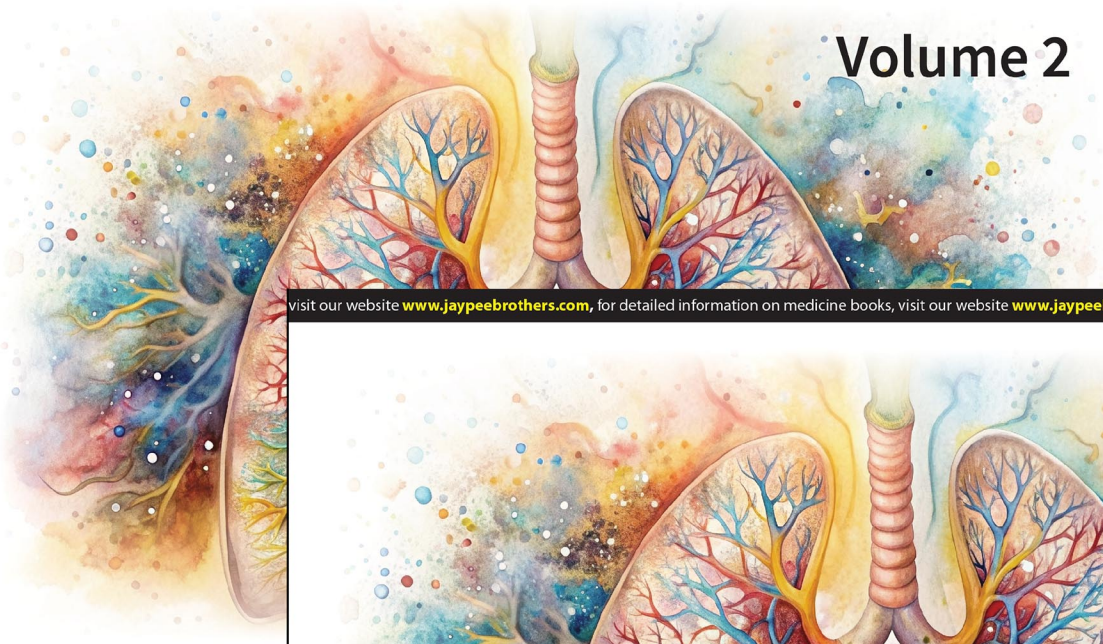

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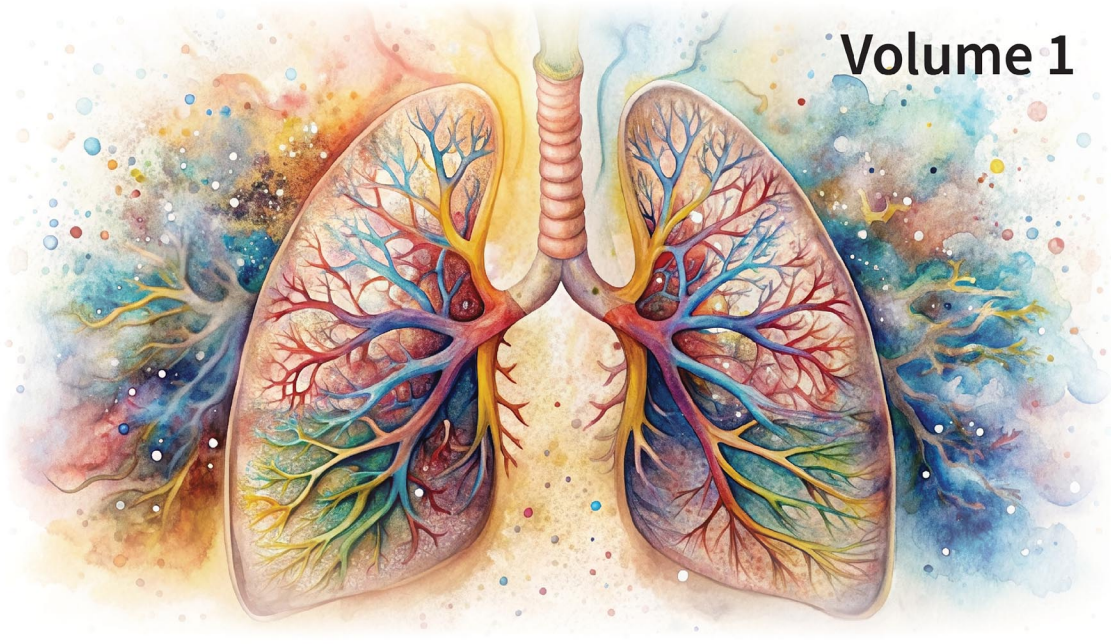

Textbook of Pulmonary & Critical Care Medicine

Editor-in-Chief
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Forewords
JS Guleria
Atul C Mehta

3rd Edition

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Oxygen Transport and Tissue Oxygenation

CHAPTER 7

Surinder K Jindal

INTRODUCTION

The delivery of oxygen to the tissues for cellular metabolism is a three-step process: (1) Oxygen consumption ($\dot{V}O_2$) in the lungs (i.e., external respiration), (2) oxygen transport through the blood to the tissues, (3) diffusion of oxygen from the capillaries to the cells (i.e., internal respiration or tissue oxygenation).

OXYGEN TRANSPORT

Oxygen is transported in the blood bound to hemoglobin (Hb), a protein comprised of four subunits, two alpha subunits, and two beta subunits. Each Hb molecule can bind four oxygen molecules, forming oxyhemoglobin. The quantity of oxygen bound to Hb is dependent on the partial pressure of oxygen. The sigmoidal S-shape curve representing the content of oxygen in blood at various partial pressures of oxygen is called the oxygen–dissociation curve **(Fig. 1)**. There is a steep slope at low partial pressures of oxygen and a more gradual slope at higher partial pressures. The affinity of Hb for oxygen results in a shift in the oxygen–hemoglobin dissociation curve. An increase in oxygen affinity results in the curve shifting to the left, whereas a decrease in oxygen affinity results in the curve shifting to the right **(Fig. 1)**. The affinity of Hb for oxygen is affected by various factors **(Table 1)**.

Tissue oxygenation is the final step in the *oxygen cascade*; it occurs when oxygen molecules delivered to the tissues enter the cells. The process of diffusion from the capillaries to the tissues is sometimes called *internal respiration*. The oxygen is consumed by the tissues for energy production (aerobic respiration) which is a far more effective method than the anaerobic glycolysis.

The main determinant of tissue oxygenation is a balance between oxygen delivery ($\dot{D}O_2$) and $\dot{V}O_2$. An imbalance between the two results in oxygen debt. Both $\dot{D}O_2$ and $\dot{V}O_2$ depend upon several factors which can be differently influenced in health and disease **(Box 1 and Table 2)**.

OXYGEN DELIVERY

Oxygen delivery constitutes the total amount of oxygen delivered to the whole body. Tissue $\dot{D}O_2$ depends on two factors: (1) Arterial O_2 content (CaO_2) and (2) cardiac output (Q), $\dot{D}O_2 = Q \times CaO_2$.

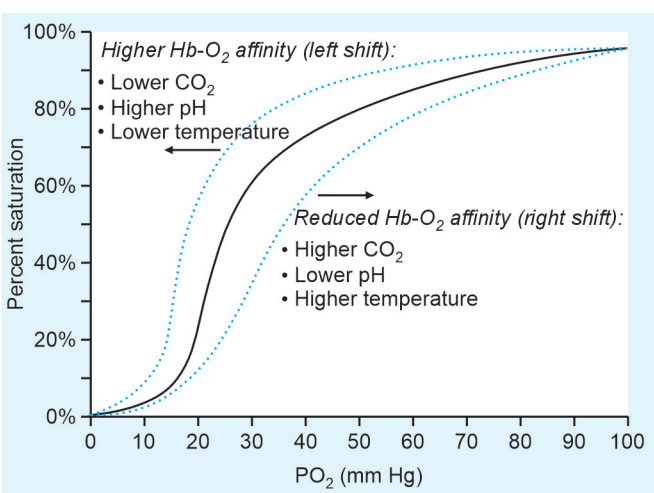

FIG. 1: Oxygen dissociation curve.

TABLE 1: Factors which affect the Hb affinity for oxygen.

Factor	Effect of increase	Effect of decreased level
• pH (Increased H^+/pCO_2)	• Affinity for O_2 increases (Bohr effect)	• Affinity for O_2 decreases (Bohr effect)
• 2,3-diphosphoglycerate (2,3-DPG)	• Decreases the Hb affinity	• Increases affinity
• Temperature	• Decreases the affinity	• Increases affinity

The normal range for $\dot{D}O_2$ is 520–570 mL/min/m^2 and under normal physiological conditions, $\dot{D}O_2$ is considerably in the excess of $\dot{V}O_2$ (110–160 mL/min/m^2). This "spare capacity" enables the body to cope with a fall in $\dot{D}O_2$ without initially compromising aerobic respiration.

Factors Influencing Oxygen Delivery

Arterial O_2 Content

Arterial O_2 content (CaO_2) is the total amount of O_2 present in blood, i.e., combined with Hb and dissolved in plasma.

$$CaO_2 = (1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)$$

The contribution of Hb is described by the first part of the equation. This relationship states that each gram of Hb will bind 1.34 mL of O_2, when it is fully saturated with oxygen. The SaO_2 is expressed as a fraction, not a percentage (i.e., 1.0 instead of 100%). Therefore, at a Hb level of 15 g/dL and an SaO_2 of 98%, the oxygen carried by Hb will be:

$$1.34 \times 15 \times 0.98 = 19.7 \text{ mL/100 mL.}$$

From the second part of the equation, one can infer that at a PaO_2 of 100 mm Hg, the expected concentration of dissolved O_2 in blood is 0.0031 × 100 = 0.3 mL/100 mL. Therefore, the total concentration of O_2 in arterial blood is 19.7 + 0.3 = 20 mL/100 mL. Thus, it is clear that CaO_2 primarily depends on Hb and SaO_2 and to a lesser extent on PaO_2.

BOX 1 Factors affecting $\dot{D}O_2$ and $\dot{V}O_2$.

Factors affecting $\dot{D}O_2$

- *Arterial O_2 content*:
  - Hemoglobin
  - Arterial oxygen saturation and PaO_2
- *Cardiac output, depends upon*:
  - Preload
  - Afterload
  - Cardiac contractility

Factors affecting $\dot{V}O_2$

- *Causes of decreased $\dot{V}O_2$*:
  - Decreased blood supply to tissues: Shock (cardiogenic/hypovolemic)
  - Cytotoxicity
  - Increased O_2 demand, e.g., sepsis, acute pancreatitis, burns
- *Causes of Increased $\dot{V}O_2$*:
  - Stress or tissue injury
  - Fever, tachypnea, shivering, and seizures

Cardiac Output

$\dot{D}O_2$ is directly related to changes in cardiac output, which is the product of heart rate and stroke volume. Any alteration in either of these two parameters alters the cardiac output. Stroke volume, the amount of blood ejected per beat is affected by the following factors:

- *Preload:* It is the load imposed on a muscle before the onset of contraction and is synonymous with the initial length (or stretch) of cardiac fibers. An increase in preload augments muscle length and leads to a more forceful cardiac contraction (Frank–Starling phenomenon). In fact, in the normal heart, the diastolic volume/preload is the principal force that governs the strength of ventricular contraction. This emphasizes the value of avoiding hypovolemia and correcting volume deficits promptly when they exist. The relationship between preload and cardiac output is, however, not linear and is also influenced by changes in ventricular compliance and geometry. Since ventricular end-diastolic volume is not easily measured at the bedside, end-diastolic pressure (EDP) and central venous pressure (CVP) are more commonly used as reflections of preload in clinical practice.
- *Afterload:* It is the sum of all forces opposing ventricular ejection. It is influenced by aortic and pulmonary arterial pressures, systemic and pulmonary vascular resistance, and compliance of ventricular muscle. As the determination of these forces is complex, systolic

TABLE 2: Normal values and equations of tissue oxygenation parameters.

Parameter	Equation	Normal range
Arterial O_2 content (CaO_2)	$(1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)$	20 mL/dL
Cardiac output (Q)	hr × sv	4–8 L/min
Cardiac index (CI)	Q/BSA	2.4–4.0 L/min/m^2
Oxygen delivery ($\dot{D}O_2$)	$Q \times 1.34 \times Hb \times SaO_2$	900–1,000 mL/min
Oxygen delivery index ($\dot{D}O_2$ index)	DO_2/BSA	520–570 mL/min/m^2
Oxygen consumption ($\dot{V}O_2$)	$Q \times 1.34 \times Hb \times (SaO_2 - SvO_2)$	180–280 mL/min/m^2
Oxygen consumption index ($\dot{V}O_2$ index)	VO_2/BSA	110–160 mL/min/m^2
Oxygen extraction ratio (O_2ER)	$(SaO_2 - SvO_2/SaO_2) \times 100$	20–30%

(BSA: body surface area; Hb: hemoglobin; hr: heart rate; PaO_2: partial pressure of O_2 in arterial blood; SaO_2: arterial O_2 saturation; SvO_2: mixed venous O_2 saturation; sv: stroke volume)

left ventricular pressure is usually used as a reasonable measure of afterload. In addition, since afterload is a transmural force, it is influenced by the pleural pressures at the surface of the heart. Positive pleural pressures can promote ventricular emptying by facilitating the inward displacement of the ventricular wall during systole, and this is one of the mechanisms by which noninvasive positive-pressure ventilation is beneficial in cardiogenic pulmonary edema.

- *Contractility:* It refers to the intrinsic contractile property of cardiac myocytes and is influenced by catecholamine levels, as well as extracellular calcium concentration. Cardiac contractility is measured indirectly by impedance cardiography and Doppler echocardiography.

The delivery of O_2 to the cells, i.e., the cellular O_2 supply is not equal to all cells although all arteries in the body carry virtually identical concentrations of O_2. This is because of the following factors:

- *Differences in regional blood flow:* The gatekeeper of blood supply to a capillary network is the local arteriole. Arterioles may dilate or constrict in response to various local and central regulatory factors. Local factors causing dilatation include hypoxia, increased CO_2, increased temperature, and decreased pH. The release of catecholamines is a central mechanism that attempts to preferentially distribute blood to vital organs when $\dot{D}O_2$ is compromised. When the body is confronted with a declining $\dot{D}O_2$, both central and local mechanisms are stimulated. In the short term, central effects predominate while if the O_2 shortage persists, local effects override and generalized vasodilatation occurs.
- *Differences in capillary architecture:* Some cells are simply closer to capillaries than others. Because movement of O_2 depends on pressure gradients, the cells farthest away from capillaries are most vulnerable to hypoxia. In addition, many capillaries are normally closed and open only when perfusion to that particular region increases. For example, an actively contracting muscle may have 10 times more open capillaries than a resting muscle.

OXYGEN CONSUMPTION

Oxygen consumption refers to the rate of uptake of O_2 by tissues from microcirculation. It is a product of the cardiac output and the difference in oxygen content between arterial and venous blood.

$\dot{V}O_2 = Q \times (CaO_2 - CvO_2)$ $\dot{V}O_2 = Q \times 1.34 \times Hb \times (SaO_2 - SvO_2)$

The normal range for $\dot{V}O_2$ is 110–160 mL/min/m^2.

Measurement of Oxygen Consumption

$\dot{V}O_2$ can be measured in three ways:

1. Using Fick's equation (as above). It requires the placement of a pulmonary artery catheter.
2. By measurement of inspired and expired minute ventilation (Vi and Ve) and of fractional concentrations of O_2 (FiO_2 and FeO_2) in the two samples. This is a noninvasive method but is relatively unreliable in mechanically ventilated patients on high FiO_2.
   $\dot{V}O_2 = (Vi \times FiO_2) - (Ve \times FeO_2)$
3. $\dot{V}O_2$ can also be measured directly with the help of a rebreathing spirometer system filled with oxygen; the expired CO_2 is absorbed from the system and any change in the volume of gas in the spirometer reflects the $\dot{V}O_2$.

Cellular O_2 utilization: Metabolic utilization of O_2 in cells occurs by the oxidation of pyruvic acid in the Krebs cycle. This series of reactions takes place in mitochondria and results in the production of 38 molecules of adenosine triphosphate (ATP). The availability of O_2 is crucial in the production of ATP from adenosine diphosphate (ADP) in the Krebs' cycle. The actual process of ATP formation is called oxidative phosphorylation as phosphate is added to ADP by using the energy from oxidation. In the absence of O_2, metabolism is less efficient and only 2 molecules of ATP are generated by the metabolism of glucose (anaerobic glycolysis). Furthermore, anaerobic metabolism results in the production of lactic acid, which may lead to systemic metabolic acidosis.

More than 90% of the body's $\dot{V}O_2$ is utilized by a single enzyme, cytochrome oxidase, during the process of oxidative phosphorylation, which generates ATP. This is the most efficient means of producing ATP, since a total of 38 molecules of ATP are generated per molecule of glucose. Aerobic cellular respiration depends on the efficient supply of oxygen to the mitochondria, which is a function of the coordinated interaction between the respiratory and circulatory systems. When oxygen supply is inadequate, anaerobic metabolism sets in and generates only 2 molecules of ATP per molecule of glucose. In addition H^+ ions are formed, which can lead to a systemic metabolic acidosis. Tissue oxygenation is often impaired in critically ill patients, who have poor cardiopulmonary reserve and optimizing $\dot{D}O_2$ to meet oxygen demand, has the potential to improve outcomes in these patients.

Calculated versus Measured Oxygen Consumption ($\dot{V}O_2$)

$\dot{V}O_2$ is usually derived from Fick's equation and not directly measured. The derivation is based on four measured variables: Cardiac output (Q), hemoglobin concentration (Hb), arterial O_2 saturation (SaO_2), and mixed venous O_2 saturation (SvO_2). Each of these measurements varies and their summed contribution can lead to considerable variability in the final calculated $\dot{V}O_2$. Therefore, to be considered a physiologically significant change, the calculated $\dot{V}O_2$ should change by at least 15%.

OXYGEN EXTRACTION RATIO

Oxygen extraction ratio (O_2ER) is the ratio of oxygen consumption to oxygen delivery ($\dot{V}O_2/\dot{D}O_2$) and reflects the fraction of O_2 delivered to the microcirculation that is taken up by the tissues. The O_2ER varies between different organs. For example, the brain has an O_2ER of 34% while exercising muscle can remove all O_2 from its microcirculation and thus have an O_2ER approaching 100%. Overall, the normal O_2ER is 20–30%. Thus, only a small fraction of the available O_2 delivered to the capillaries is taken up into the tissues. Oxygen extraction is adjustable, and in conditions where O_2 delivery is impaired, the O_2ER can increase up to 50–60%.

OXYGEN DELIVERY–OXYGEN CONSUMPTION CURVE

The relationship between $\dot{D}O_2$ and $\dot{V}O_2$ is described by the curve in **Figure 2**. As $\dot{D}O_2$ decreases below normal, the O_2ER increases proportionally to keep $\dot{V}O_2$ constant. When O_2ER reaches its maximum level (50–60%), further decreases in $\dot{D}O_2$ result in proportional decreases in $\dot{V}O_2$. Since under normal physiological conditions, $\dot{D}O_2$ is considerably in excess of the $\dot{V}O_2$, tissue oxygenation to a large extent is supply independent. However, when $\dot{D}O_2$ falls below a certain critical level, $\dot{V}O_2$ becomes supply dependent and this condition, in which cellular metabolism is limited by the supply of O_2, is called dysoxia. This *critical O_2 delivery point* (critical $\dot{D}O_2$) varies between 150 and 1,000 mL/min/m^2 in critically ill patients, though on an average it is approximately 300 mL/min/m^2. When $\dot{D}O_2$ falls below this level, tissue hypoxia ensues, blood lactate increases, and prognosis becomes poor. Thus, maintenance of $\dot{D}O_2$ in excess of the critical delivery point is crucial in the management of critically ill patients. This is particularly true when positive end-expiratory pressure (PEEP) is being used because PEEP may be associated with a fall in $\dot{D}O_2$ despite improvements in PaO_2 because of its effect on cardiac output.

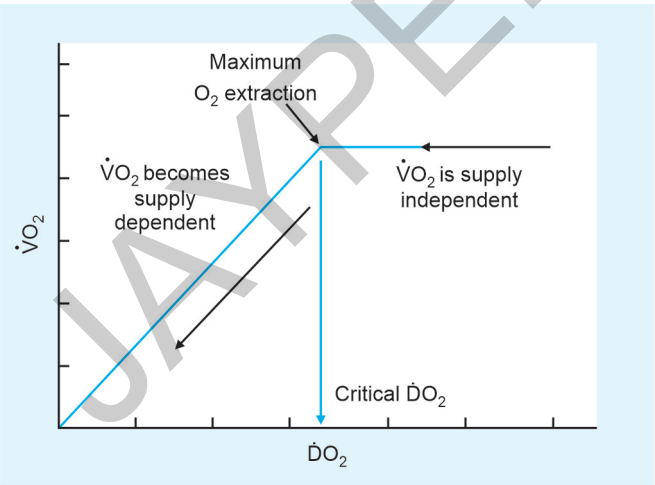

FIG. 2: Graph describing the relationship between oxygen delivery ($\dot{D}O_2$) and O_2 consumption ($\dot{V}O_2$). As $\dot{D}O_2$ decreases below normal, O_2 extraction increases proportionally to keep $\dot{V}O_2$ constant and therefore is "supply independent". When $\dot{D}O_2$ falls below a critical level, $\dot{V}O_2$ becomes "supply dependent".

Factors Influencing Oxygen Consumption

- *Causes of decreased $\dot{V}O_2$:*
  - *Decreased blood supply to tissues:* Shock (cardiogenic/hypovolemic).
  - *Cytotoxicity:* An intrinsic defect in O_2 utilization at the cellular level is seen in carbon monoxide and cyanide poisoning, as well as in sepsis.
  - *Increased O_2 demand:* This is seen in most critically ill patients with increased metabolic rates, e.g., acute pancreatitis and burns. It is noteworthy that tissue hypoxia in sepsis involves all the three mechanisms mentioned above: (1) Decreased blood supply as a result of redistribution of blood flow due to pathologic capillary dilatation and arteriovenous shunting, as well as microvascular occlusion due to platelet and fibrin microthrombi; (2) disruption of cellular metabolism by cytokines and free radicals; and (3) increased O_2 demand.
- *Causes of increased $\dot{V}O_2$:* Whenever stress or tissue injury occurs, there is an increase in metabolic rate and $\dot{V}O_2$. In normal subjects, exercise increases $\dot{V}O_2$, almost simultaneously with the onset of work. Most of this increase is accounted for by an increase in cardiac output. A relative hemoconcentration and therefore increased O_2 content may also occur with the high levels of exercise. The $\dot{V}O_2$ may increase 10–15-fold during exercise. In addition, O_2 extraction (*see above*) may also increase to as much as 80% of $\dot{V}O_2$ in order to meet the additional O_2 requirement. This is made possible by capillary dilatation and recruitment in exercising muscles.

Causes of increased $\dot{V}O_2$ in sick patients include fever, tachypnea, shivering, and seizures. In a very ill patient, even innocuous activities, such as chest physiotherapy, getting up or turning in bed, and tracheal suctioning, can increase $\dot{V}O_2$ and tilt the already precarious O_2 balance.

Oxygen Debt ($\dot{V}O_2$ Deficit)

Oxygen debt or $\dot{V}O_2$ deficit is the difference between the metabolic demand for O_2 and the actual $\dot{V}O_2$. As demand increases, $\dot{V}O_2$ must increase to preserve aerobic metabolism. This is met with by increasing $\dot{D}O_2$ either by physiological compensation, e.g., an increase in cardiac output or O_2ER, or by therapeutic interventions, such as intravenous fluids or inotropes. If this increase in $\dot{D}O_2$ is delayed, O_2 debt continues to grow and a stage is reached from where recovery is not possible. Studies of the O_2 debt after resuscitation from

hemorrhagic shock and in postoperative patients show a direct relationship between the magnitude of O_2 debt and the risk of multiorgan failure and death. This indicates that the early correction of $\dot{V}O_2$ deficits is warranted to limit the severity of tissue ischemia.

ASSESSMENT OF TISSUE OXYGENATION

Unlike hypoxemia which denotes a low PaO_2 and has standard normal and abnormal values, there are no normal values for tissue PO_2 and it cannot be routinely measured at the bedside. Tissue hypoxia is defined as abnormal O_2 utilization by cells and should be distinguished from other terms, such as hypoxic, anemic, histotoxic, and stagnant hypoxia, which can lead to but are not synonymous with tissue hypoxia. There are three ways to detect tissue hypoxia.

Clinical Assessment

Clinical examination should be the first step in assessing tissue oxygenation. A number of well-known signs (mental obtundation, oliguria, abnormal vital signs, delayed capillary refill) often indicate specific organ dysfunction as a sequel of tissue hypoxia. However, clinical signs are often insensitive as they occur late during the course of tissue hypoxia. Direct or indirect measurements of local tissue oxygenation of an organ suspected to suffer from hypoxia will facilitate the assessment. Local tissue oxygen probes have been used in critical care areas in some instances (e.g., brain).

Physiological Parameters

Mixed Venous O_2 Saturation (SvO_2)

Mixed venous blood represents blood returning from all the venous beds of the body, "mixed" together in the right ventricle. It is obtained from the distal end of the pulmonary artery with the help of a specialized pulmonary artery catheter, the tip of which emits infrared light and records light reflected back from Hb in circulating erythrocytes. This technique is called *reflectance spectrophotometry* (whereas pulse oximeters use *transmission spectrophotometry*). SvO_2 can also be measured intermittently by withdrawing blood from the catheter. In the proximal part of the pulmonary artery, blood from the two vena cavae and coronary sinus is not fully blended and therefore does not represent total body venous gas values. SvO_2 is a marker of the balance between whole body $\dot{D}O_2$ and O_2 demand and is normally between 65 and 75%; that is, O_2 demand is usually about 25–35% that of O_2 delivery.

Causes of Decreased SvO_2

- *Decrease in $\dot{D}O_2$*: This may occur due to hypovolemia, decreased cardiac output, low Hb, low PaO_2 and SaO_2.
- *Increase in O_2 demand*: Critical illness, sepsis, thyrotoxicosis, etc.

Causes of Increased SvO_2

- *Increased DO_2*: Increased cardiac output (e.g., exercise, use of inotropes), increased Hb (hypertransfusion).
- *Decrease in O_2 demand*: Deep sedation and paralysis in ventilated patients.
- *Decreased tissue O_2 utilization*: Cyanide and CO poisoning, sepsis.
- *Left-to-right shunts*: These can usually be diagnosed by an abnormal "step-up" of SvO_2 at the level of the defect as the pulmonary artery catheter is passed into the right atrium or ventricle.

A limitation of SvO_2 as a parameter for assessing tissue oxygenation is that normal or increased values do not always mean that tissue oxygenation is adequate. For example, in sepsis and CO poisoning, impaired tissue O_2 utilization results in a normal or high SvO_2. In addition, pathologic vasodilatation and increased cardiac output in sepsis also tend to increase SvO_2 even though tissue hypoxia is ongoing.

Dual Oximetry

By simultaneously measuring SaO_2 by pulse oximetry, one can get a continuous measurement of whole-body O_2 extraction, i.e., SaO_2 – SvO_2. This method is known as dual oximetry and its normal value is 20–30%.

$\dot{D}O_2/\dot{V}O_2$ Measurements

The measurement of changes in $\dot{V}O_2$ in response to changes in $\dot{D}O_2$ has been suggested as a sensitive method of determining whether tissue hypoxia exists. However, it entails multiple measurements at baseline and after various interventions carried out to increase $\dot{D}O_2$ (such as the administration of fluids and inotropes) and is therefore impractical.

Blood Lactate Level

Blood lactate levels increase when tissue hypoperfusion results in anaerobic metabolism. This is known as type A lactic acidosis and is different from type B or nonhypoxic causes of lactic acidosis, e.g., delayed clearance of lactate due to liver disease, thiamine deficiency (blocks pyruvate metabolism), and metabolic alkalosis (stimulates glycolysis). A blood lactate value >4 mmol/L is generally taken as abnormal. It is easy to measure and can be followed sequentially to assess prognosis as well as response to therapy. Recent studies indicate that blood lactate concentrations are a better prognostic indicator than oxygen-derived physiological variables.

Gastric Tonometry

Physiological variables of oxygen transport detailed above and lactate are the indices of global tissue oxygenation and cannot identify oxygen deficits in individual organs. This leads to the development of gastric tonometry to measure regional perfusion in the gut that employs a balloon in the stomach to measure intramucosal pH (pHi). Despite its

complexity, tonometry is a reasonably good prognostic indicator in critically ill patients.

Sublingual Capnography

Recently capnography in the sublingual area, a technique that is less invasive and easier to use, has been shown to yield tissue PCO_2 measurements that correlate with those obtained by gastric tonometry.

Nuclear Magnetic Resonance Spectrometry

This laboratory technique, not applicable at the bedside, can measure biochemical processes at the cellular level, e.g., levels of ATP, NADH, and cytochrome oxidase. Radionuclide imaging, such as positron emission tomography (PET) scanning, has emerged as an important tool to characterize tumor oxygenation to optimize and individualize therapy for cancers.

Most of the different parameters of in vivo oxygen measurements measure different things and differ in their sensitivity, accuracy, and repeatability. It has been proposed that a proper model that relates the various measurements to each other can serve as a powerful tool to assess tissue oxygenation. Unfortunately, such a functional model is not available as yet, whereas the measurement of SvO_2 requires the placement of a pulmonary arterial catheter.

SUMMARY

Tissue oxygenation involves the amount of oxygen delivered and subsequently consumed by the tissues for its metabolic needs. While delivery of oxygen depends upon the arterial oxygen content and cardiac output, its consumption by the tissues is more complex, varies for different organ tissues depending upon the normality of function. Failure to maintain oxygenation results in tissue hypoxia, cellular malfunction and death. Adequate of tissue oxygenation is assessed with measurements of both clinical and physiological parameters which have been discussed earlier in the chapter.

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Textbook of
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