Oxygen Delivery

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M. R. Pinsky et al. (eds.), *Hemodynamic Monitoring*, Lessons from the ICU,
https://doi.org/10.1007/978-3-319-69269-2_9

Learning Objectives

- Oxygen delivery and its determinants, how to measure them and how to interpret their possible derangements.
- Recognize oxygen delivery impairment before energy crisis and cellular damage develop.
- Recognize any impairment of energy production even if oxygen delivery is still adequate.
- "Supernormal" values theory and early goal-directed therapy (EGDT).

9.1 Introduction

Oxygen plays an essential role in aerobic life, acting as final acceptor of electrons in mitochondria from which energy, as ATP, is supplied to the whole organism. We may recognize three primary essential steps for oxygen utilization: first, the transport of oxygen-rich gas mixture from the ambient to the lung by ventilation and then its transfer from alveoli to blood; second, the transport of oxygenated blood to tissues; and, third, oxygen reduction to water in mitochondria. Oxygen movement from inspired gas toward mitochondria is possible thanks to pressure gradients: oxygen partial pressure is indeed 150 mmHg in the inspired gas and between 4 and 25 mmHg in its final destination, the mitochondria. After the oxygen has been delivered to tissues, the mixed venous blood returns to alveoli, and another cycle of oxygen transport and utilization begins. Mixed venous blood contains an amount of oxygen that represents oxygen that has been delivered but not consumed and can be considered as a sort of reserve. Although the term oxygen transport, strictly speaking, should refer to all the processes through which oxygen is transferred from inhaled gas to the final place of utilization, in the intensive care literature, it usually refers only to the hemodynamic phase. In this chapter, we will analyze primarily the hemodynamic phase of oxygen transport, and we will give some hints about oxygen utilization. It should not be forgotten, indeed, that in several conditions which may be common in intensive care patients, primarily sepsis and septic shock, the real problem is not only in the hemodynamic phase of oxygen delivery but also the oxygen utilization. This step relates to all the processes occurring in mitochondria where oxygen, acting as final acceptor of the electron cascade, makes possible the high levels of aerobic energy production.

9.2 Oxygen Transport

Oxygen transfer from lung to blood requires an adequate ventilation-perfusion ratio of terminal lung units. Ventilation is the process that provides fresh oxygen in an amount equal to the oxygen that is extracted from blood. Once in the blood, oxygen combines immediately to hemoglobin, and only a small amount of it remains in blood in a dissolved form. These two forms of oxygen transport, the dissolved one (measured as oxygen partial pressure, PO_2) and the combined one (measured as hemoglobin saturation, SO_2), together represent the total oxygen blood content, and their relationship is best described by hemoglobin dissociation curve.

9.2.1 Oxygen Bound to Hemoglobin

Before analyzing oxygen dissociation curve, it is necessary to know which is the maximum capability of hemoglobin to carry oxygen. At a hypothetical hemoglobin saturation of 100%, each mole of hemoglobin is able to carry four moles of oxygen. Given a molecular weight of hemoglobin of 64,500 Da, corresponding to a molar weight of 64,500 g, the total oxygen bound at 0 °C should be 22.4 L of oxygen for each hemoglobin mole equal to 89.6 oxygen liters in total [1]. In the Eq. 9.1, k represents the volume of oxygen that is transported by a single gram of completely saturated hemoglobin and is referred as hemoglobin carrying capacity.

$$k = \frac{89,600\,\mathrm{L}}{64,500\,\mathrm{g}} = 1.389\,\mathrm{mL/g} \tag{9.1}$$

The hemoglobin carrying capacity is 1.39 mL/g; this means that each gram of completely saturated hemoglobin is able to bind 1.39 mL of oxygen. Surprisingly, however, the literature provides different coefficients, ranging from 1.32 to 1.39, which is due to the different molecular weights that are attributed to the hemoglobin molecule as a result of the existence of several hemoglobin subtypes with their own molecular weights. The amount of oxygen carried by hemoglobin is easily computed using Eq. 9.2.

$$\mathrm{cHbO_2}\left(\mathrm{mL/dL}\right) = 1.39 \times \mathrm{Hb} \times \mathrm{SO_2} \tag{9.2}$$

The hemoglobin oxygen binding capacity depends on the possible structural changes that the hemoglobin molecules undergo in different conditions. This hemoglobin behavior is graphically explained by hemoglobin dissociation curve (Fig. 9.1). The sigmoid shape of the curve comes from changes in protein structure caused by progressive oxygen binding as the more oxygen is bound by the hemoglobin, the more hemoglobin affinity for oxygen increases [2]. This is true until hemoglobin has reached its maximum binding capacity that corresponds to the plateau part of the curve. At this point even big changes in blood PO_2 will produce only a small difference in oxygen saturation. There are many other factors that affect hemoglobin affinity for oxygen determining a shift of the curve toward the right or the left (i.e., decreasing or increasing its oxygen affinity). These factors include pH, temperature, carbon dioxide (CO_2) tension, and the concentration of 2,3-diphosphoglycerate. In the presence of low concentration of 2,3-DPG, lower CO_2 tension, high pH levels, and low temperature, the hemoglobin curve shift toward the left. This phenomenon is translated in a reduction in hemoglobin affinity for oxygen and an increased oxygen dissociation. In the opposite conditions (high 2,3-DPG, higher CO_2, low pH, and high temperature), the curve will shift to the right. The value that better describes this behavior is the P_{50} which represents the partial oxygen pressure at which the hemoglobin saturation is 50%. For example, if P_{50} increases from its normal value (26 mmHg in standard condition, i.e., pH 7,4, $PaCO_2$ 40 mmHg, 37 °C), the Hb dissociation curve shifts to the left, meaning that in order to obtain the same oxygen saturation of 50%, oxygen partial pressure must increase. These changes in hemoglobin oxygen affinity produce relevant consequences both on the arterial side, where oxygen is loaded and CO_2 is released, and on the capillary side, where oxygen is delivered and CO_2 is charged.

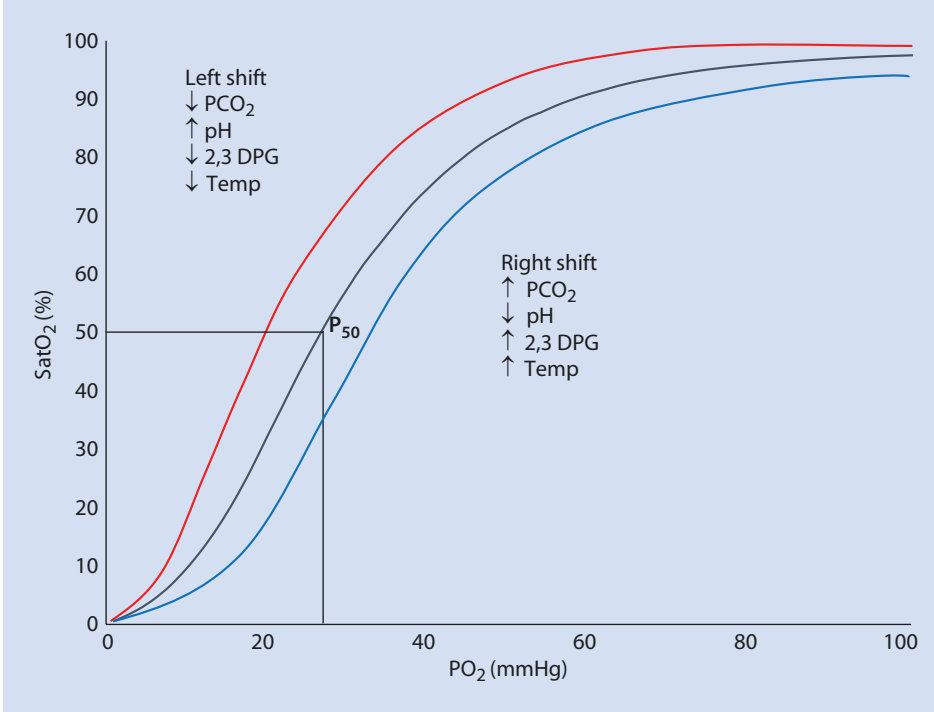


Fig. 9.1 Hemoglobin dissociation curve. The table displays an arterial hemoglobin dissociation curve at PCO_2 40 mmHg, pH 7.4, normal values of 2,3-DPG (5 mmol/L circa), and blood temperature 37 °C (black line). An increase in PCO_2, 2,3-DPG, or temperature or a decrease in pH produces a shift of the curve to the right (blue line). A decrease in PCO_2, 2,3-DPG, or temperature or an increase in pH produces a shift of the curve to the left (blue line)

The sigmoid shape of the curve and its affinity has been extensively studied in the 1970s, and several equations are available in order to compute hemoglobin oxygen saturation starting from oxygen partial pressure and correcting for pH, base excess, temperature, and PCO_2 [3]. The best known of these equations is the one developed by Kelman in 1966 [4]: this equation uses seven different coefficients in order to generate a curve. Most of these models, however, have intrinsic biases coming from the fact that they have been built not considering the possible presence of "abnormal" types of hemoglobin, such as methemoglobin, sulfhemoglobin, and fetal hemoglobin. Furthermore, their reliability decreases at low PO_2 levels and with most of the conditions that may cause a shift in the curve position. All these scenarios are quite common in clinical practice while referring to critical care patients and even more common while analyzing different kind of blood such as the arterial and the venous one. This means that results provided by different authors may be very similar when regarding to arterial blood, but great discrepancy may be observed when these equations are used to compute venous saturation. This problem comes from the fact that every single body district has his own hemoglobin dissociation curve: in other words, each given PO_2 corresponds to a hemoglobin saturation in each blood compartment. Therefore, when there is the need to compute other variables (i.e., oxygen content) starting from saturation, it is far better to rely on saturation measurements instead of computed ones [3].

9.2.2 Dissolved Oxygen

A small part of the oxygen transported by the blood is dissolved both in plasma and in red cells. The concentration of oxygen present as molecular oxygen unbound in blood, according to Henry's law of gases, depends on the partial pressure of oxygen in the gas phase.

$$C = k \times P \tag{9.3}$$

where C is gas dissolved concentration, P is gas partial pressure in gas phase, and k is a fixed constant that represents the solubility for each gas, temperature, and solvent. The equilibrium is reached when an equal number of oxygen molecules go from gas to blood and vice versa. Talking about oxygen and blood, at a body temperature of 37 °C, oxygen solubility coefficient equals to 0.00314 $mL \cdot dL^{-1} \cdot mmHg^{-1}$; this means that each mmHg of PO_2 corresponds to 0.003 mL of oxygen for each deciliter of blood.

Therefore, the amount of oxygen dissolved in blood (csO_2) is

$$csO_2\left(mL/dL\right) = 0.003 \times PaO_2 \tag{9.4}$$

Considering a normal PaO_2 of 100 mmHg, the amount of oxygen dissolved in the arterial blood will be 0.3 mL/dL, a volume that represents only 1.5% of the total arterial oxygen content, and that could reasonably be negligible in clinical calculations.

9.2.3 Oxygen Total Content

After this brief discussion, we are able to talk about oxygen blood content in its totality as the sum of oxygen transported by hemoglobin and free blood oxygen:

$$cO_2 = cHbO_2 + csO_2 \tag{9.5}$$

$$cO_2\left(mL/dL\right) = 1.39 \times Hb \times SO_2 + 0.003 \times PaO_2 \tag{9.6}$$

Normal arterial oxygen content value (cO_2), considering a pH equal to 7.4, a temperature of 37 °C, base excess (BE) equal to zero, a PO_2 of 100 mmHg, and Hb of 14 mL/dL, is about 20 mL/dL.

9.3 Blood Oxygen Measurement Techniques

Blood gas analysis represents a fundamental tool in clinical practice. It is an accessible, reliable, and rapid instrument that could guide the clinician in the management of most of the clinical settings starting from respiratory diseases going to hemodynamic impairment passing through metabolic issues. In this chapter, we will discuss oxygen-related parameters of blood gas analysis and pulse oximetry; these values can come from a direct measurement made by blood gas analyzer or from a computation (Table 9.1).

Table 9.1 Blood gas analyzer parameters DO_2 related

Parameter	Method
PO_2 (mmHg)	Measured (polarography)
HHb (g/dL)	Measured (spectral analysis)
O_2Hb (g/dL)	Measured (spectral analysis)
COHb (g/dL)	Measured (spectral analysis)
MetHb (g/dL)	Measured (spectral analysis)
tHb (g/dL)	Computed from the above values
HHb (%)	*HHb/tHb*100*
COHb (%)	*COHb/tHb*100*
MetHb (%)	*MetHb/tHb*100*
SO_2 (%)	$O_2Hb/(O_2Hb + HHb)$ (Eq. 9.7)
O_2Hb (%)	*O_2Hb/tHb*100*
cSO_2 (%)	Computed from PO_2 and corrected for PCO2, BE, and pH (see text for details)

In this table we briefly summarize blood gas analysis parameters related to DO_2 and how they are obtained. Note that there are three ways to compute $cHbO_2$: 1,39*Hb*SO_2 (1); 1,39*Hb*O_2Hb% (2); 1,39*Hb*cSO_2 (3). The reliability of the values obtained varies depending on the clinical condition, but we recommend not to use the third one (see text for details)

PO_2 oxygen partial pressure, *HHb* deoxyhemoglobin, *O_2Hb* oxyhemoglobin, *COHb* carboxyhemoglobin, *MetHb* methemoglobin, *tHb* total hemoglobin, *SO_2* hemoglobin oxygen saturation, *cSO_2* computed hemoglobin oxygen saturation, *BE* base excess

9.3.1 Oxygen Blood Partial Pressure (Polarography)

This technique was firstly described by Clark in 1956 [5]. Clark's sensor, using amperometry principles, is able to quantify oxygen concentration in biological fluids. The system can be simplified as composed by an anode, a cathode, and an oxygen-permeable membrane between the sample and the electrolyte solution. Thanks to the oxygen-permeable membrane, the oxygen concentration quickly equilibrates between electrolyte solution and the sample, and when a potential difference is applied to the conductor, the electricity current that passes through the system will be directly proportional to the oxygen concentration of the system. Many factors regarding the collection and conservation of blood samples could affect the accuracy of the measurement such as temperature, analysis delay, and even syringe type. Therefore, attention to the pre-analytic phase is needed in order to maintain this measurement accuracy.

9.3.2 Oxygen Blood Saturation ($SatO_2$)

Modern blood gas analyzer measures Hb oxygen saturation using spectral analysis of the hemoglobin released from a sample of hemolyzed arterial blood. Indeed, using dedicated wavelengths for different hemoglobin species (oxyhemoglobin, HbO_2; reduced hemoglo-

bin, HHb; carboxyhemoglobin, COHb; and methemoglobin, MetHb), modern blood gas analyzer is able to measure total hemoglobin (tHb), (Eq. 9.7).

$$\mathrm{tHb} = \mathrm{HHb} + \mathrm{O_2Hb} + \mathrm{COHb} + \mathrm{MetHb} \tag{9.7}$$

After the machine has measured the concentrations of hemoglobin subtypes, it gives three values related to hemoglobin oxygen saturation (HbO_2, SO_2, and cSO_2) using the following equations (Table 9.1).

$$\mathrm{HbO_2}(\%) = \frac{\mathrm{cHbO_2}}{\mathrm{HHb} + \mathrm{O_2Hb} + \mathrm{COHb} + \mathrm{MetHb}} \tag{9.8}$$

$$\mathrm{SO_2}(\%) = \frac{\mathrm{cHbO_2}}{\mathrm{cHbO_2} + \mathrm{cHHb}} \tag{9.9}$$

Or:

$$\mathrm{SO_2}(\%) = \frac{\mathrm{cHbO_2}}{\mathrm{tHb} - (\mathrm{COHb} + \mathrm{MetHb})} \tag{9.10}$$

The last value is computed oxygen saturation (cSO2). This value comes (as previously discussed) from one of the available equations that compute hemoglobin oxygen saturation as a function of PO_2, pH, base excess, temperature, and PCO_2 [3].

It must be noted that among all the detected hemoglobin species, COHb and MetHb are not involved in oxygen transport as they are not able to bind oxygen. In normal conditions, considering a negligible amount of COHb and MetHb, HbO_2 and SO_2 values should overlap. However, in some pathological conditions (e.g., carbon oxide intoxication), HbO_2 and SO_2 will be significantly different. In this particular condition, a patient may have a normal SO_2 (or a SpO_2) and arterial oxygen partial pressure (PaO_2), but the effective oxygen saturation may be extremely low. This condition is brought by a very low value of HbO_2 and high levels of COHb.

9.3.3 Pulse Oximetry (SpO_2)

Pulse oximetry is a noninvasive and simple technique that allows, using spectral analysis, continuous measurement of hemoglobin oxygen saturation at the bedside. The two wavelengths commonly used are at 660 nm and at 940 nm. These two different wavelengths are able to distinguish between reduced hemoglobin and oxyhemoglobin, as the first one adsorbs the first wavelength (660 nm) ten times more than O_2Hb, while the opposite happens with the 940 nm wavelength. The pulse oximetry probe emits these two different wavelengths through the cutaneous vascular bed, and the system analyzes the pulsatile characteristics of arterial blood flow neglecting all the background stationary signals coming from tissues, venous blood, and the non-pulsatile arterial blood. A limitation of the traditional two wavelengths pulse oximetry is the capability of measuring only O_2Hb and HHb, assuming a blood concentration of COHb and MetHb of zero. In the presence of these two altered hemoglobin forms, SpO_2 becomes less reliable as COHb causes a falsely high level of SpO_2, and MetHb in significant concentrations forces SpO_2 result toward 85% regardless of real hemoglobin saturation [6]. Some modern pulse oximeters, using a more wave lengths, are able to measure both COHb and MetHb [7].

9.4 Cardiac Output

Once oxygen has been transferred to the blood, bound or unbound to hemoglobin, the cardiocirculatory function is of crucial importance to the delivery of oxygen to the peripheral tissues. Cardiac output (CO) represents the volume of blood that is ejected by the heart each minute and is generally measured as the product between heart rate (HR) and stroke volume (SV):

$$\mathrm{CO}\left(\mathrm{L}/\mathrm{min}\right) = \mathrm{HR} \times \mathrm{SV} \tag{9.11}$$

Cardiac output is the most important determinant of oxygen delivery, and its modulation represents the best compensatory mechanism in bioenergetic crises. Cardiac output is modulated by the autonomic nervous system and by many chemical and mechanical stimuli. Among chemical factors, PO_2, PCO_2, and pH are key factors in the hemodynamic response to tissue hypoperfusion and hypoxia [8]. Indeed, a decrease in oxygen arterial content is promptly compensated by an increase in cardiac function. The opposite usually doesn't happen, as normal arterial saturation (very near to 100%) lies on the plateau portion of hemoglobin dissociation curve and hemoglobin concentration cannot change in acute if sudden impairment of hemodynamic function happens.

Cardiac output can be measured using several methods. The more common are briefly summarized in Table 9.2 and recently reviewed by Laher [9].

9.5 Oxygen Delivery (DO_2) and Extraction

Oxygen delivery is the oxygen volume transferred from lungs to the tissues in 1 min time. Therefore, it may be represented as

$$\mathrm{DO}_2\left(\mathrm{mL}/\mathrm{min}\right) = \mathrm{caO}_2 \times \mathrm{CO} \tag{9.12}$$

In normal conditions at rest (CO equal to 5 L/min, $SatO_2$ 100%, and PaO_2 100 mmHg), therefore, the volume of oxygen transferred from lungs to peripheral tissues is about 1000 mL/min. If tissue oxygen consumption is, at rest, about 250 mL/min, the oxygen amount that returns to the lung will be 750 mL/min. This means that only 25% of oxygen is extracted by the tissues. Oxygen extraction ratio (O_2ER) can be expressed as

$$\mathrm{O}_2\mathrm{ER}\left(\%\right) = \frac{\mathrm{VO}_2}{\mathrm{DO}_2} \times 100 \tag{9.13}$$

Therefore, oxygen that remains in mixed venous blood corresponds to 75% of total oxygen that has been delivered. This percentage corresponds approximately to normal mixed venous blood hemoglobin saturation (SvO_2). SvO_2 can be precisely computed as an oxygen fraction function, using the equation below:

$$\mathrm{SvO}_2\left(\%\right) = \mathrm{SaO}_2 \times \left(1 - \frac{\mathrm{VO}_2}{\mathrm{DO}_2}\right) \tag{9.14}$$

Table 9.2 Principal cardiac output monitoring techniques

Method	Vascular access	Principle	Pros	Cons	Timing
Swan Ganz catheter	Pulmonary artery cannulation	Thermodilution	Gold standard	Invasiveness	Intermittent
Transthoracic echocardiography	None	Ultrasound and Doppler effect	Noninvasive, measurement of cardiac output and other cardiac parameters	Operator dependency, variable quality echocardiographic windows in ICU patients	Intermittent
Transesophageal echocardiography	None	Ultrasound and Doppler effect	Direct measurement of cardiac output and cardiac structures	Minimally invasive, operator dependent	Intermittent
Calibrated pulse contour analysis	Arterial and venous access	Thermodilution plus pulse contour analysis	Measurement of CO plus other variables	Minimally invasive	Intermittent and continuous
Uncalibrated pulse contour analysis	Arterial access	Pulse contour analysis	Measurement of CO plus other variables	Minimally invasive, inaccuracy in unstable patients or during use of vasoactive drugs	Continuous

Every situation that causes a decrease in SaO_2 or an increase in oxygen extraction will result in a decrease in the saturation of the mixed venous blood.

This approach underlines the importance of measuring SvO_2 as an indicator of the balance between oxygen delivery and oxygen consumption. Equation 9.15 can be rewritten as.

$$SvO_2 = SaO_2 - \frac{VO_2\left(L/\min\right)}{CO\,L/\min} \times \frac{1}{0.00139 \times Hb\left(g/L\right)} \tag{9.15}$$

This equation makes explicit the importance of SvO_2 monitoring. Indeed, abnormal values of SvO_2 (below 0.65) indicate a change in Hb levels or a worsening in the relationship linking arterial saturation (SaO_2), tissue metabolism (VO_2), and hemodynamics (CO). Therefore, it is important to keep in mind that a decrease in SvO_2 does not specify which of its determinants is altered but that one or more of them are out of range. An altered SvO_2 dictates a detailed search of the underlying causes, and each of them may be life

threatening. If mixed venous blood sampling is not possible, central venous blood saturation ($ScvO_2$) is an acceptable surrogate even if, depending on the clinical condition, it may be higher or lower than SvO_2 [10].

9.6 Step Toward Energetic Crisis

In patients suffering from conditions that may affect oxygen transport, appropriate monitoring during the course of the disease should indicate if one of the following conditions is developing:

1. Energy production is adequate to the patient needs.
   The definition of adequate oxygen supply does not depend on a given amount of hemoglobin, cardiac output, or oxygen saturation but may only be defined in clinical practice by indirect methods. In other words, in different conditions a cardiac output of 3.6 L or more could be equally adequate to satisfy the energy needs, as well as a PO_2 of 90, 100, or 120 mmHg or an oxygen saturation of 90% or 100%. Defining the best PO_2, the best cardiac output or the best hemoglobin level, ignoring their association with the energetic needs is, in our view, not only useless but potentially dangerous. What should help the clinician to identify if there is a problem in satisfying the energy needs of the system is the identification of the compensatory mechanisms.
2. Energy production is still adequate but compensatory mechanisms are operating.
   It is well known for decades that oxygen consumption, when plotted as a function of oxygen transport remains constant until a critical point, which may vary, depending on the underlying disease [11]. Below this critical point, oxygen consumption starts to decrease while lactate starts to increase (Fig. 9.2).

   All compensatory mechanisms are operating to maintain the aerobic energy production constant in the range of oxygen supply that goes from normal values to the critical point. The decrease in oxygen consumption and the increase in lactate levels are signal of the energy crisis. The most sensitive indicator of oxygen transport is the central venous saturation.

   Figure 9.3 displays the relative weight of each of the determinants of SvO_2 as they decrease in a 10% step from the initial value, while other factors remain constant. As shown, arterial saturation changes (SaO_2) are linearly related to the changes in SvO_2. As the SaO_2 is easily measured by pulse oximetry, changes in SvO_2 due to changes in SO_2 may be easily estimated considering their proportional relationship. It is interesting to note that a 10% change in hemoglobin or cardiac output produces exactly the same change in venous saturation. Therefore, the decrease in SvO_2 clearly indicates that some of the oxygen transport mechanisms are impaired but not necessarily indicates that energy crisis is taking place. Physical activity, even in normal individuals, is associated with an increase in oxygen consumption, i.e., energy demand. In this situation, the hemodynamic response to the augmented energy demand is represented by an increase in cardiac output and a decrease in venous oxygen saturation. In intensive care patients however, in whom muscle activity is near to zero, a change in SvO_2 requires a diagnosis of the underlying causes. While the meaning of a decrease in SvO_2 is well established, the pathophysiological meaning of an increased SvO2 is less evident. Theoretically, whatever increase in cardiac output exceeding the energy requirement should produce an increase in SvO_2. The most likely explanation, however, although not clearly defined quantitatively, is that high SvO_2 is the result of one of these conditions indistinguishable from each other:

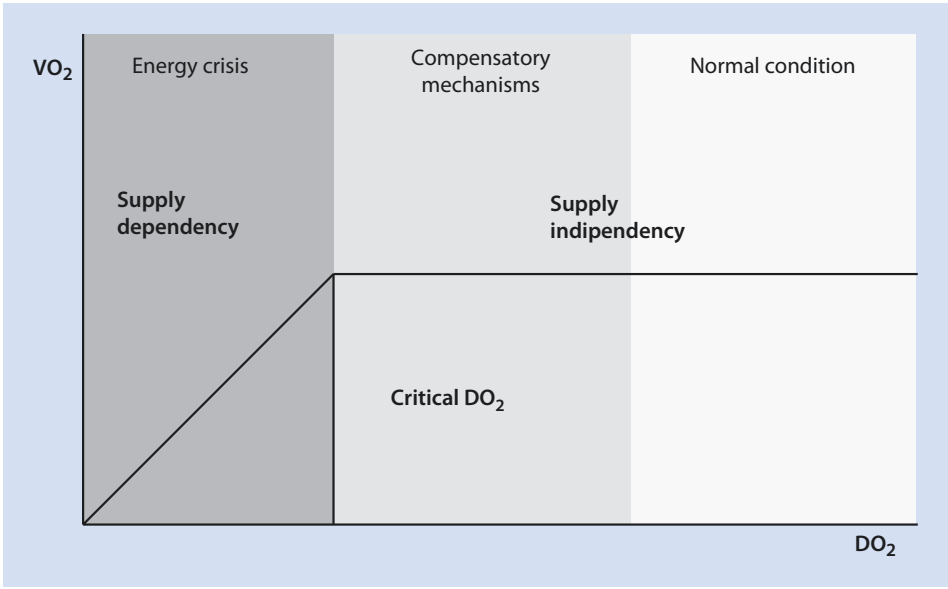


Fig. 9.2 Critical oxygen delivery. Table shows oxygen consumption trend when oxygen supply is impaired. In "supply independency phase," system responds to a decrease in oxygen delivery with an increase in oxygen extraction in order to maintain a normal value of oxygen consumption. When a critical value of oxygen delivery is reached, oxygen consumption becomes oxygen delivery dependent and starts to decrease (energy crisis). VO_2 oxygen consumption, DO_2 oxygen delivery

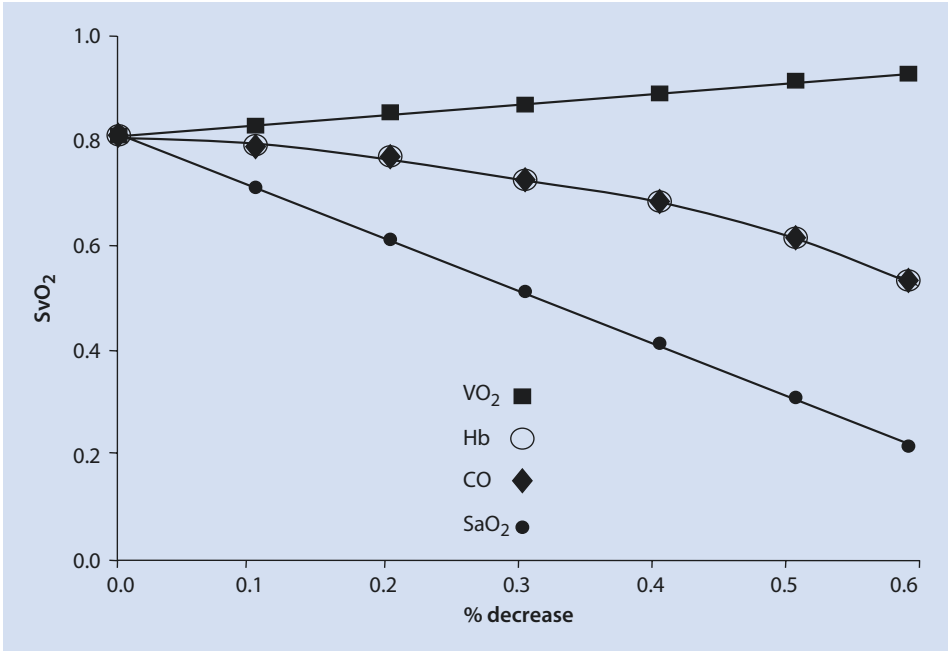
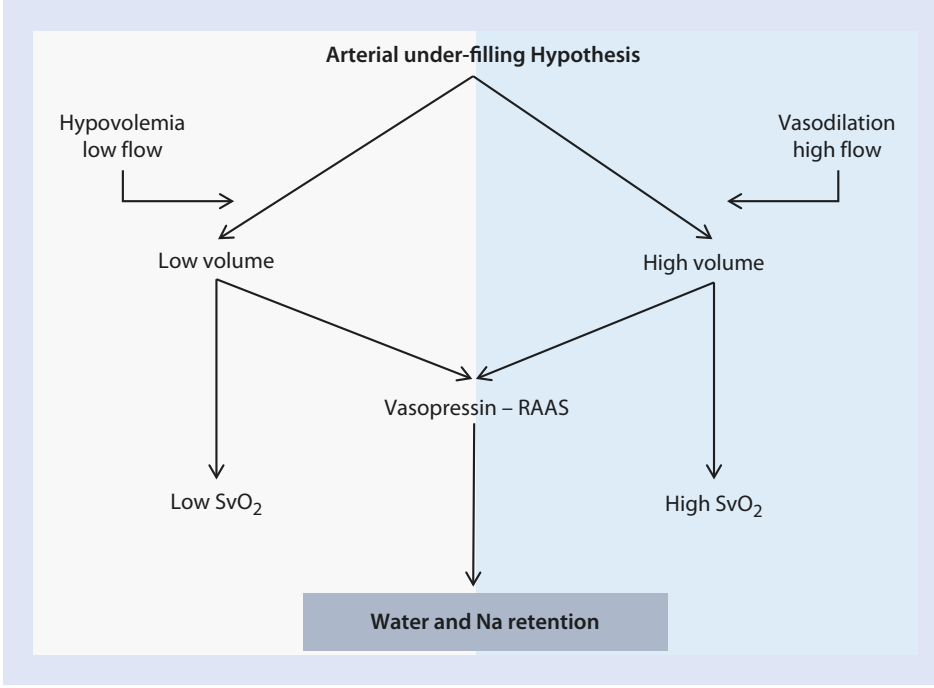


Fig. 9.3 Relative "weight" of mixed venous saturation determinants. This table shows in a graphical way the impact of a decrease (with 10% steps) in VO_2, Hb, CO, and SaO_2 on SvO_2. Data coming from institutional database, unpublished. SvO_2 mixed venous blood oxygen saturation, VO_2 oxygen consumption, Hb hemoglobin concentration, CO cardiac output, SaO_2 arterial oxygen saturation

peripheral shunting or respiratory chain alterations and uncoupling between oxygen consumption and energy production.

Another important signal of a precritical situation comes from the kidney. In mammalians, a hemodynamic impairment leading at the end to tissue hypoxia dictates a flow redistribution that will be promptly sensed by the kidney that will activate all its mechanisms devoted to volume conservation. The main players of kidney response are renin-angiotensin-aldosterone system (RASS) and vasopressin. These mediators are responsible for a contraction in urine output and a Na retention that will be easily recognized by urinary electrolytes inversion (low urinary Na and relatively high urinary K). Although this kidney response may seem not directly related to the oxygen transport but to a reflex response to pressure changes coming from baroceptors, we believe that hemodynamic in general cannot be separated from the oxygen transport concept as all our hemodynamic apparatus evolved just with the function of providing sufficient oxygen delivery to tissues. A complete set of hemodynamic impairment that may anticipate tissue hypoxia or be its actual cause is shown in ◘ Fig. 9.4 adapted from Schrier [12].

3. Energy production is inadequate.
The energy crisis likely begins with the appearance of anaerobic metabolism. It is possible that it may occur at different times in different organs, but a rapid rise in



◘ **Fig. 9.4** Arterial under-filling hypothesis. In this table we show kidney response to hypoperfusion. Hypovolemia and low flow (i.e., hemorrhage and heart failure) cause decrease in kidney perfusion and oxygenation, with activation of RASS, vasopressin release, increase in O_2ER, and consequent SvO_2 decrease (on the left). Vasodilatation and high flow (i.e., cirrosis and sepsis) are conditions in which "high volume" is associated to a relatively hypoperfused kidney (right) with consequent activation of the same mechanisms

lactate is an unquestionable sign, when associated with problems of oxygen transport/utilization, of a life-threatening condition. When oxygen delivery is severely impaired and reaches its critical value, a further increase in oxygen extraction is not possible. In this situation, at cellular level, tissue hypoxia, through hypoxia inducible factors (HIFs), activates a series of emergency mechanisms to maintain energy production [13]. This include an increased production of glycolytic enzymes and a decreased production of the enzymes necessary for Krebs cycle preparing cellular metabolism to the production of energy through anaerobic metabolism.

The energy production by anaerobic glycolysis, however, is only 5–6% of the one associated with aerobic metabolism. One mole of glucose (180 g) produces two moles of lactate and two moles of ATP. As the lactate is the final acceptor of electrons, in absence of oxygen 2 moles of ATP is the total amount of energy that is produced compared to the 32/36 moles of ATP produced during aerobic metabolism.

Some of the mechanisms operating during an overt energy crisis reflect in part what has been observed in hibernated animals. These animals decrease dramatically their energy requirement by decreasing protein synthesis and increasing enzymes half-life. They develop channel arrest and decrease proton movement through the ATPase as well as the electron transport in the respiratory chain and the proton leaks through the mitochondrial membranes. In humans, the oxygen supply dependency is a pale representation of the mechanism operating in hibernating animals and consists in similar systems for saving energy primarily through a decrease in protein synthesis. Unfortunately, this energy sparing condition may last only few hours after which irreversible changes in mitochondria may occur with final apoptosis and, in particular conditions, necrosis. Therefore, when the energetic crisis appears, we know that only few hours are available for correction and an immediate diagnosis of the underlying causes and a prompt intervention to correct them is needed.

Summarizing, the largely accepted view of oxygen transport impairment is the following:

- A decrease in tissue oxygenation is compensated at least in part by a greater oxygen release from hemoglobin and increase in oxygen extraction.
- When tissue partial oxygen pressure and oxygen concentration reach critical levels (which are clinically difficult to be defined), lactate production increases while oxygen consumption is partially decreased.
- When energy is insufficient, despite all the compensatory mechanisms, cellular dysfunction and damage begin: protein synthesis decreases, reactive oxygen species increases, and hypoxic damages, including necrosis and apoptosis, unavoidably follow.

There are conditions, however, which may occur in intensive care in which the decrease in oxygen consumption is not due to the decrease of transport to tissues but instead to the oxygen utilization. This may happen, as an example, if the complex molecules of the respiratory chain are structurally altered as may occur in sepsis. In addition, it is also possible that in some conditions, the underlying mechanism is the uncoupling between oxygen consumption and ATP production. This may occur in all the conditions which may impair proton concentration in the intermembrane space of the mitochondria. In this case the electrons flow down to the molecular oxygen to form water regularly, but the concentration of protons in the intermembrane space is decreased by the presence of intermediates (uncoupling agents) which shuttle the protons from inside to outside the membrane.

Therefore, three conditions of tissue dysoxia may be recognized which require different interventions and attention:

- Classical decrease in oxygen transport to tissues typically represented by hemodynamic impairment, hypoxemia, or anemia
- Respiratory chain impairment with decrease in ATP production
- Presence of uncoupling agents which dissociates oxygen consumption from energy production

Of note all the three conditions may present together at different extent in severe sepsis, and it is worth to underline that what really matters is not the oxygen transport "per se" but the energy production.

9.7 Oxygen Transport and Goal-Directed Therapy

A remarkable part of intensive care is devoted directly or indirectly to the control of oxygen transport and to the prevention of its impairment or to its correction when altered. When oxygen transport is impaired because of cardiac failure or volume depletion as in hemorrhage, the causes of tissue hypoxia are clear, and the correction is straightforward to renovate CO and circulating volume. The issue is less clear when other severe conditions as sepsis are involved.

Indeed the issue of oxygen transport originated a lot of debates and controversies after Shoemaker, one of the giants of intensive care, promoted the concept of "supernormal" oxygen delivery [14]. This was defined as a cardiac index greater than 4.5 L/min/m^2, an oxygen delivery greater than 600 mL/min/m^2, and an oxygen consumption greater than 170 mL/min/m^2. Shoemaker's observations derived from his experience in high-risk surgical patients in whose targeting therapies in order to reach "supernormal values" showed to improve clinical outcome. Early trials suggested that an increase in oxygen delivery would prevent organ failures and improve survival rates in such patients [15, 16]. The concept of "supernormal values," firstly developed in a particularly subset of patients, was immediately translated to other conditions up to ICU general population. However when the hypothesis of "supernormal" oxygen delivery was tested in clinical trials on general ICU population, no benefits were observed and these two trials signed the end of "supernormal" values [17, 18].

Ten years later Rivers found an impressive improvement in survival applying to severe sepsis and septic shock patients an approach targeted primarily to a central venous saturation of 70% and a MAP greater than 65 mmHg, defined as early goal-directed therapy (EGDT) [19]. The early goal-directed therapy became immediately popular and produced in intensive care physicians an increased attention to hemodynamics. Ten years later, three studies together retested Rivers' hypothesis and compared patients with severe sepsis and septic shock treated with normal care or treated following Rivers' goals [20–22]. No benefits could be demonstrated, and this lead to the implicit conclusion that $Scvo_2$ monitoring is useless. These studies rose a series of discussion which still persist, but we believe that these results should be discussed after two considerations:

- Beyond all the unavoidable differences in study populations, it must be noted that the success of supernormal values were obtained in patients treated before the intensive care, i.e., in the perioperative period by Shoemaker et al. and in emergency room by Rivers et al.

- Baseline Svo_2 in Rivers' study was extremely low (around 50%), while it was higher around 70% in all the studies performed in intensive care, meaning that Rivers' patients were sicker.

We believe anyway that, in patients with septic shock, time of intervention plays a crucial role, but we also believe that the negative results of these trials should switch the attention to the fact that in patients with sepsis or septic shock, the problem is not always related to oxygen transport to periphery per se but also to its final utilization. In our opinion this is what all the recent studies have suggested, and the logical conclusion is not that Svo_2 monitoring is useless but that the problems of most septic patients is not the oxygen transport.

Practical Implications

DO_2 monitoring should be performed in all those patients at risk of "energy crisis." This kind of patients include those in which one or more DO_2 determinants are at risk of impairment as cardiovascular, hemorrhagic, and patients with respiratory insufficiency but also those patients in which, even if DO_2 is still satisfactory, there is a difficulty in oxygen utilization, such as septic patients (see ◘ Fig. 9.4).

In all these patients urinary output, mixed venous saturation (or central venous saturation if a pulmonary catheter is not in place), urinary electrolytes, and, at the end, lactate represent very informative tools in identifying a situation in which compensatory mechanisms are activated and energy crisis is about to show.

A mixed venous saturation under 65% (or a negative trend), urinary output contraction, reversal in urinary electrolytes (Na lower than K), and a positive lactate trend dictate an accurate evaluation of DO_2 determinants.

Take-Home Messages

- Oxygen delivery is a parameter that is important to consider in critical patients management. What is of crucial importance, anyway, is not oxygen delivery per se but the early identification of all those parameters that are indirect signals of an insufficient oxygen supply or, lately, of an energetic crisis.
- Oxygen delivery concept should go beyond the simple result of the computation of cardiac output times oxygen content and should be thought in a more comprehensive way starting from pulmonary gas exchange and ventilation and arriving to mitochondria's utilization.
- Sepsis and septic shock are conditions in which a discrepancy between DO_2 and VO_2 is more evident.

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