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Anemia tolerance mechanisms

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ABSTRACT

Understanding the physiological concepts of oxygen delivery is essential to discern the mechanisms that influence its increase, reduction or maintenance in the body. This text explores the different mechanisms that help maintain oxygen delivery even in the face of reduced hemoglobin levels. Adequate oxygen delivery ensures tissue and metabolic balance, which is crucial to avoid harmful consequences such as metabolic acidosis and cellular dysoxia. The complex interaction between variables such as cardiac output, hemoglobin and heart rate (HR) plays a fundamental role in maintaining oxygen delivery, allowing the body to temporarily adjust to situations of anemia or high metabolic demand. It is important to emphasize that blood transfusions should not be based on fixed values,

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but rather on individual metabolic needs. Strategies to reduce myocardial consumption and monitor macro and micro hemodynamics help in making rational decisions. Individualizing treatment and considering factors such as blood viscosity in relation to the benefits of transfusion are increasingly relevant to optimize therapy and minimize risks, especially in complex clinical scenarios, such as neurocritical patients and trauma victims.

Introduction

Understanding the physiological concepts of oxygen delivery (DO_2) is fundamental to understanding the variables that are capable of increasing, reducing or maintaining the supply of oxygen (O_2) to the body. Based on this reasoning, this text discusses the possible mechanisms for maintaining DO_2 even with reduced hemoglobin levels.

Adequate O_2 supply guarantees tissue homeostasis within a physiological pattern of dynamic balance (Figure 1). This balance is guaranteed through adequate DO_2 and nutrients and the removal of carbon dioxide, free radicals and other metabolic products. With a multifactorial cause, the imbalance between supply and demand can lead to harmful consequences for the body, such as accumulation of acidic metabolic products and, consequently, metabolic acidosis, cellular dysoxia, multiple organic dysfunctions, prolonged hospitalization and even death.[1,2]

As can be seen from Figure 1, O_2 distribution is a product of blood flow and arterial O_2 content. When the DO_2 decreases below a critical point, O_2 consumption is impaired, leading to anaerobic metabolism and lactic acidosis.

It is well known that prolonged cellular dysoxia, both in the surgical and intensive care environments, is associated with increased mortality. One of the vital goals of healthcare professionals is ensuring the adequacy of DO_2 in critically ill patients, whether in the operating room or in the intensive care unit (ICU).

To better understand the mechanisms of anemia tolerance, it is important to remember the DO_2 variables and their physiological interactions.

Physiological aspects of oxygen delivery

DO_2 is a consequent product of arterial O_2 content and cardiac output (CO). Therefore, it is necessary to understand all related variables with their deficits and treatment potential to optimize DO_2. DO_2 is calculated by Formula 1.

Formula 1. Oxygen delivery

$$DO_2 = CaO_2 \times CO$$

DO_2 = oxygen delivery; CaO_2 = arterial oxygen content; CO = cardiac output

The arterial oxygen content (CaO_2 - Formula 2 below) is guaranteed, for the most part, by the amount of O_2 transported bound to hemoglobin and, to a lesser extent, by the amount of O_2 transported dissolved in the plasma. It is known that the solubility coefficient of O_2 in plasma is low and, therefore, a small quantity of O_2 is transported. Therefore, increases in DO_2 are not possible through this means of transport under normal temperature and pressure conditions. On the other hand, we are aware that a hemoglobin molecule carries up to 1.37 mL of O_2, that is, the DO_2 can be increased by improving the hemoglobin level. However, it is known that very high hemoglobin levels are associated with worse viscosity and thus worse blood flow and that poorly indicated transfusions, for this reason alone, can worsen patients' clinical outcomes. It is also important to highlight that as the carrying capacity of hemoglobin is also finite (1.37 mL x Hb), this means that we cannot achieve a "scaled and proportional" improvement in DO_2 through an isolated increase in the fraction of inspired O_2 (FiO_2).

Formula 2. Arterial oxygen content

$$CaO_2 = 1.37 \times Hb \times SaO_2 + (0.003 \times PaO_2)$$

CaO_2 = arterial oxygen content; Hb = hemoglobin in grams per 100 mL of blood (14 to 15 g/dL); SaO_2 =% oxyhemoglobin - fractional saturation of hemoglobin; 1.37 = number of milliliters of O_2 linked to 1 g of saturated Hb; 0.003 = O_2 solubility in plasma, vol% mmHg refers to the arterial blood sample; PaO_2: Partial pressure of oxygen

Hypoxemia is defined as a reduction in arterial O_2 content, while cellular dysoxia is defined as a metabolic imbalance, either due to a lack of O_2 or due to an inadequate flow, which creates an imbalance between the generation and removal of toxic radicals resulting from cellular metabolism. Therefore, reductions in DO_2 can lead to tissue dysoxia. An imbalance between delivery and demand leads to increased production or accumulation of markers resulting from anaerobic metabolism such as lactate, which can be measured in the laboratory.

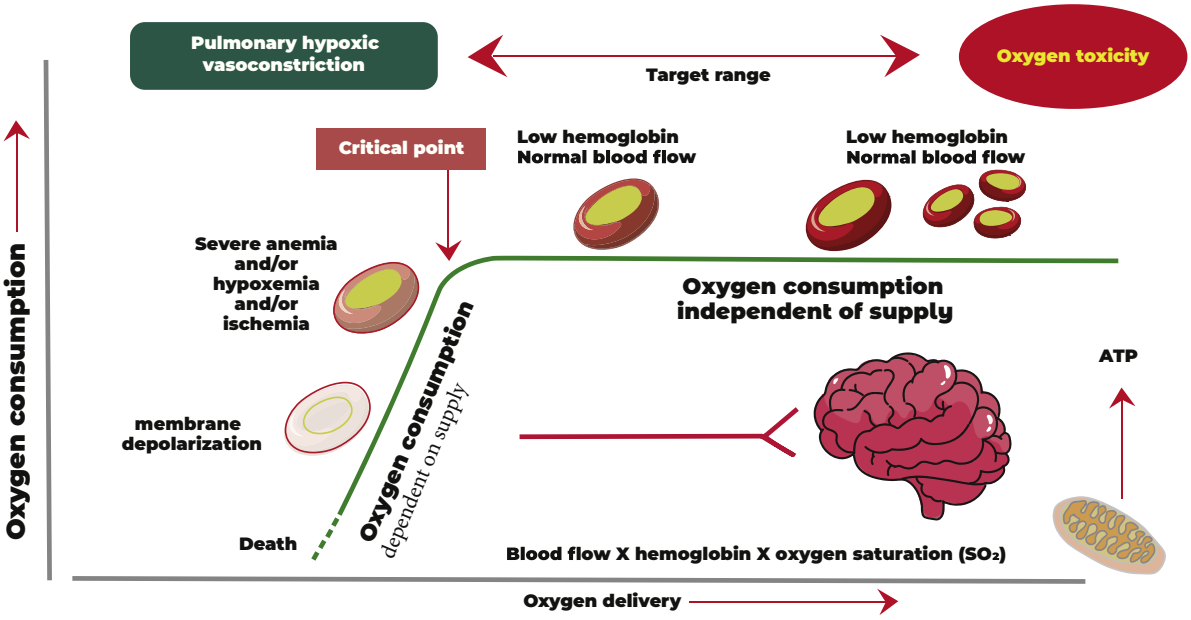
Another important point to understand DO_2 is CO (Formula 3), where CO is the product of stroke volume and HR.

Formula 3. Cardiac output

$$CO = SV \times HR$$

DC= cardiac output; SV= stroke volume; HR= heart rate

When analyzing CO variables, we know that the systolic volume will have its performance subordinated to the physiological properties of the myocardium such as preload, afterload and contractility, that is, changes in volume, in systemic vascular resistance and in contractility can lead to changes (for more or for less) in the CO and, consequently, impact DO_2. Patients with very high systemic vascular resistance may experience worsening of myocardial function due to increased cardiac work and a consequent drop in DO_2. On the other hand, dramatic drops in systemic vascular resistance can also generate



Oxygen consumption	Pulmonary hypoxic vasoconstriction	Target range		Oxygen toxicity
	Critical point	Low hemoglobin Normal blood flow	Low hemoglobin Normal blood flow	
	Severe anemia and/or hypoxemia and/or ischemia	Oxygen consumption dependent on supply	Oxygen consumption independent of supply	
	Membrane depolarization			ATP
	Death		Blood flow x hemoglobin x oxygen saturation (SO_2)	
	Oxygen delivery			

Figure 1 – Relationship between oxygen delivery and demand.

tissue perfusion pressures so low that blood flow becomes unsatisfactory to meet the patient's tissue metabolic demand.[3]

Patients with impaired myocardial performance, such as those with severe heart failure or in cardiogenic shock, may not have sufficient stroke volume to guarantee tissue demand. This situation can also generate a drop in DO_2, an increase in lactate, an accumulation of metabolic waste (metabolic acidosis and renal failure) and a 'slower' venous return which can be observed in the laboratory with an increase in delta CO_2 (difference in CO_2 between arterial and venous blood gases of >6 mmHg) and a drop in central venous saturation (less than 65–70%).

It is always very important, however, to individualize the conduct for each patient, closely observing their responses to interventions and their evolution. It is not true that every heart patient needs high hemoglobin values to improve their DO_2. In a systematic review that included patients submitted to cardiac surgery, it was concluded that a restrictive transfusion strategy of 7–8 g/dL is safe and reduced the use of red blood cell transfusions by 24%. The review also emphasizes that more research is necessary to define the ideal transfusion threshold in patients with acute myocardial infarction.[4]

Changes in HR tend to impact DO_2 at its extremes. Very high frequencies that are not compatible with age (e.g., tachyarrhythmias) can impair systolic filling and coronary flow and, consequently, reduce CO and DO_2. However, extremely low HRs (symptomatic bradycardias) can also impair CO and there is also a drop in coronary flow.[3,5]

Our organic systems interact to seek homeostasis and balance so that, even in cases of extreme anemia or a drop in

Table 1 – Correlation between the main clinical situations and the variables affected by oxygen delivery.

Situation	CaO_2 1.37 x Hb x SaO_2 x PaO_2	CO CO = SV x HR	Desired intervention
Anemia (dependent on the hemoglobin level and each patient`s comorbidities	Drop in CaO_2	Can compensate with increase in HR	Improve the supply/Hb production (if possible): correction of the anemia (see the possibility of iron, erythropoietin, etc.)
Severe anemia (hemorrhagic shock)	Drop in CaO_2 dependent on the hemoglobin level	Can compensate with increase in HR, however hypotension and signs of bad clinical perfusion are evident (drop in diuresis, cold and clammy skin, alteration in awareness, etc.)	Consider concentrated red blood cell transfusions and/or volume replacement (escalation of therapy depends on the degree of shock - from I to IV)
Drop in oxygenation (e.g.: lack of intubation, hypoxemic respiratory failure)	Drop in CaO_2	Initial increase in HR as compensatory mechanism; if not resolved, drop in SV and CO – bradycardia and cardiorespiratory arrest	Improve DO_2 depending on underlying cause
Tachyarrhythmia	Initially it is unaffected in well-oxygenated patients	Pathologic increase in HR with impairment of diastolic filling – drop in SV and CO. Can evolve to cardiorespiratory arrest	Treat the arrhythmia according to Advanced Cardiac Life Support guidelines of the American Heart Association
Bradyarrhythmia	Initially it is unaffected in well-oxygenated patients	Pathologic drop in HR (impairment of coronary perfusion) can lead to ischemia, drop in CO and even cardiorespiratory arrest	Treat the arrhythmia according to Advanced Cardiac Life Support guidelines of the American Heart Association (drugs or pacemaker)
Cardiogenic shock	Initially it is unaffected in well-oxygenated patients	Patient may present with impaired CO, SV or both	Depending on the cause (inotropic agents, antiarrhythmics or invasive ventricular assist devices (such as IAB, ECMO) may be necessary
Obstructive shock	CaO_2 may drop depending on the cause (e.g.: massive pneumothorax or hemothorax)	Drop in CO due to reduced venous return or filling of the right ventricle (tamponade for example) and consequent drop in SV	Make a correct diagnosis and intervene
Distributive shock	Initially it is unaffected in well-oxygenated patients	Vasoplegia may lead to a drop in arterial pressure with a reduction in venous return and SV; Although the CO may be hyperdynamic in some situations	Make a correct diagnosis and intervene
Hypothermia	Initially it is unaffected in well-oxygenated patients – in situations of deep hypothermia (a rare condition), the CaO_2 may be augmented due to an increase in solubility of O_2 in the liquid (plasma)	Initially there is a compensatory increase in the CO to attempt to supply the organism and maintain homeostasis; if it persists the HR and CO drop	Gradual rewarming
Sedation/analgesia	Initially it is unaffected in well-oxygenated patients. In sedated and badly oxygenated patients, it may lead to a drop in the CaO_2	Well indicated, analgesics and sedation normally promote anxiolysis, with consequent reduction in HR, and improvement in diastolic filling, SV and CO. Excessive sedation or inappropriate use of sedative drugs can cause hypotension, a drop in SV and consequently a drop in CO	Adequate analgesia and sedation for each nociceptive stimulation

CaO_2: Arterial oxygen content; Hb: Hemoglobin; SaO_2: Oxygen saturation; PaO2: Partial pressure of oxygen; CO: Cardiac output; SV: Stroke volume; HR: Heart rate; IAB: intra-aortic balloon; ECMO: extracorporeal membrane oxygenation.

stroke volume (e.g. hemorrhagic shock, extensive acute myocardial infarction), CO will try to compensate and maintain DO_2 typically by increasing the HR. On the other hand, a significant reduction in HR or exaggerated pathological increases (tachyarrhythmias) will generate a state of tissue hypoperfusion and activation of sympathomimetic receptors. This activation of receptors leads to a reflex increase in systemic vascular resistance (SVR), in the body's compensatory attempt to maintain tissue perfusion pressure and guarantee DO_2, and coronary and cerebral perfusion. It is known, however, that this persistent increase in SVR can result in impaired organic perfusion and lead to cellular dysoxia if the cause of the imbalance is not resolved.

It is extremely important to remember that all of these compensatory mechanisms have synergistic and temporary effects and that if the underlying cause of the 'disorder' is not resolved, the patient may progress to refractory shock and death.

Table 1 illustrates the main clinical situations related to the variables affected by poor DO_2 and the necessary interventions.

Laboratory markers of cellular dysoxia

Laboratory markers and diagnostic devices can be used to monitor tissue perfusion. However, in the clinical practice, many of these devices are expensive and are not readily available in healthcare units. In most services, there is arterial and venous blood gas analysis for decision making. With blood gases, indirect signs of anaerobic metabolism are observed as likely reasons for the drop in DO_2. It is very important to correlate clinical data with laboratory findings always. Therefore, the presence of metabolic acidosis may be a frequent finding in initial cases of shock. The progressive drop in bicarbonate, as well as more negative base excess (BE) values, should make the healthcare professional pay attention to a likely progressive to hypoperfusion even if the blood pressure is maintained.

Lactate is the result of anaerobic metabolism and its progressive increase should serve as a warning about a metabolic deviation that is taking place; measures must be initiated to begin its 'clearance'. Its rise to critical levels is associated with increased mortality especially in septic patients and trauma victims. Delta CO_2 is the difference in CO_2 between venous and arterial blood gases. When this difference is wide (>6 mmHg), this indicates tissue low blood flow.

The reduced blood flow through tissues (e.g. cardiogenic shock) in cases of anemia can also lead to a drop in central venous saturation (SvO_2). Therefore, it can also be an indirect indicator of tissue hypoperfusion.

Although several factors affect the SvO_2 causing overestimations even with a concomitant drop in DO_2 (e.g.:

Table 2 – Technologies that measure tissue oxygen with potential use for transfusions.

Technology	Enhancement agents used	What this technology measures	Tissue thickness	Examples in transfusion (ref #)
Near infrared spectroscopy (NIRS)	Endogen: Total Hb, oxy-Hb, deoxy-Hb	% oxygen saturation ($\%SO_2$)	Soft tissue: 5–10 mm Brain: variable	Clinical [38##, 39#, 40]
Photoacoustic tomography (PAT)	Endogen: Total Hb, oxy-Hb, deoxy-Hb	% oxygen saturation ($\%SO_2$), partial oxygen pressure (pO_2 - mmHg)	Mathematical model dependent (1–12 mm)	No available study
Positron emission tomography	Exogen: radiolabeled O_2 (oxygen-15)	Distribution and metabolism of oxygen in tissue	Total thickness of the tissue	Clinical [58]
Blood oxygen level dependent magnetic resonance (BOLD-MRI)	Endogen: deoxy-Hb with or without exogen (dimeglumine gadopentetate)	Partial oxygen pressure (pO_2 - mmHg)	Depends on the resonators used: 1–10 mm for surface resonators and up to 80 mm for implantable resonators	Pre-clinical [4#]
Electronic paramagnetic resonance (EPR-imaging)	Exogen: composed of trityl base (Oxo63, TAM-H)	Partial oxygen pressure (pO2 mmHg) Tissue mapping	10–20 mm	No available study
Phosphorescence quenching	Exogen: Oxyphor R2 Oxyphor G4	Partial oxygen pressure (pO_2 mmHg)	Depends on the distribution of the quenching agent in the tissue	Pre-clinical [59]
Hypoxyprobe™	Exogen: pimonidazole	Nitroimidazole adducted proteins (occur at <10 mmHg pO_2) that can be detected by immunohistochemistry, Western blot and mass spectrometry	Total thickness of the tissue	Pre-clinical [3#]

oxy-Hb: oxyhemoglobin; deoxy-Hb: Deoxygenated hemoglobin.
Adapted from Bock and Buchler (2019).

hypothermia, sepsis, hyperdynamic patients), low values tend to be more valued when analyzed within the patient's clinical context.

Non-invasive or minimally invasive technologies can provide relevant information about tissue O_2 before and after red blood cell transfusions. The application of oximetry techniques, such as electronic paramagnetic resonance (EPR-imaging), near infrared spectroscopy (NIRS), photoacoustic tomography (PAT) and blood oxygen level dependent magnetic resonance (BOLD-MRI), are interesting opportunities to measure O_2 concentration (EPR) and saturation (NIRS, PAT and BOLD-MRI - Table 2).[6] Unfortunately, due to their high cost, they are not yet widely available.

Anemia tolerance mechanisms

In view of what was previously discussed, it is more understandable that the mechanisms of tolerance to anemia depend directly on DO_2 variables. Thus, strategies that reduce myocardial consumption, which range from analgesia to HR control, are applicable in different scenarios in the clinical practice.

Another important point that we must remember is that patients should not be transfused considering fixed parameters, but rather based on metabolic needs.[7,8] Monitoring macro hemodynamics and, more notably, micro hemodynamics is extremely important in making a rational decision. A clear example that we can highlight is neurocritical patients, victims of trauma, in which the ideal hemoglobin is not yet a well-established consensus. Although responsible for delivering O_2, it is also known that increases in hemoglobin can lead to increased viscosity with worse regional microcirculatory in some clinical situations.[9] Given this, increasingly new ways to monitor and individualize patients are being considering in an attempt to meet their real needs and rationalize transfusion indications.

Recommendations

1. Directly or indirectly monitor whether oxygen delivery is adequate in critical patients.
2. Measures to improve metabolism should be a priority in patients with signs of hypoperfusion or clear signs of poor tissue perfusion.
3. Transfusion of packed red blood cells should not be based on pre-established numbers; it is recommended that decisions be individualized for each patient, taking into account their comorbidities, their current clinical status and tissue perfusion markers.

Conclusion

The main objective of the clinical indication for red blood cell transfusion is to restore or maintain adequate oxygenation. Oxygen transport after transfusion is affected by numerous factors such as perfusion, allosteric saturation/desaturation of hemoglobin and tissue oxygen concentration.

Bioavailable oxygen maintains tissue homeostasis. Homeostasis imbalance can be measured indirectly by tissue and technological markers at the bedside. The 'active search' for this imbalance in critically ill patients can be valuable to assess the quality of oxygen delivery, the real need for transfusions and, thus, guide appropriate action.

Conflicts of interest

The authors declare no conflicts of interest.

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