Oxygen delivery and haemoglobin

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Oxygen must be transported effectively from the atmosphere to the tissues in order to sustain normal metabolism. An understanding of oxygen delivery is therefore central to the management of patients during anaesthesia, resuscitation and during critical illness. This review deals specifically with the transport of oxygen from the lungs to non-pulmonary tissues.

Definitions

Oxygen delivery

Global oxygen delivery ($\dot{D}_{O_2}$) is the amount of oxygen delivered to the whole body from the lungs. It is the product of total blood flow or cardiac output (CO) and the oxygen content of arterial blood (Ca_{O_2}) and is usually expressed in ml min^{-1}:

$$\dot{D}_{O_2} = CO \times Ca_{O_2}$$

The oxygen content of arterial blood (Ca_{O_2}) is described using the equation:

$$Ca_{O_2} = (k_1 \times Hb \times Sa_{O_2}) + (k_2 \times Pa_{O_2})$$

Where Hb is the haemoglobin concentration (g litre^{-1}), Sa_{O_2} is the arterial Hb oxygen saturation and Pa_{O_2} is arterial oxygen partial pressure. Arterial oxygen content is the sum of the two forms in which oxygen is carried. In health >98% of oxygen is bound to Hb (Table 1). The oxygen combining capacity of Hb is represented by the constant k_1 above and is sometimes termed Hüfner's constant. The exact value for this constant is controversial and differs between authors. In theory, each gram of Hb binds 1.39 ml of oxygen. However, in practice, the presence of abnormal forms of Hb, such as carboxyhaemoglobin and methaemoglobin, reduces the oxygen combining capacity of Hb to 1.31 ml g^{-1}. Most modern co-oximeters measure the proportion of these Hb types. Dissolved oxygen in plasma is determined by the solubility coefficient of oxygen at body temperature (k_2 above; 0.23 ml litre^{-1} kPa^{-1}) and the Pa_{O_2}. Even at high FI_{O_2}, this oxygen is insignificant (Table 1) at normal atmospheric pressure.

Table 1 The relative influence of anaemia on oxygen delivery

Parameter	Normal	Anaemic	Anaemic + oxygen therapy
Inspired oxygen (%)	21	21	100
Pa_{O_2} (kPa)	12	12	85
Sa_{O_2} (%)	98	98	98
Hb concentration (g litre^{-1})	150	75	75
Dissolved oxygen (ml litre^{-1})	3	3	19
Hb-bound oxygen (ml litre^{-1})	197	98	98
Total Ca_{O_2} (ml litre^{-1})	200	101	117
$\dot{D}_{O_2}$ (ml min^{-1}), assuming a cardiac output of 5 litre min^{-1*}	1000	505	585

Pa_{O_2}, arterial partial pressure of oxygen; Sa_{O_2}, arterial oxygen saturation; Hb, haemoglobin; Ca_{O_2}, oxygen content of arterial blood; $\dot{D}_{O_2}$, oxygen delivery.
*In practice the cardiac output increases during anaemia because blood viscosity and cardiac afterload decrease.

At present, it is only practical to routinely measure global $\dot{D}_{O_2}$. If regional blood flow is available, the same principles can be used to measure regional oxygen delivery.

Oxygen consumption

Global oxygen consumption ($\dot{V}_{O_2}$) is the volume of oxygen consumed by the tissues per minute. Under aerobic conditions, oxygen is consumed to generate energy so that $\dot{V}_{O_2}$ corresponds to the metabolic rate. Measurements of $\dot{V}_{O_2}$ are sometimes used to assess the adequacy of $\dot{D}_{O_2}$ on the assumption that if $\dot{D}_{O_2}$ is inadequate $\dot{V}_{O_2}$ becomes supply-dependent (see below). $\dot{V}_{O_2}$ can be measured directly by analysis of respiratory gases or derived from cardiac output and arterial and venous oxygen contents. Gas analysis techniques require specialized equipment that accurately measures gas volumes and concentrations adjusting for temperature and pressure changes and other sources of inaccuracy. Calculation from cardiac output and arterial-mixed venous oxygen content difference is simpler and can be done using a pulmonary artery catheter. The reverse/inverse Fick principle is used:

$$\dot{V}_{O_2} = CO \times (Ca_{O_2} - Cv_{O_2})$$

Key points

Oxygen is carried in arterial blood dissolved in solution (<2% when breathing air) and combined with haemoglobin (>98% in air).

Tissue hypoxia is a deficiency of oxygen at the tissue level; it may be caused by increased demand, decreased supply or abnormal cellular utilization.

The main physiological responses to acute normovolaemic anaemia are increased cardiac output and increased oxygen extraction ratio.

The 'critical' haemoglobin concentration is that below which tissue hypoxia occurs; it is ~50 g litre^{-1} in healthy humans.

Most stable perioperative and critically ill patients can be managed with a haemoglobin transfusion threshold of 70 g litre^{-1}.

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Oxygen extraction ratio

The oxygen extraction ratio (O_2ER) is the ratio of $\dot{V}_{O_2}$ to $\dot{D}_{O_2}$ and represents the fraction of oxygen delivered to the microcirculation that is taken up by the tissues.

$$O_2ER = \dot{V}_{O_2}/\dot{D}_{O_2}$$

The normal O_2ER is 0.2 to 0.3, indicating that only 20–30% of the delivered oxygen is utilized. This spare capacity enables the body to cope with a fall in $\dot{D}_{O_2}$ without initially compromising aerobic respiration and $\dot{V}_{O_2}$. O_2ER varies between organs; the heart has a high O_2ER (~0.6) so it is particularly sensitive to reductions in coronary artery $\dot{D}_{O_2}$.

Hypoxia

Hypoxia is a deficiency of oxygen at the tissue level. It follows that the chance of hypoxia is influenced by the demand of the tissues for oxygen (Table 2). Under anaesthesia, metabolic rate decreases so a lower $\dot{D}_{O_2}$ is needed to meet demands. The same situation applies during hypothermia. Critically ill patients are at increased risk of tissue hypoxia because critical illness can increase oxygen demand and impair $\dot{D}_{O_2}$.

From the equations above, it is apparent that tissue hypoxia may be caused by:

A decrease in arterial oxygen content

This can result from a decrease in oxygen carrying capacity (anaemic hypoxia) or a decrease in the amount of oxygen bound to Hb (hypoxic hypoxia). Anaemic hypoxia is most frequently attributable to a low Hb although it can also be caused by the presence of abnormal forms of Hb that cannot bind oxygen, such as carboxyhaemoglobin and methaemoglobin. Hypoxic hypoxia is attributable to inadequate transfer of oxygen across the lungs. This usually results from a low $F_{I_{O_2}}$, ventilation–perfusion mismatch, or shunts.

Table 2 Factors that influence oxygen consumption and oxygen delivery

Factors increasing $\dot{V}_{O_2}$
Surgery
Trauma
Burns
Inflammation
Sepsis
Pyrexia
Shivering
Seizures
Agitation/anxiety/pain
Adrenergic drugs
Weaning from ventilation
Factors decreasing $\dot{V}_{O_2}$
Sedation/analgesics
Muscle paralysis
Shock/hypovolaemia
Hypothermia/cooling
Mechanical ventilation
Antipyretics
Starvation/hyponutrition

A decrease in blood flow

This is usually a result of an inadequate circulating volume or poor cardiac function or a focal obstruction, such as atheroma. It is usually termed stagnant or ischaemic hypoxia

Inability of cells to utilize oxygen

This form of hypoxia has been termed histotoxic or cytopathic hypoxia; the classical example is cyanide poisoning. However, cytopathic hypoxia may also occur in critically ill patients, especially those with inflammation and sepsis. Critical illness can reduce the capability of cells to utilize oxygen despite an adequate oxygen supply. This may be caused by inhibition of mitochondrial oxidative phosphorylation by substances such as nitric oxide and proinflammatory cytokines. It is important to recognize this possibility, because attempts to correct tissue hypoxia, by increasing $\dot{D}_{O_2}$ to supra-normal levels, are ineffective and may increase the oxygen demands of unaffected tissues making them more susceptible to hypoxia.

Oxygen supply and demand relationship

In health

The normal relationship between $\dot{V}_{O_2}$ and $\dot{D}_{O_2}$ is shown in Figure 1. The oxygen transport system normally operates to maintain $\dot{V}_{O_2}$ in conditions where $\dot{D}_{O_2}$ varies widely. If global $\dot{D}_{O_2}$ decreases then O_2ER increases to maintain adequate oxygen supply. If $\dot{D}_{O_2}$ continues to decrease, a point is reached where the O_2ER is maximal and cannot increase further. This point is called the 'critical $\dot{D}_{O_2}$', and it is the point below which energy production in cells becomes limited by the supply of oxygen. When the decrease in $\dot{D}_{O_2}$ is caused by anaemia the Hb concentration at the critical $\dot{D}_{O_2}$ is termed the 'critical Hb concentration'. Any further reduction in $\dot{D}_{O_2}$ will result in tissue hypoxia, conversion to anaerobic metabolism and the production of lactic acid. The critical $\dot{D}_{O_2}$ is not a fixed value, but varies between organs and is dependent on the metabolic activity of the tissue.

The lack of a fixed threshold for critical $\dot{D}_{O_2}$ indicates the need to monitor $\dot{D}_{O_2}$ and $\dot{V}_{O_2}$ on an individual basis preferably for individual organs. At present our ability to monitor this is limited and
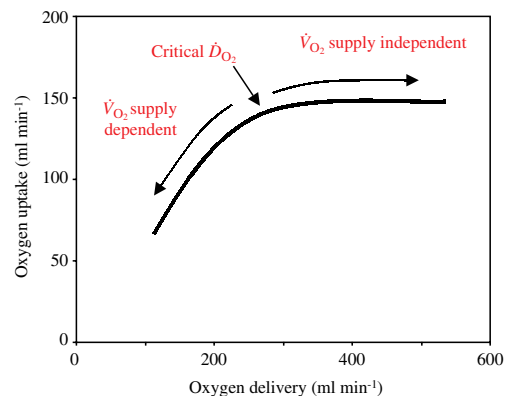

Fig. 1 The oxygen supply and demand relationship in health.

inadequate. Global measurements of $\dot{D}_{O_2}$ and $\dot{V}_{O_2}$, and global markers of tissue hypoxia (plasma acidosis and lactate concentration) are useful, but are insensitive and non-specific. Regional indices, such as gastric tonometry and near infrared spectroscopy (NIRS), are indirect methods of measuring tissue oxygenation, which are still being evaluated. The value for critical $\dot{D}_{O_2}$ has been estimated to be $\sim$4 ml kg^{-1} min^{-1} in humans.

In critical illness

Tissue hypoxia is common during critical illness. As a result, understanding the relationship between $\dot{D}_{O_2}$ and $\dot{V}_{O_2}$ during critical illness is central to intensive care. Early studies suggested that many critically ill patients had inadequate $\dot{D}_{O_2}$ because when $\dot{D}_{O_2}$ was increased by blood transfusions, fluids or inotropic drugs the $\dot{V}_{O_2}$ also increased. This implied that $\dot{V}_{O_2}$ was dependent on $\dot{D}_{O_2}$ over a much wider range than normal and that there was a persistent oxygen debt caused by ischaemic hypoxia. This was termed 'pathological oxygen supply dependency'. However, many of these studies were complicated by methodological problems and many were detecting physiological, rather than pathological, supply dependency.

A linear 'dependent' relationship between $\dot{D}_{O_2}$ and $\dot{V}_{O_2}$ can occur when there is a primary change in metabolic rate and $\dot{D}_{O_2}$ changes proportionately to match the newly created oxygen requirements. This is normal physiological coupling, as would occur during exercise. Minute to minute changes in metabolic rate occur commonly in patients in the intensive care unit. In particular, therapeutic interventions such as physiotherapy can result in large increases in metabolic rate (Fig. 2). Recent work shows that pathological oxygen supply dependency is much less common and much less severe than previously thought in most clinically resuscitated critically ill patients. Abnormal oxygen extraction capabilities do exist in critically ill patients, particularly in organs such as the gut that has a circulation that is prone to hypoxia. At present, there are no reliable monitors that detect pathological supply dependency in individual organs.

Goal-directed therapy

This is the use of therapeutic goals to guide the management of oxygen delivery in patients. The idea came from the observation that patients with higher $\dot{D}_{O_2}$ are more likely to survive than those with lower $\dot{D}_{O_2}$ and the belief that they had pathological oxygen supply dependency. Various therapeutic goals have been proposed for cardiac output, $\dot{D}_{O_2}$, $\dot{V}_{O_2}$, mixed venous oxygen saturation, central venous oxygen saturation and other physiological measures. The goals are often 'supra-normal' levels. Many of these have been tested in randomized trials using goal-directed protocols. Interpreting these trials is difficult and controversial. The results seem to indicate that, for patients who do not yet have organ failures but are at high risk of developing them, a goal-directed approach to managing $\dot{D}_{O_2}$ is beneficial. Patients with sepsis who are treated early in the clinical course before organ failures are well established also benefit from this approach. However, patients
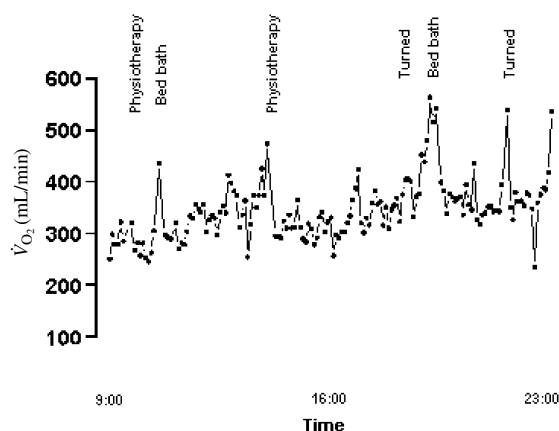

Fig. 2 The variability of oxygen consumption ($\dot{V}_{O_2}$) in a critically ill patients.

with established critical illness and organ failures do not seem to benefit and in some cases may be harmed by aggressive $\dot{D}_{O_2}$-directed protocols. It is not clear if the benefit from this approach comes from the specific goals and protocols used or if it relates to the improved overall care that may be associated with them.

What is an adequate haemoglobin concentration?

The normal physiological response to anaemia

When patients become anaemic a number of physiological responses occur that maintain $\dot{D}_{O_2}$ until the critical Hb concentration is reached (Table 3). The main responses are increased cardiac output and increased oxygen extraction ratio.

Cardiac output increases during normovolaemic anaemia; the magnitude of this increase is closely related to the reduction in blood viscosity. A reduction in blood viscosity decreases the resistance to blood flow, which consequently increases venous return and facilitates left ventricular emptying by decreasing afterload. The net effect is an increase in cardiac output. Sympathetic activation also occurs, which may increase heart rate and/or myocardial contractility, but these play a minor role in increasing the cardiac output of a normal heart in anaemia as long as normovolaemia is maintained. This is advantageous because of the increase in myocardial oxygen consumption associated with these two factors.

Increased oxygen extraction by the tissues occurs during anaemia by improved matching of oxygen delivery to oxygen demand. There is a redistribution of blood flow to areas of high demand, such as the myocardium and the brain. In the microcirculation a number of mechanisms help to maintain tissue oxygenation. Red blood cells normally lose oxygen as they travel through the arterial tree. However, in the anaemic state, blood flow is increased and the pre-capillary oxygen loss is reduced. The net effect of all of these changes is a more efficient utilization of the remaining red cell mass. In addition, normovolaemic anaemia has little effect on the capillary haematocrit because the latter is normally very low because of an effect called 'plasma skimming'. The 'normal' capillary haematocrit has been estimated to be $\sim$8.5%.

Table 3 Physiological response to anaemia

Response	Comment
Increase in cardiac output	Anaemia causes a decrease in blood viscosity that reduces the resistance to blood flow. The net effect is an increase in blood flow to and from the heart (increased preload and decreased afterload). Increases in heart rate and/or myocardial contractility play a minor role as long as normovolaemia is maintained.
Increase in o_2ER	*At the systemic level*: there is a redistribution of blood flow to areas of high demand, like the myocardium and the brain. *At the micro-circulatory level*: capillary blood flow is increased and pre-capillary oxygen loss is reduced.
The red blood cell 2,3-disphosphoglycerate (2,3-DPG) concentration increases	Occurs in chronic anaemia. 2,3-DPG competes with oxygen to bind to Hb. An increased concentration of 2,3-DPG will promote the offloading of oxygen to the tissues (i.e. a right shift of the oxygen Hb dissociation curve).

The haemoglobin transfusion threshold

Assuming that patients are normovolaemic, it is important to appreciate what level of Hb is safe to achieve an adequate $\dot{D}_{O_2}$ that avoids tissue hypoxia. This is of increasing interest because blood transfusions carry risks and blood is an increasingly scarce resource that must be used carefully. The 'critical haemoglobin' has been studied in a series of experiments in healthy volunteers and surgical patients undergoing normovolaemic haemodilution. At a haemoglobin concentration of 50 g litre^{-1} heart rate, stroke volume, and cardiac output were increased but oxygen delivery was decreased. Despite this, calculated $\dot{V}_{O_2}$ and plasma lactate concentration remained relatively unchanged. Overall, this degree of severe anaemia was well tolerated but there were subtle effects on cognitive function and a small number of individuals developed asymptomatic ST-segment depression on the electrocardiograph. These experiments suggest that, in healthy young humans who are normovolaemic, the critical haemoglobin threshold is about 50 g litre^{-1}.

In practice, a haemoglobin transfusion threshold is required that allows a margin of safety above the critical haemoglobin but avoids unnecessary blood transfusions. A large multicentre study, the Transfusion Requirements In Critical Care (TRICC) trial, found that a restrictive transfusion strategy (maintaining the haemoglobin concentration between 70 and 90 g litre^{-1}) was at least as effective as and, possibly superior to, a liberal transfusion strategy (maintaining the haemoglobin concentration between 100 and 120 g litre^{-1}) in critically ill patients. Based on this study and other available evidence, guidelines have been produced that are a compromise between the critical haemoglobin threshold and the reassurance of a safety margin. These guidelines suggest that most stable critically ill patients, including those with mild ischaemic heart disease, can be managed with a haemoglobin transfusion threshold of 70 g litre^{-1}, aiming to keep the haemoglobin concentration between 70 and 90 g litre^{-1}. Critically ill patients with
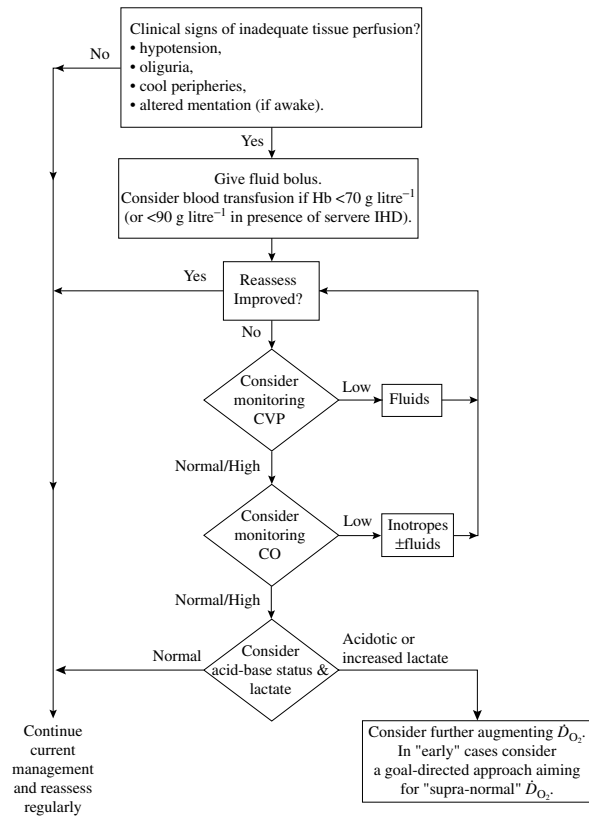

Fig. 3 Algorithm for the management of oxygen delivery.

severe ischaemic heart disease should probably have a transfusion threshold nearer 90–100 g litre^{-1}. These guidelines should be used in conjunction with clinical assessment of the oxygen supply/demand balance of individual patients.

What is an adequate oxygen delivery?

Assessing the adequacy of $\dot{D}_{O_2}$ in an individual patient can be difficult. A sensible stepwise approach is depicted in Figure 3.

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See multiple choice questions 87–89.