mass of muscle, the molecular aspects of muscular contraction, the degree of stimulation by catecholamines, and the concentration of electrolytes such as calcium, potassium, and magnesium. Factors that increase cardiac contractility move the Frank-Starling curve upward and to the left.

In addition to preload, stroke volume is determined by contractility. Cardiac contractility is defined as the extent of shortening that occurs in cardiac myocytes when stimulated independent of preload or afterload. It refers to the intrinsic strength of the myocardial muscle and is measure of cardiac muscle performance. It depends on many factors including the mass of muscle, the molecular aspects of muscular contraction, the degree of stimulation by catecholamines, and the concentration of electrolytes such as calcium, potassium, and magnesium. Factors that increase cardiac contractility move the Frank-Starling curve upward and to the left (Fig. 2-2). Thus, for the same preload, increased contractility usually results in increased stroke volume. As with preload, clinically determining contractility is difficult. Techniques such as the thermodilution derived cardiac function index and the echocardiographic stress index have been developed, but their application to pediatrics has been limited to date. Doppler tissue imaging represents a new echocardiographic technique that may assist in the determination of contractility by measuring the velocity of myocardial motion. However, echocardiographic determination of the shortening fraction and the ejection fraction remain the most commonly utilized surrogates of contractility. The shortening fraction is the percent change in the diameter of the left ventricle which occurs with contraction. It is determined by taking the difference in left ventricular diameter between diastole and systole, and dividing that value by the left ventricular end diastolic diameter. Definitions of normal values vary, but typically are in the 30–40% range. Unfortunately, these values are influenced by the state of volume loading of the patient. The ejection fraction is another parameter that can be used to assess left ventricular function. It is determined in a manner similar to the shortening fraction, but it utilizes end diastolic volumes rather than diameters. Normal values tend to range from the mid 50% to the mid 60%.

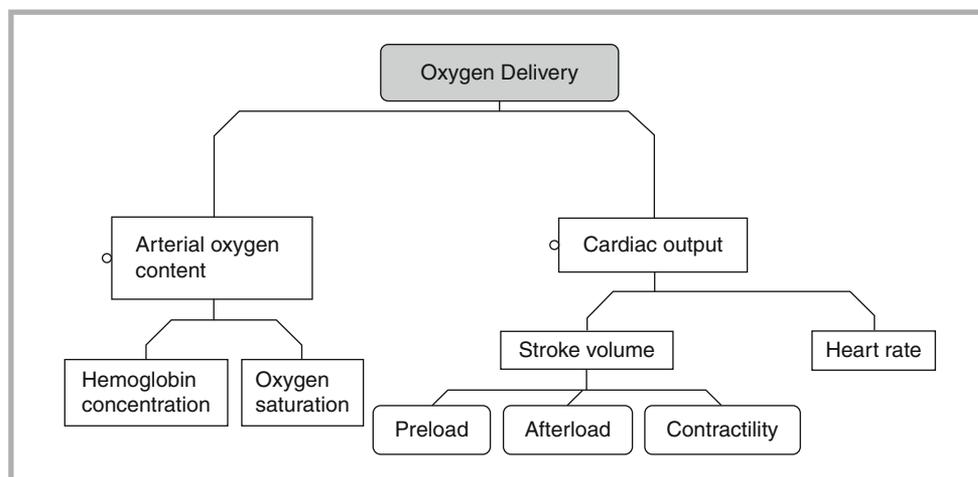


FIGURE 2-3

Factors influencing oxygen delivery

Afterload may be defined as the force opposing contraction of the left ventricular myocytes during systole. It can be quantified as the left ventricular wall stress. The left ventricular wall stress may be estimated using the Law of LaPlace which relates wall stress to the pressure, radius and thickness of a sphere or cylinder in the following formula:

$$\text{Wall stress} = (\text{Pressure})(\text{Radius}) / (\text{Wall thickness})$$

Because the left ventricle is not a sphere or cylinder, the application of the Law of LaPlace is an oversimplification. In using this equation to assess left ventricular afterload, the pressure refers to the transmural left ventricular pressure, the radius refers to the left ventricular end systolic dimension, and the wall thickness to the left ventricle. These measures should all be taken at the end of left ventricular systole. The left ventricular wall thickness and dimension may be determined echocardiographically. The transmural left ventricular pressure is the difference between the pressure inside the ventricle minus the pressure outside the ventricle. Extraventricular pressures have been determined using esophageal or pleural pressure monitoring, although clinically these values are not commonly measured. It is important to note that the use of positive pressure ventilation will change the intrathoracic pressure from a negative to a positive. As such, positive pressure ventilation will actually decrease left ventricular preload because subtracting a positive from a positive (the intraventricular pressure) is a smaller number. In contrast, normal, negative pressure ventilation results in increased left ventricular afterload because subtracting a negative (intrathoracic pressure) from a positive (intraventricular pressure) results in a higher number (i.e. increased afterload).

Quantitatively, oxygen delivery is the result of multiple factors, all of them intimately interrelated. Any of the multiple factors that can affect arterial oxygen content (hemoglobin concentration, oxygenation) or the cardiac output (preload, contractility, afterload, or heart rate), will affect oxygen delivery (Fig. 2-3). Therefore, a clear understanding of the interdependence of these factors and the therapies that influence them is essential to the management of critically ill children.

INTERDEPENDENCE OF THE HEART, LUNGS AND BLOOD ON PERIPHERAL OXYGEN DELIVERY

The lungs have the primary role of extracting oxygen from inspired gas. The blood has the primary role of carrying that oxygen to the tissues, and the heart has the primary responsibility

The determinants of the cardiac output (heart rate, preload, afterload and contractility) and the arterial content of oxygen (hemoglobin and oxygenation) can each become deranged in critically ill patients. Careful monitoring and adjustment of these variables is required in order to achieve the best clinical outcome.

Hypoxemia is detected by special nerve chemical receptors located in the carotid and aortic bodies. When these chemoreceptors are triggered by hypoxemia ($\text{PaO}_2 < 60$ mm Hg, corresponding to $\text{SaO}_2 < 93\%$), there is stimulation of the respiratory area of the medulla. This results in an increase in minute ventilation, a higher alveolar oxygen concentration (PAO_2), and ultimately, an increase in the arterial oxygen content as a result of the increase in the oxygen saturation and the PaO_2 . Furthermore, signals are sent from the chemoreceptors to the vasomotor center of the brainstem, leading to increased sympathetic tone. This sympathetic stimulation increases the heart rate, improves the preload by venous constriction, and increases contractility, all of which improve cardiac output, and thereby, augment oxygen delivery.

In the presence of acidosis, such as that likely to be present in the capillary circulation during hypoxia, the affinity of hemoglobin for oxygen decreases, facilitating the release of oxygen to the starved cells. The affinity of hemoglobin for oxygen also decreases with increases in the concentration of 2,3 diphosphoglycerate (2,3 DPG) which occur in the presence of hypoxemia.

of circulating that blood and oxygen to the tissues. These three systems work interdependently to assure adequate oxygen delivery to the tissues. This interdependence is best exemplified by reviewing the physiologic responses to alterations in any of these systems.

One of the most common causes of inadequate oxygen delivery in pediatrics is acute hypoxemia, usually defined as a low PaO_2 or SaO_2 (Chap. 1). Hypoxemia is detected *in vivo* by special nerve chemical receptors located in the carotid and aortic bodies called peripheral chemoreceptors. When these chemoreceptors are triggered by hypoxemia ($\text{PaO}_2 < 60$ mm Hg, corresponding to $\text{SaO}_2 < 93\%$), there is stimulation of the respiratory area of the medulla. This results in an increase in minute ventilation, a higher alveolar oxygen concentration (PAO_2), and ultimately, an increase in the arterial oxygen content as a result of the increase in the oxygen saturation and the PaO_2 . Furthermore, signals are sent from the chemoreceptors to the vasomotor center of the brainstem, leading to increased sympathetic tone. This sympathetic stimulation increases the heart rate, improves the preload by venous constriction, and increases contractility, all of which improve cardiac output, and thereby, augment oxygen delivery. However, this sympathetic-mediated compensatory response has the potential to become maladaptive as the result of hypertension and increased oxygen consumption by the myocardium. When prolonged, this compensatory response may lead to myocardial dysfunction, especially in the setting of preexisting cardiac disease. These compensatory mechanisms are not well developed in newborns who often develop hypotension, bradycardia, and apnea in response to acute hypoxemia.

Hemoglobin is the molecule responsible for carrying oxygen in the blood. It can adapt to physiologic changes associated with hypoxia to improve oxygen delivery to the tissues. In the presence of acidosis, such as that likely to be present in the capillary circulation during hypoxia, its affinity for oxygen decreases, facilitating the release of oxygen to the starved cells (Fig. 2-4). The affinity of hemoglobin for oxygen is decreased in the presence of increased concentrations of 2,3 diphosphoglycerate (2,3 DPG) which occur in the presence of hypoxemia. Of note, the concentration of 2,3 DPG declines with time in stored packed red

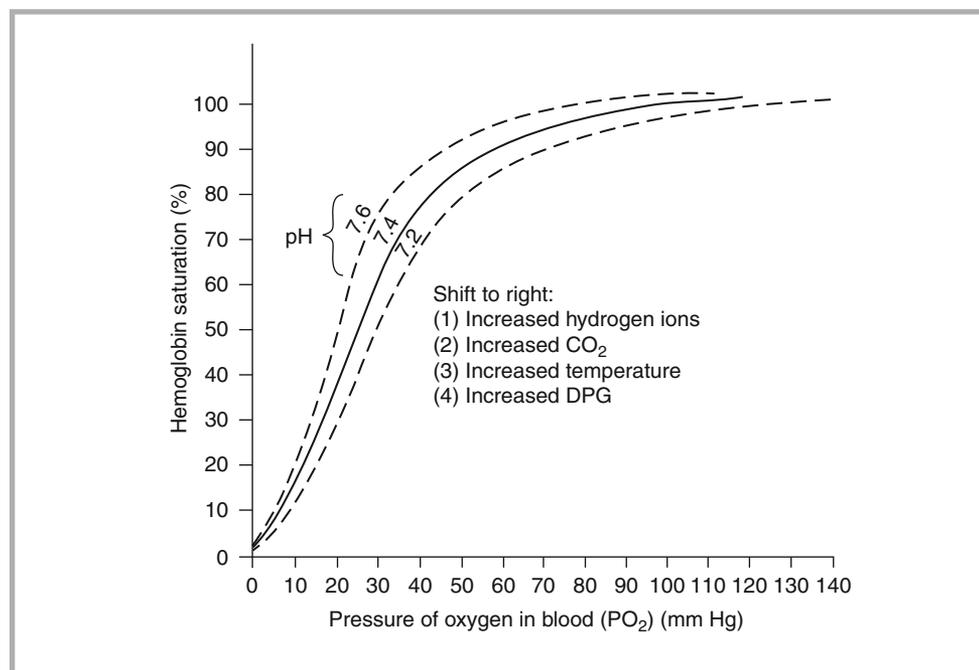


FIGURE 2-4

The oxygen hemoglobin dissociation curve. The curve is shifted to the right by factors that enhance oxyhemoglobin dissociation and allow oxygen to be more readily available to the tissues. These factors include 2,3-diphosphoglycerate (2,3 DPG) which may be increased by glycolysis, exercise, hypoxemia, fever and/or acidosis. The curve is shifted to the left by severe alkalosis, the depletion of 2,3 DPG, the presence of fetal hemoglobin, and certain hemoglobinopathies (Adapted from Guyton and Hall (2006))

blood cells potentially degrading the ability of PRBC transfusion to release oxygen at the tissue level. In addition, in considering the role of hemoglobin in oxygen delivery, it is important to recognize that there are different forms of hemoglobin with different affinities for oxygen. For example, fetal hemoglobin constitutes a significant proportion of the total hemoglobin in newborns and small infants. This form of hemoglobin has an increased affinity for oxygen, which facilitates the transfer of oxygen from the maternal adult hemoglobin across the placenta. However, following birth, when the oxygen concentration at the pulmonary alveolar level is much higher, this increased affinity for oxygen is no longer needed. In fact, this elevated affinity for oxygen may impair the unloading of oxygen at the tissue level postnatally which may be problematic in conditions associated with decreased oxygen delivery.

Sustained hypoxia induces changes in cellular gene expression. A family of transcription factors known as hypoxia-inducible factors (HIF) has been characterized furthering the understanding of the molecular response to hypoxia. When oxygen saturation is chronically low, as in cyanotic heart disease, the bone marrow responds by increasing the red blood cell production, leading to an increased hemoglobin concentration and improved CaO_2 . The molecular signal in this response is the hormone erythropoietin secreted by the kidney. Erythropoietin stimulates the bone marrow to increase the production of red blood cells. This process is not finely controlled, and when hypoxemia is chronic and severe as in the presence of uncorrected cyanotic heart disease, the resultant polycythemia increases blood viscosity and the resistance to blood flow in the microcirculation. The net result may be compromised oxygen delivery to tissues of the body.

When hemorrhagic shock is the cause of inadequate oxygen delivery with an acute drop in hemoglobin, baroreceptors located in the carotid sinus, aortic arch and venoarterial junctions of both atria are triggered. Triggering of these baroreceptors stimulate the brainstem to increase the cardiac output primarily through an increase in the heart rate, in an effort to compensate for the low arterial oxygen content. When hypovolemia compromises cardiac output, peripheral vasoconstriction results, optimizing perfusion of vital organs and minimizing the risk of ongoing bleeding.

When physiological changes occur gradually over time, adequate compensation is more likely to occur. This is especially true in regard to the development of anemia. Chronic anemia, as occurs with iron deficiency, allows for maintenance of oxygen delivery by gradual increases in preload and heart rate, and therefore, cardiac output. Additional capillary beds open within vital organs minimizing the distance from the oxygen supply to the cells. These opened capillary beds result in a decreased systemic vascular resistance which fosters an increased cardiac output and manifests itself as a widened pulse pressure with decreased diastolic pressures. Unlike acute anemia, intravascular volume is not only maintained, but may actually be elevated. Even children with a hemoglobin concentration less than 4 g/dL are able to compensate remarkably well when the anemia has developed slowly. However, it is critical to recognize that compensation results in a hypervolemic, high cardiac output state. Therefore, the anemia must be corrected slowly or in a euvolemic manner to prevent the development of acute pulmonary edema. While traditional recommendations support the use of very small aliquots of red blood cells transfused over 3–4 h in the correction of long-standing severe anemia, larger transfusion volumes (5–10 mL/kg packed red blood cells), given concomitantly with diuresis may be well tolerated.

The most common cause of poor cardiac output in children is inadequate preload from dehydration or hypovolemia. The compensatory responses to this physiologic state are aimed at improving preload by conserving salt and water in the kidneys, and increasing heart rate and contractility. Selective vasoconstriction of the peripheral circulation leads to cold, poorly perfused extremities, but optimizes oxygen delivery to vital organs including the brain and heart. When the primary etiology of inadequate oxygen delivery is poor cardiac function, receptors throughout the body sense the inadequate flow and the compensatory mechanisms begin. In an attempt to increase preload, renin/angiotensin/aldosterone and antidiuretic hormone (ADH, vasopressin) are secreted resulting in salt and water retention. The heart rate increases in response to endocrine and autonomic release of catecholamines compensating for the decreased stroke volume secondary to the decreased contractility. The respiratory rate increases thereby lowering the CO_2 , improving alveolar oxygen (alveolar gas equation), and ultimately, increasing the arterial

Tissue hypoxia triggers the kidney to secrete the hormone erythropoietin, stimulating the bone marrow to increase the production of red blood cells.

Chronic anemia, as occurs with iron deficiency, allows for maintenance of oxygen delivery by gradual increases in preload and heart rate, and therefore, cardiac output. Unlike acute anemia, intravascular volume is not only maintained, but may actually be elevated. Even children with a hemoglobin concentration less than 4 g/dL are able to compensate remarkably well when the anemia has developed slowly. However, it is critical to recognize that compensation results in a hypervolemic, high cardiac output state. Therefore, the anemia must be corrected slowly or in a euvolemic manner to prevent the development of acute pulmonary edema.

oxygen content. With disease progression, these compensating mechanisms may produce physiologic impairment with fluid retention resulting in pulmonary and peripheral edema. In addition, the elevated norepinephrine levels from the compensatory response result in an increased systemic afterload maintaining blood pressure at the expense of cardiac output.

OXYGEN CONSUMPTION

Energy expenditure can be measured directly with calorimetric methods, or can be estimated from oxygen consumption, using specific formulas to convert it to energy.

The measurement of oxygen *consumption* is an integral part of the evaluation of oxygen metabolism. Oxygen consumption is related to energy expenditure which is the amount of energy consumed from the substrate (carbohydrates, lipids, amino acids) during the process of energy generation. Energy expenditure can be measured and/or estimated from the oxygen consumption and the carbon dioxide production. This concept is part of the nutritional evaluation of critical illness and is discussed further in Chapter 21.

In the critically ill patient, there may be concern with both abnormally high and low oxygen consumption. Oxygen consumption may be low because the metabolic activity of the tissues has decreased (e.g. barbiturate-induced coma), because the tissues are unable to utilize the oxygen (e.g. cyanide toxicity) or because the tissues are not receiving enough oxygen. When oxygen consumption is low because of inadequate supply, the cause may be the result of a deficiency in any of the components of oxygen delivery. In addition to conditions associated with low oxygen consumption, cellular hypoxia may occur in the setting of mismatched oxygen consumption and oxygen delivery. In some circumstances, the absolute value of oxygen consumption may be high when compared to normal values, but the tissues may still be starving because oxygen demands are higher yet. Most tissues have the ability to increase their extraction of oxygen several fold in an attempt to satisfy their oxygen needs.

Determining if the measured oxygen consumption is appropriate, is often difficult. Traditionally, this question has been addressed by increasing the level of oxygen delivery. Under normal conditions, oxygen delivery is determined by the oxygen needs of the tissues. If the cells do not need additional oxygen, increasing oxygen delivery will only minimally impact oxygen consumption (supply independent). However, if the tissues are starving for oxygen despite increasing the amount of oxygen extracted from the blood, consumption will begin to fall linearly with decreasing oxygen delivery. The point at which this occurs is termed the critical point of oxygen delivery. Below that point, cells are resorting to anaerobic metabolic pathways to survive, and oxygen consumption will increase with increased supply. This is termed the supply dependent portion of the oxygen consumption curve (Fig. 2-5). However, in critically ill patients with sepsis or the acute respiratory distress syndrome (ARDS), this normal biphasic relationship does not occur. Instead, oxygen consumption remains supply dependent to much higher levels of oxygen delivery (Fig. 2-6). The reason

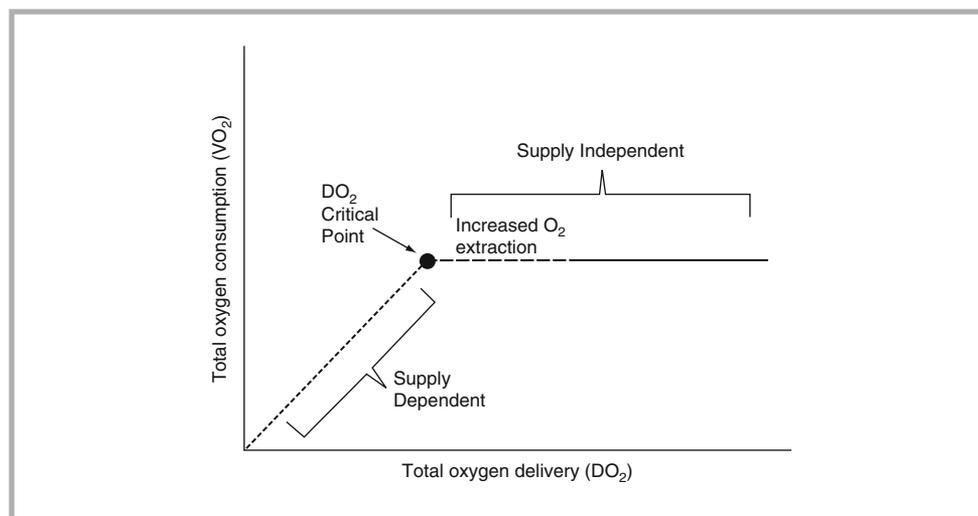


FIGURE 2-5

Oxygen consumption/oxygen delivery relationship

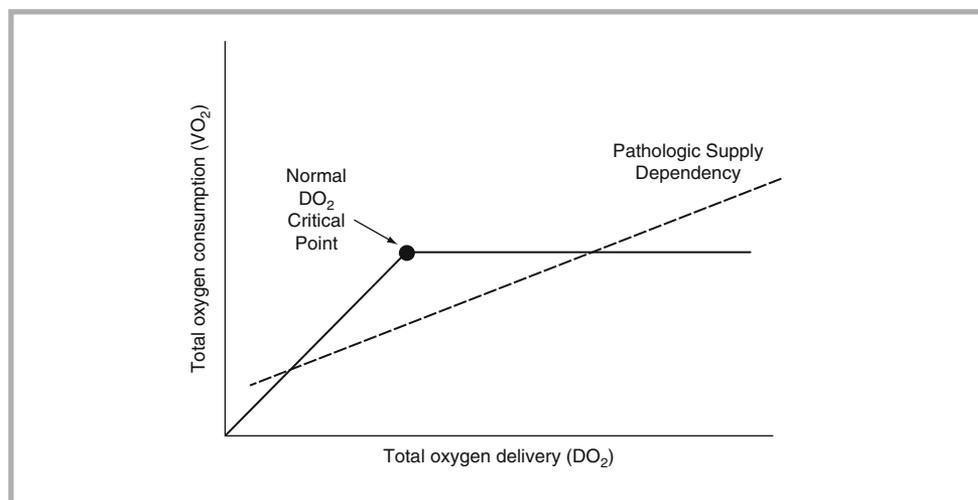


FIGURE 2-6

The oxygen consumption/oxygen delivery relationship in pathologic states such as ARDS and sepsis. In this figure, the *solid line* represents the normal biphasic relationship between oxygen consumption and delivery. The *dotted line* represents the pathologic relationship observed in critically ill patients with sepsis or ARDS. In this conditions, supply dependency is observed at much higher levels of oxygen delivery (Adapted from Crocetti and Krachman (2002))

for this alteration in the normal relationship between oxygen supply and delivery has not been clearly elucidated. It has been suggested that it occurs because the critical point of oxygen delivery has been reset to a much higher point. Alternatively, it has been offered that it is the result of impaired ability of the tissues to increase the extraction ratio of oxygen.

Given these complexities of oxygen metabolism, in conjunction with the many interconnected mechanisms and regional variations, it is not surprising that the measurement of oxygen consumption has not developed into a routine tool for the clinician. In fact, other imperfect indicators of tissue starvation such as acidosis and lactate levels may be more clinically useful. Despite this, a clear understanding of the concepts of oxygen delivery and utilization is fundamental to the care of critically ill children.

Measurement Techniques

The determination of oxygen consumption provides insight into the adequacy of oxygen delivery and utilization at the tissue level. However, accurately determining oxygen consumption at the tissue level is extremely difficult. Several methods for the determination of oxygen consumption have been developed for clinical use. One approach is to assess the content of gases being inhaled and exhaled by the patient and determine oxygen consumption using indirect calorimetry. Indirect calorimetry is based on the basic law of thermodynamics that energy utilization entails the consumption of oxygen with the production of carbon dioxide, nitrogenous waste, and water in a stoichiometric fashion. Commercially available indirect calorimetry machines require that the patient breathes through a valved system that separates inspired and expired gases. The inspired gas has a known concentration of oxygen, nitrogen, and carbon dioxide. The volume of expired gas is measured and the amount of expired oxygen and carbon dioxide is determined. With these values, oxygen consumption ($\dot{V}O_2$) can be determined using the following equation:

$$\dot{V}O_2 = \dot{V}_I(F_I O_2) - \dot{V}_E(F_E O_2) \quad (\dot{V}CO_2) = \dot{V}_E(F_E CO_2) - \dot{V}_I(F_I CO_2)$$

where $\dot{V}O_2$ is the oxygen consumption, \dot{V}_I is the volume of inspired gas, $F_I O_2$ is the fraction of oxygen in the inspired gas, \dot{V}_E is the volume of exhaled gas, $F_E O_2$ is the fraction of oxygen

in the exhaled gas, $\dot{V}O_2$ is the production of carbon dioxide, $F_I CO_2$ is the fraction of carbon dioxide in the inspired gas, V_E is the volume of exhaled gas, and $F_E CO_2$ is the fraction of carbon dioxide in the exhaled gas. This approach can be fraught with error particularly if there are leaks in the respiratory circuit (including around the endotracheal tube) and if the $F_I O_2$ is greater than 0.40. Consequently, other methods to estimate oxygen consumption have been developed.

The reversed Fick equation uses the arterio-venous oxygen saturation difference to estimate oxygen consumption. It requires determination of the cardiac output, the arterial oxygen content, and the mixed venous oxygen content. The measurement of cardiac output and mixed venous oxygen content requires the placement of a pulmonary artery catheter.

The reversed Fick equation uses the arterio-venous oxygen saturation difference to estimate oxygen consumption. It requires determination of the cardiac output, the arterial oxygen content and the mixed venous oxygen content. In this procedure, oxygen consumption will be equivalent to the difference between the arterial and mixed venous oxygen content, multiplied by the cardiac output (See Chap. 5).

$$\dot{V}O_2 = (CaO_2 - CmvO_2) \times CO$$

Oxygen consumption is measured in units of mLs of oxygen consumed per minute. As such, the above equation is multiplied by a scaling factor of 10 to account for units.

$$\dot{V}O_2 (\text{mL} / \text{min}) = (CaO_2 (\text{mL} / \text{dL}) - CmvO_2 (\text{mL} / \text{dL})) \times CO (\text{L} / \text{min}) \times 10 (\text{dL} / \text{L})$$

Optimally, the measurement of cardiac output and mixed venous oxygen content requires the placement of a pulmonary artery catheter. This calculation was routinely performed when the use of pulmonary artery catheter was more commonplace. This can be technically difficult particularly in small infants. Other methods can be used to estimate the cardiac output such as Doppler or thoracic impedence. Also, the mixed venous oxygen content can be approximated by using the central venous oxygen content from the superior vena cava or right atrium. The oxyhemoglobin saturation of the mixed venous blood ($SmvO_2$ or SvO_2) can be an estimate of the adequacy of global oxygen delivery. For example, if the oxygen delivery is insufficient for the oxygen demands, oxygen extraction by the starved tissues will increase, and therefore, the oxygen saturation in the central venous circulation will decrease. On the other hand, adequate oxygen delivery results in normal oxygen extraction and normal central venous oxygen saturation usually greater than 70%. This approach has the theoretical advantage of assessing the relative adequacy of oxygen delivery, perhaps a more important parameter for the individual patient, and the simplicity of not requiring an estimate of cardiac output. Its use has grown as an endpoint of resuscitation in large adult studies and at least one pediatric study.

In most circumstances, oxygen consumption will be estimated at one point in time although the physiologic state of the critically ill patient changes over the course of his illness. Central venous oxygen saturations can be measured continuously, thus overcoming the time limitation of the classic Fick procedure.

Similar to indirect calorimetry, the reversed Fick procedure has several limitations that must be taken into consideration when interpreting its results. For example, it provides an estimation only of global oxygen consumption; important regional differences may not be detected by this method (Table 2-1). In addition, oxygen extraction may be blocked by metabolic toxic factors. In this setting, the oxygen extraction would be normal or decreased, resulting in a high central or mixed venous saturation despite the presence of tissue oxygen starvation. Although cyanide poisoning is the classic example of impaired oxygen

TABLE 2-1

DISTRIBUTION OF BLOOD FLOW AND OXYGEN UTILIZATION BASED ON AN ADULT WITH CO = 6 L/MIN

ORGAN	PERCENT OF CARDIAC OUTPUT	BLOOD FLOW (ML/MIN)	OXYGEN UPTAKE (ML/MIN)
Brain	14	840	52
Heart	5	300	34
Splanchnic bed	28	1,680	83
Kidney	23	1,380	19
Skeletal muscle	16	960	57
Skin	8	480	12

Adapted from Crocetti and Krachman (2002)

utilization, experimental studies suggest that endotoxin may block oxygen metabolism under certain circumstances. Additionally, as described above, the classic Fick procedure requires the placement of a pulmonary artery catheter. The risk benefit ratio of these catheters has been questioned, and by most accounts, it appears that their use has been decreasing. Moreover, the presence of an intracardiac, left to right shunt will complicate interpretation of the Fick equation as the pulmonary artery saturations will be “contaminated” with the highly saturated blood returning from the lungs to the left side of the heart. As such, depending on the degree of the shunt, the oxygen saturations will be higher than that of the central venous system. Finally, a traditional critique of the Fick equation was that it provided an estimate of oxygen consumption at isolated points in time. Given that the physiology of the critically ill child may change rapidly, clinically significant changes may not be detected. However, with the advent of oximetric catheter technology, the central or mixed venous oxygen saturation can now be measured continuously. It is important to note that when continuous oximetric monitoring is performed in a central vein rather than the pulmonary artery, the position of the catheter may influence the venous saturation. For example, a central venous catheter placed in the inferior vena cava is likely to reveal a higher oxygen saturation because the kidneys, acting primarily as filters, typically consume relatively little oxygen (Table 2-1). In contrast, a central venous catheter placed in proximity to the coronary sinus may reveal low venous saturations as the oxygen extraction of myocardial tissue is higher than other tissues. The pediatric guidelines in the Surviving Sepsis Campaign list goals for SvO₂ in the resuscitation of pediatric septic shock.

OXYGEN CONSUMPTION VARIABILITY

Factors That Increase Oxygen Consumption

A multitude of factors can affect oxygen consumption (Fig. 2-7). Oxygen consumption can be increased by several pathological conditions including catabolic states (sepsis, burns, etc.), fever (oxygen metabolism must be increased to generate the excess of energy lost as heat) and infections (the increase accounts for the activation of immune and compensatory

$\dot{V}O_2$ is increased by catabolic states, fever, infection, increased motor activity, increased work of breathing and the use of inotropic agents. $\dot{V}O_2$ is decreased by sedation and paralysis, mechanical ventilation, barbiturate coma, hypothermia, and severe anoxic-ischemic brain injury.

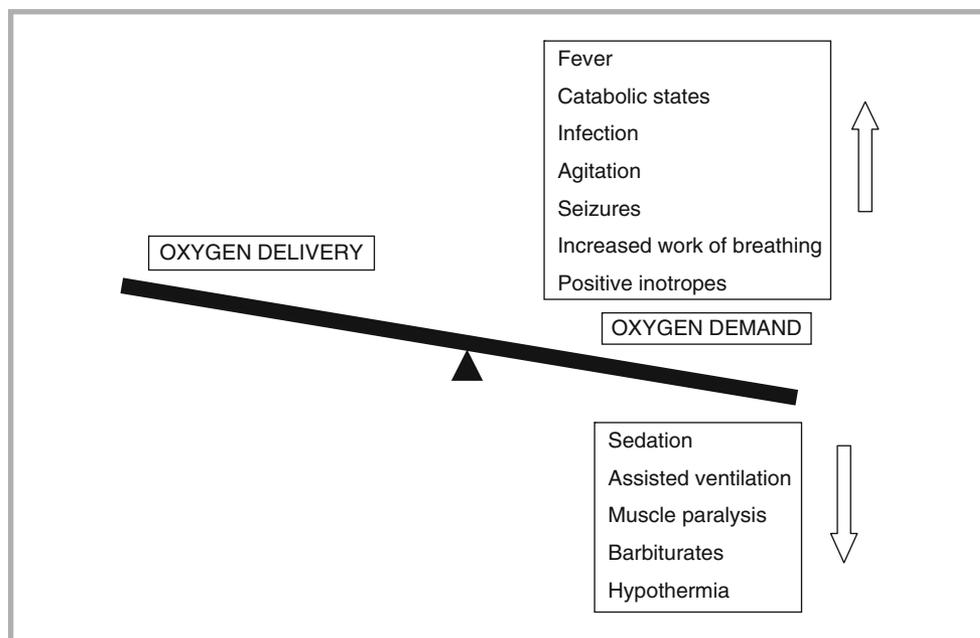


FIGURE 2-7

Factors affecting oxygen utilization

mechanisms used to fight infection). In addition, oxygen consumption is increased during episodes of increased motor activity. This increased motor activity may take many forms and, in the PICU, is commonly associated with agitation, shivering, or seizures. Seizures, in particular, can profoundly increase oxygen consumption. In addition, increased work of breathing may substantially increase the consumption of oxygen; as much as 40% of the cardiac output may be required to support the work of breathing. Infusions of inotropic medications inherently increase myocardial oxygen consumption. The increase is associated with the excess energy needed to increase the contractile force of the myocardial tissue, as well as the associated increase in heart rate caused by most catecholamines. In addition, the use of vasopressor medications may further increase myocardial oxygen consumption secondary to the additional energy needed to pump against the increased vascular resistance. Phosphodiesterase III inhibitors such as milrinone and amrinone increase the contractility without chronotropic or alpha-adrenergic effects. However, myocardial oxygen consumption will still increase in response to the additional myocardial work.

In contrast, several clinical conditions and medical interventions may result in a decrease in oxygen consumption. For example, the use of sedation and neuromuscular blockade may result in decreased muscular activity, decreased agitation, and inhibition of catecholamine production thereby decreasing the consumption of oxygen. In addition, given that the brain is one of the most metabolically demanding organs, any condition that results in significantly diminished brain activity will be associated with dramatically decreased oxygen consumption. Barbiturate-induced coma to treat brain injury or status epilepticus represents one such example. Brain death is perhaps the most extreme example. Similarly, hypothermia globally decreases the metabolic demands of the body including the brain, and therefore, may be associated with decreased oxygen consumption. This effect of hypothermia is used clinically to reduce the oxygen needs of the body in certain settings such as during cardiac surgery or following cardiac arrest. Additionally, the implementation of mechanical ventilation in the setting of respiratory distress can be used to substantially decrease the consumption of oxygen. In fact, the need to decrease oxygen demand is an indication for the use mechanical ventilation in the treatment of shock.

OXYGEN EXTRACTION

The oxygen extraction ratio (O_2ER) is the fraction of the arterial oxygen content that is consumed as the blood traverses the organ or tissue. It is determined by dividing the difference of the arterial and venous oxygen content by the arterial oxygen content:

$$O_2ER = (CaO_2 - CvO_2) / CaO_2$$

The normal O_2ER is only 0.2–0.3 indicating a significant excess of oxygen being delivered to the tissues. This excess allows for a cushion should oxygen delivery be compromised, thereby, minimizing the need for anaerobic metabolism. The oxygen extraction ratio varies widely with differences in the basal metabolic activities of different tissues (Table 2-1). Organs with higher metabolic demand will consume more oxygen. Consequently, the venous oxygen content in these tissues will be lower, and they will have higher oxygen extraction ratios.

The oxygen saturation, and hence the oxygen content, of the coronary venous blood is the lowest in the body, i.e., the myocardial oxygen extraction ratio is very high (~0.6). As such, there is not much ability to increase the oxygen extraction during conditions of reduced supply. This makes the myocardial tissue vulnerable to ischemia. The brain is also characterized by high metabolic demands thereby creating a high oxygen extraction ratio. The adequacy of oxygen delivery to the brain has been evaluated by measuring the venous saturation of the blood in the jugular bulb. Other organs such as the skin and the intestinal tract have relatively low oxygen demands. In conditions of compromised oxygen delivery, blood flow is shunted away from these tissues and reserved for the more integral organs. This process is usually well tolerated, but may be conducive to tissue ischemia in certain circumstances. For example, the use of vasoactive infusions such as epinephrine or norepinephrine during conditions

The normal oxygen extraction ratio is 0.2–0.3, indicating a significant excess capacity of oxygen being delivered under normal circumstances.

of compromised oxygen delivery, may increase the vasoconstriction of the intestinal vessels and further decrease the oxygen delivery to these tissues. The relative ischemia of the intestinal tissue has been considered to be one of the precipitating factors for the systemic inflammatory response syndrome. According to this theory, the relative ischemia compromises the integrity of the intestinal epithelium allowing bacteria and bacterial products to gain access to the circulation and activate the inflammatory response. This is the rationale for the use of gastric tonometry as a surrogate for splanchnic oxygen delivery.

In addition to variations among individual organs, oxygen extraction will vary with changes in the clinical condition. For example, in the setting of septic shock, the oxygen extraction ratio may be low, high, or normal depending on the balance of oxygen demand, supply, and utilization. Additionally, as described above, in conditions that block the utilization of oxygen such as cyanide poisoning, the oxygen extraction ratio will appear low to normal despite hypoxia at the tissue level.

ASSESSMENT OF OXYGEN DELIVERY/OXYGEN CONSUMPTION

The clinical evaluation of the match between oxygen delivery and oxygen consumption is integral to the practice of pediatric critical care medicine. Clinical signs of poor cardiac output such as poor peripheral perfusion, tachycardia, or altered mental status must be considered. Cyanosis or extreme pallor may indicate decreased oxygen arterial content, the first by deficient oxygen hemoglobin saturation, the second by a decrease in the concentration of hemoglobin. The clinical evaluation of end-organ delivery of oxygen is quickly performed by assessment of the level of consciousness and urine output. The use of central venous oxygen saturation to estimate the adequacy of oxygen delivery has been discussed earlier, as well as the use of pulmonary artery catheters. However, the rapid physical exam performed in real time by a trained clinician is still the most useful tool in estimating the adequacy of oxygen transport. This is the basic premise of the Pediatric Advanced Life Support (PALS) course established by the American Heart Association.

The significant components of CaO_2 , the hemoglobin and the oxygen saturation, should obviously be measured whenever oxygen delivery is suspected to be inadequate. However, the laboratory studies relevant to cardiac output are less obvious. Electrolytes that impact cardiac contractility should be evaluated and include the levels of ionized calcium, potassium and magnesium. Arterial blood pH should be measured as severe acidosis can negatively affect contractility. As described earlier, anaerobic metabolism will lead to an elevation in the hydrogen proton concentration in the blood and will be manifested as metabolic acidosis and a rising base deficit. In addition, the Krebs cycle will stop in the oxygen starved tissues because the metabolites can no longer exit the cycle by proceeding to the cytochrome complex or the electron chain transport. As such, pyruvate will be converted to lactate, which will leak out of the intracellular space and result in elevated levels of lactate in the blood. Elevation of blood lactate in the presence of acidosis should alert the clinician to the likelihood of tissue hypoxia. Assuming that there are no other processes affecting the clearance of lactate, a reduction in lactate levels can be used as indirect evidence of improving oxygen delivery. As a result of this, lactate levels are frequently used as indicators of adequate or inadequate resuscitation. Unfortunately, simple laboratory tests are either late (hours to days) manifestations of inadequate blood flow and oxygen delivery (creatinine) or too nonspecific (BUN, transaminases) to be meaningful surrogates for oxygen consumption. Two relatively newer tests that can provide some insight into the cardiac function component of oxygen delivery are troponin levels and brain natriuretic peptide (BNP). Troponin is increased in the setting of cardiac ischemia but it is also elevated in cardiac trauma, following CPR and cardiac surgery. BNP is a reflection of atrial stretch and excessive preload which is a common coexistent finding in the presence of decreased cardiac function, but BNP is not itself an estimate of oxygen delivery or consumption.

The clinical evaluation of the match between oxygen delivery and oxygen consumption is integral to the practice of pediatric critical care medicine. Clinical signs of poor cardiac output such as poor peripheral perfusion, tachycardia, or altered mental status must be considered.

SUMMARY

The physiology of oxygen transport and its manipulation has a central role in the management of the critically ill patient. In this chapter, the tools used to assess oxygen delivery and oxygen consumption have been reviewed. Oxygen delivery is primarily dependent on the hemoglobin concentration, the arterial oxygenation and the cardiac output. The cardiac output is determined by the combined effects of preload, afterload, contractility and heart rate. Oxygen consumption in critically ill infants and children is influenced by many factors. A clear understanding of these is essential to the practice of pediatric critical care medicine.

REVIEW QUESTIONS

- Which statement is correct regarding the biochemical consequences of tissue hypoxia?**
 - Anaerobic metabolism is as equally efficient as aerobic metabolism in producing energy, but produces acid byproducts such as lactate.
 - Elevated lactate levels can be readily buffered by the addition of sodium bicarbonate.
 - Lactate is produced as a byproduct of anaerobic glycolysis during tissue hypoxia, but may also be produced in the absence of tissue hypoxia.
 - Restoring tissue perfusion and oxygenation results in lactate being reconverted into glucose in the liver.
 - The reduction in pH seen during states of tissue hypoxia is primarily due to the accumulation of lactate.
- A 12 year old 50 kg male is admitted after correction of severe scoliosis via a combined anterior and posterior approach. Upon admission, he is mildly tachycardic to 108 bpm, normotensive and well perfused. His oxygen saturation is 99%, PaO₂ is 198 mm Hg on 30% FiO₂ and his hemoglobin is 10.9 g/dL. You are called to the bedside due to a steady increase in chest tube output. He is now tachycardic to 149 bpm, has a blood pressure of 96/58 mm Hg and is cool distally. His oxygen saturation is 87% and PaO₂ is 65 mm Hg on 30% FiO₂. Current hemoglobin is 7.6 g/dL. What percent decrease in arterial oxygen content has occurred?**
 - 10%
 - 15%
 - 30%
 - 40%
 - 50%
- The above child is ordered a transfusion of packed red blood cells. While awaiting transfusion, he is placed on 100% FiO₂ resulting in an oxygen saturation of 99% and PaO₂ of 265 mm Hg. Which of the following is true regarding oxygen administration in this patient awaiting transfusion?**
 - Administration of oxygen will increase the arterial oxygen content from 9 to 11 mL/dL.
 - Administration of oxygen will increase the arterial oxygen content from 9 to 13 mL/dL.
 - Administration of oxygen will increase the arterial oxygen content from 10 to 12 mL/dL.
 - Administration of oxygen will increase the arterial oxygen content from 10 to 13 mL/dL.
 - Administration of oxygen will increase the arterial oxygen content from 10 to 14 mL/dL.
- Which of the following is true regarding oxygen-hemoglobin dissociation curve?**
 - Fetal hemoglobin increases oxyhemoglobin dissociation in the capillary circulation thereby making more oxygen available at the tissue level.
 - Hypoxemia increases oxyhemoglobin dissociation in the capillary circulation thereby making more oxygen available at the tissue level.
 - Increased temperature decreases oxyhemoglobin dissociation in the capillary circulation thereby making less oxygen available at the tissue level.
 - Severe acidosis decreases oxyhemoglobin dissociation in the capillary circulation thereby making less oxygen available at the tissue level.
 - Severe alkalosis decreases oxyhemoglobin dissociation in the capillary circulation thereby making more oxygen available at the tissue level.

5. Which is the following is a true statement regarding physiologic determinants of oxygen delivery?
- Arterial oxygen content can be maximized, yet a state of decreased oxygen delivery may persist.
 - Oxygen delivery is primarily determined by the rate of oxygen extraction.
 - The determinants of cardiac output and the determinants of arterial oxygen are different and have limited interdependence.
 - The fractional inspired oxygen content impacts arterial oxygen content, and therefore, oxygen delivery greater than the hemoglobin concentration.
 - Therapies aimed at improving oxygen delivery are primarily related to maintaining alveolar oxygenation.
6. Which of the following is most correctly matched?
- Dobutamine 5 mcg/kg/min – decreased myocardial oxygen consumption
 - Low oxygen delivery – increased oxygen extraction
 - Mitochondrial poisoning – increased oxygen extraction
 - Neuromuscular blockade – increased oxygen consumption
 - Seizure – decreased oxygen consumption
7. Which statement best reflects the ability of the body to extract oxygen?
- Baseline oxygen extraction varies among individual organs, but remains constant during changes in clinical conditions.
 - High oxygen extraction is reflected in a lower venous oxygen content.
 - The normal oxygen extraction ratio (O_2ER) is approximately 50% of the oxygen being delivered to the tissues. The excess in delivered oxygen allows for an increase during stress states, thereby, minimizing the need for anaerobic metabolism.
 - Organs with lower metabolic demand will consume less oxygen and consequently, will have a lower venous oxygen content.
 - The oxygen extraction ratio (O_2ER) is determined by dividing the difference of the arterial and venous oxygen content by the cardiac output.
8. A 5 year old presents with pallor, a murmur, and a heart rate of 140 bpm. He is afebrile and his oxygen saturation via pulse oximetry is 97%. There is no history of acute blood loss and his mom explains that his symptoms have evolved over several weeks. Laboratory analysis reveals a white blood cell count of 12,300 cells/mL, hemoglobin of 4.5 g/dL, and a platelet count of 210,000/mL. His red blood cell indices are microcytic and hypochromic. His electrolytes are unremarkable except for a bicarbonate of 18 mmol/L. His arterial blood gas reveals pH 7.32, $PaCO_2$ 33 mm Hg, PaO_2 65 mm Hg, base deficit (-) 9, and an oxygen saturation of 97%. The most appropriate next course of action is which of the following?
- Transfuse 15 mL/kg of packed red blood cells over 2 h.
 - Transfuse 5 mL/kg packed red blood cells over 4 h and administer a dose of sodium bicarbonate.
 - Transfuse 5 mL/kg packed red blood cells over 4 h and begin iron supplementation and erythropoietin.
 - Transfuse 5 mL/kg of packed red blood cells over 4 h and begin supplemental oxygen.
 - Transfuse 15 mL/kg of packed red blood cells over 4 h and monitor for signs of pulmonary edema utilizing furosemide if necessary.
9. A 14 year old multiple trauma victim with adult respiratory distress syndrome is admitted to the PICU. To optimize his care, you have placed an intravenous oximetric catheter with its tip in the superior vena cava to monitor venous oxygen saturation continuously. The patient is intubated, mechanically ventilated, and heavily sedated. His superior vena cava saturation has consistently been in the low 80 range, but has suddenly begun to decrease into the low 70s. His pulse oximeter is unchanged and continues to read 99%. His vital signs are stable except for a fever spike up to 39.8° Celsius and a 5–10 beat increase in his heart rate. He remains heavily sedated on a midazolam infusion. The most likely explanation for his sudden decrease in superior vena cava saturation is which of the following?
- Acute occult blood loss
 - Decreased cardiac output
 - Fever
 - Migration of the catheter into the right atrium
 - Subclinical seizure
10. Hypoxemia is detected by special nerve chemical receptors located in the carotid and aortic bodies. When these chemoreceptors are triggered by hypoxemia ($PaO_2 < 60$ mm Hg, corresponding to $SaO_2 < 93\%$), which of the following physiologic responses ensue?
- Stimulation of the respiratory area of the medulla resulting in a decrease in minute ventilation, respiratory pauses, and potentially apnea.
 - Stimulation of the respiratory area of the medulla resulting in an increase in minute ventilation, a higher alveolar oxygen concentration (PAO_2), and ultimately, an increase in the arterial oxygen content.
 - Stimulation of the vasomotor center of the brainstem leading to decreased sympathetic tone and bradycardia.
 - Stimulation of the vasomotor center of the brainstem resulting in decreased sympathetic tone, decreased metabolic rate, and decreased oxygen consumption.
 - Stimulation of the vasomotor center of the brainstem resulting in increased sympathetic tone, increased systemic vascular resistance, and decreased cardiac output.

ANSWERS

- | | |
|------|-------|
| 1. C | 6. B |
| 2. D | 7. B |
| 3. A | 8. D |
| 4. B | 9. C |
| 5. A | 10. B |

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