Physiology of oxygen transport

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Key points

- The transport of oxygen is fundamental to aerobic respiration.
- Oxygen transport within the human body occurs through both convection and diffusion.
- Within the pulmonary capillaries, one haemoglobin molecule binds up to four oxygen molecules in a cooperative manner.
- Global oxygen delivery, or oxygen dispatch, describes the total amount of oxygen delivered to the tissues each minute, and is a product of the cardiac output and arterial oxygen content.
- Oxygen diffuses from both the alveoli into the pulmonary capillaries and the systemic capillaries into the tissues, according to Fick’s laws of diffusion and the random walk of the diffusing particles.

Oxygen is vital for life-sustaining aerobic respiration in humans and is arguably the most commonly administered drug in anaesthesia and critical care medicine. Within the mitochondrial inner membrane, oxygen acts as the terminal electron acceptor at the end of the electron transport chain whereby oxidative phosphorylation results in the synthesis of adenosine triphosphate (ATP), the coenzyme that supplies energy to all active metabolic processes. This article will discuss the key physiological concepts underpinning the movement of oxygen within the human body and also highlight some clinical applications that serve as examples of these concepts.

Convective vs diffusive oxygen transport¹–⁴

With respect to human physiology, oxygen transport can be divided into that occurring through convection and that occurring by diffusion. In this context, convection describes the movement of oxygen within the circulation, occurring through bulk transport. This is an active process requiring energy, in this case derived from the pumping of the heart. On the other hand, diffusion describes the passive movement of oxygen down a concentration gradient, for example, from the microcirculation into the tissues (and ultimately the mitochondria).

Section 1: convective oxygen transport

Oxygen uptake into the blood

Deoxygenated venous blood becomes oxygenated in the pulmonary capillaries after diffusion down a concentration gradient across the alveolar capillary membrane (see Section 2: diffusive oxygen transport). The physiology of control of ventilation and the determinants of alveolar oxygen partial pressure, ventilation-perfusion matching, and diffusion within the alveolar-capillary unit are dealt with elsewhere.¹,⁵
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Haemoglobin and the oxygen dissociation curve\(^1,5-7\)

Oxygen is carried in the blood bound to haemoglobin and dissolved in plasma (and intracellular fluid). Haemoglobin, an allosteric protein, consists of four protein (globin) chains, to each of which is attached a haem moiety, an iron-porphyrin compound. Two pairs of globin chains exist within each haemoglobin molecule. Haemoglobin A consists of two \(\alpha\) and two \(\beta\) chains (denoted \(\alpha_{2}\beta_{2}\)), and accounts for more than 95% of normal adult haemoglobin. Mutations in the amino acid sequences in the globin chains give rise to both pathological [e.g. haemoglobin S (\(\alpha_{2}\beta_{2}\), sickle-cell disease) and non-pathological haemoglobin variants [such as haemoglobin A2 (\(\alpha_{2}\delta_{2}\))]. Fetal haemoglobin is denoted haemoglobin F (\(\alpha_{2}\gamma_{2}\)) and is replaced by haemoglobin A during the first year of life.

Once oxygen has diffused across the alveolar membrane, it binds reversibly to haemoglobin within the pulmonary capillaries in a cooperative manner forming oxyhaemoglobin. Up to four molecules of oxygen can be carried simultaneously by one haemoglobin molecule. When a molecule of oxygen binds to haem, the shape of the globin chain is altered, leading an overall change in the quaternary structure of haemoglobin. Subsequent oxygen molecules are then bound with greater affinity. This relationship is best described by the sigmoid-shaped oxyhaemoglobin dissociation curve (ODC, Fig. 1).

Haemoglobin exists in two forms: taut (T), which has a low affinity for oxygen; and relaxed (R), which has a high affinity for oxygen. The taut form predominates in the tissues (a high carbon dioxide, low pH environment) promoting oxygen release, whereas the relaxed form binds oxygen more avidly in areas of high pH, low carbon dioxide tension, and high partial pressures of oxygen (such as in the alveoli). This relationship between haemoglobin, oxygen binding, carbon dioxide tension, and pH is known as the Bohr effect.

Carbon dioxide is returned to the lungs from the tissues dissolved in the plasma, either directly or as bicarbonate, and through the formation of carbaminohaemoglobin species within the erythrocyte. Deoxygenated blood has a greater ability to transport carbon dioxide when compared with oxygenated blood, and this is known as the Haldane effect. In combination therefore, the Bohr and Haldane effects promote oxygen binding and carbon dioxide release in the pulmonary capillaries, with the reverse occurring in the tissues.

Haemoglobin has a maximum theoretical oxygen-carrying capacity of 1.39 ml O\(_2\) g\(^{-1}\) Hb (known as Hüfner’s constant), and therefore, a theoretical maximum oxygen capacity of 20.85 ml O\(_2\) 100 ml\(^{-1}\) blood at a ‘normal’ haemoglobin concentration of 15 g dl\(^{-1}\) (range 13.5–18.0 in men, 11.5–16.0 in women). However, due in part to the existence of abnormal forms of haemoglobin such as methaemoglobin and carboxyhaemoglobin, which reduce the oxygen-carrying capacity of haemoglobin, empirically this value seems to be closer to 1.31 ml O\(_2\) g\(^{-1}\) Hb.\(^5,11\) Haemoglobin oxygen saturation is a percentage expression of the number of oxygen binding sites occupied out of the maximum number of oxygen binding sites available.

The \(P_{50}\) is the partial pressure of oxygen at which haemoglobin is 50% saturated. It is a marker of haemoglobin’s affinity for oxygen and is used to compare changes in the position of the curve. The ODC position changes in the face of various chemical and physiological factors, and also with different haemoglobin species. The various factors and their effects on the curve are described in Table 1, and also the effects of a change in position of the curve on oxygen loading and unloading.

2,3-Diphosphoglycerate\(^6,12,13\)

2,3-Diphosphoglycerate (2,3-DPG) is an organic phosphate produced during glycolysis and found in the red blood cell, promoting haemoglobin oxygen release. Of clinical relevance:

- Increased 2,3-DPG production is seen in anaemia, which may minimize tissue hypoxia by right-shifting the ODC and increasing tissue oxygen release.
- 2,3-DPG undergoes metabolism in banked donor blood causing reduced oxygen unloading capacity after transfusion.
- Inorganic phosphate is a substrate for the production of 2,3-DPG and thus capillary haemoglobin oxygen release may be impaired if hypophosphataemia is not corrected. Causes of hypophosphataemia can be divided into: decreased intestinal absorption (e.g. malnutrition); internal redistribution (e.g. in acute leukaemia and recovery from diabetic ketoacidosis); or increased renal excretion (e.g. following corticosteroid use and volume expansion).
- In critical care, hypophosphataemia is often seen in sepsis, after operation, in refeeding syndrome, in diabetic ketoacidosis (due to increased urinary phosphate excretion), and during renal replacement therapy. Hypophosphataemia is also noted after an acute liver injury caused by, for example, paracetamol overdose and after hepatic resection.

Table 1 Factors that affect the standard human oxygen dissociation curve. Adapted from Thomas and Lumb\(^8\) and Leach and Treacher\(^12\)

<table>
<thead>
<tr>
<th>Left-shifted ODC ((1P_{50}))</th>
<th>Right-shifted ODC ((P_{50}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes</td>
<td>Causes</td>
</tr>
<tr>
<td>(\uparrow) pH ((\text{H}^+))</td>
<td>(\uparrow) pH ((\text{H}^+))</td>
</tr>
<tr>
<td>(\downarrow) P(_{\text{ACO}})</td>
<td>(\uparrow) P(_{\text{ACO}})</td>
</tr>
<tr>
<td>(\downarrow) 2,3-diphosphoglycerate</td>
<td>(\downarrow) 2,3-diphosphoglycerate</td>
</tr>
<tr>
<td>(\uparrow) Temperature</td>
<td>(\downarrow) Temperature</td>
</tr>
<tr>
<td>Effect</td>
<td>Effect</td>
</tr>
<tr>
<td>Increased haemoglobin oxygen affinity, enhanced oxygen binding</td>
<td>Decreased haemoglobin oxygen affinity, enhanced release of oxygen in the tissues</td>
</tr>
<tr>
<td>Others</td>
<td>Others</td>
</tr>
<tr>
<td>Fetal haemoglobin</td>
<td>Adult haemoglobin</td>
</tr>
<tr>
<td>Carbon monoxide poisoning</td>
<td></td>
</tr>
<tr>
<td>Methaemoglobinenaemia</td>
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</table>
Oxygen content\textsuperscript{1,11,12}

The oxygen content of arterial blood is the sum of the oxygen bound to haemoglobin and oxygen dissolved in plasma (where the amount of oxygen dissolved is proportional to the partial pressure exerted by oxygen on the plasma at a given temperature, obeying Henry’s law). It is the amount of oxygen in each 100 ml of blood and is calculated by the equation:

\[
\text{Arterial oxygen content} = \text{bound oxygen + dissolved oxygen}
\]

\[
\text{CaO}_2 = (1.31 \times \text{Hb} \times \text{SaO}_2 \times 0.01) + (0.0225 \times \text{PaO}_2)
\]

where 1.31 is Hüfner’s constant, the directly measured maximum oxygen-carrying capacity per gram of haemoglobin [ml O\textsubscript{2} g\textsuperscript{-1} Hb], reduced from the theoretical maximum binding capacity of 1.39 ml O\textsubscript{2} g\textsuperscript{-1} Hb due to the presence of abnormal haemoglobin species in vivo (e.g. carboxyhaemoglobin and methaemoglobin), Hb the amount of haemoglobin in grams per decilitre (g dl\textsuperscript{-1}), \text{SaO}	extsubscript{2} the arterial haemoglobin saturation in per cent, 0.0225 the solubility coefficient of oxygen at body temperature; the number of millilitres of oxygen dissolved per 100 ml of plasma per kilopascal (ml O\textsubscript{2} 100 ml\textsuperscript{-1} plasma kPa\textsuperscript{-1}), and \text{PaO}\textsubscript{2} the partial pressure of oxygen in arterial blood in kilopascals (kPa).

Therefore, inserting average figures for a ‘normal’ adult male breathing air at sea level at rest [F\textsubscript{O}\textsubscript{2} 0.21, 1 atm (101.325 kPa), \text{SaO}\textsubscript{2} 100%, Hb 15 g 100 ml\textsuperscript{-1}, \text{PaO}\textsubscript{2} 13.3 kPa], the arterial oxygen content can be calculated as 19.95 ml 100 ml\textsuperscript{-1} blood.

Oxygen delivery\textsuperscript{5,11,14}

Traditionally, in anaesthesia and critical care medicine, the product of cardiac output and oxygen content has been referred to as ‘oxygen delivery’, despite the fact that this is inherently incorrect. First of all, the word delivery implies that all the oxygen so described is delivered to, and utilized by, metabolizing cells. This is clearly inaccurate, as we know that the oxygen extraction ratio at rest is \textasciitilde25%, and that this ratio rarely if ever exceeds 75%, even under conditions of exceptional metabolic stress. The term ‘oxygen dispatch’ has sometimes been preferred for this reason. Secondly, the word delivery implies an active external process responsible for ensuring arrival of oxygen at the cell. However, this set of processes can just as easily be viewed from the perspective of the cell ‘sucking in’ oxygen to meet requirements. Notwithstanding these comments, we will continue with oxygen delivery within the context of this article in order to remain consistent with common custom and usage.

Global oxygen delivery describes the amount of oxygen delivered to the tissues in each minute and is a product of the cardiac output and arterial oxygen content.

Thus:

\[
\text{Oxygen delivery} = \text{cardiac output} \times \text{arterial oxygen content}
\]

\[
\text{Do}_2 = \text{CO} \times \text{CaO}_2
\]

or

\[
\text{Do}_2 = \text{CO} \times [(1.31 \times \text{Hb} \times \text{SaO}_2 \times 0.01) + (0.0225 \times \text{PaO}_2)]
\]

With a resting cardiac output of 5 litre min\textsuperscript{-1} (and using the same figures as before), a ‘normal’ adult male has an oxygen delivery of 997.5 ml min\textsuperscript{-1}. It is important to note that this is clearly an overall measure of oxygen delivery and does not describe regional differences—oxygen flux to each tissue bed is not constant throughout the body, rather the microcirculation responds to altering tissue metabolic demands by varying the regional and local blood flow.

Factors affecting oxygen delivery\textsuperscript{5,11,14}

As can be seen from the above equation, alterations in cardiac output, arterial oxygen saturation, and haemoglobin concentration will affect oxygen delivery. Sir Joseph Barcroft first presented the causes of reduced oxygen delivery in 1920,\textsuperscript{15} classically describing ‘stagnant anoxia’ (reduced CO or reduced regional blood flow), ‘anoxic anoxia’ (arterial hypoxaemia), and ‘anaemic anoxia’ (reduced haemoglobin). Latterly, ‘crotamphathic hypoxia’ (e.g. secondary to sepsis and inflammation) and ‘histotoxic hypoxia’ (e.g. cyanide poisoning) have been recognized. Under these circumstances, cells have a relative or absolute failure of the capacity to utilize oxygen and increasing Do, will have little effect in correcting the hypoxia. Any cause of microcirculatory dysfunction will affect oxygen delivery,\textsuperscript{16} for example, sepsis where nitric oxide production is increased leading to disorders of autoregulation (matching of supply with demand within the tissues) along with the decreased vascular tone that manifests clinically as hypotension.

Manipulation of global oxygen delivery to improve patient outcome has been the focus of goal-directed haemodynamic therapy (GDT) since its inception in the 1980s. Given that continuing evidence supports equivalent outcome with low blood transfusion triggers in many clinical contexts (haemoglobin concentrations 7.0–9.0 g 100 ml\textsuperscript{-1}),\textsuperscript{17} and the increasing interest in limiting hyperoxia,\textsuperscript{18} it is clear that the greatest changes in Do, (convective oxygen delivery) will be achieved through the manipulation of cardiac output.\textsuperscript{15} Diffusive oxygen transport will be discussed later.

Oxygen consumption\textsuperscript{11,12,14}

Oxygen consumption (V\textsubscript{O}\textsubscript{2}) is the amount of oxygen consumed by the tissues per minute and can be calculated either through direct analysis of respiratory gases or indirectly, using Fick’s principle, by measuring the oxygen content of mixed venous blood (i.e. blood in the pulmonary arteries), Cv\textsubscript{O}\textsubscript{2}, and using the equations:

\[
\text{CvO}_2 = (1.31 \times \text{Hb} \times \text{SvO}_2 \times 0.01) + (0.0225 \times \text{PvO}_2)
\]

\[
\text{VO}_2 = \text{CO} \times (\text{CaO}_2 - \text{CvO}_2)
\]

Again inserting ‘normal’ values for an adult male breathing air at sea level at rest [F\textsubscript{O}\textsubscript{2} 0.21, 1 atm (101.325 kPa), S\textsubscript{vO}\textsubscript{2} 75%, Hb 15 g 100 ml\textsuperscript{-1}, P\textsubscript{vO} 5.3 kPa, C\textsubscript{aO} 19.95 ml 100 ml\textsuperscript{-1}, CO 5 litre min\textsuperscript{-1}], the mixed venous oxygen content can be calculated as 14.86 ml 100 ml\textsuperscript{-1} blood, and therefore the oxygen consumption as 254.5 ml min\textsuperscript{-1}.

Oxygen delivery (oxygen flux) and oxygen consumption are global measures. At tissue level, blood flow is denoted as Q, [O\textsubscript{2}]\text{in} describes the oxygen content of the afferent blood (analogous to Ca\textsubscript{O}_2 globally), and [O\textsubscript{2}]\text{out} describes the oxygen content of the efferent blood (analogous to Cv\textsubscript{O}_2 globally). Therefore, at tissue level:

\[
\text{Vo}_2 = Q \times ([\text{O}_2]_{\text{in}} - [\text{O}_2]_{\text{out}})
\]

Factors affecting oxygen consumption\textsuperscript{14}

The rate of oxygen consumption depends on cellular metabolic demand and can be manipulated. For example, the use of therapeutic hypothermia to reduce cerebral metabolic demand post-cardiac arrest in order to improve neurological outcome is well documented.\textsuperscript{19} Commonly encountered factors that affect Vo\textsubscript{2} are documented in Table 2.
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Table 2 Factors that affect oxygen consumption. Adapted from McLellan and Walsh \(^{11}\)

<table>
<thead>
<tr>
<th>Factors that increase (V_{O_2})</th>
<th>Factors that decrease (V_{O_2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Sedation/analgesia/neuromuscular blockings agents/antipyretics</td>
</tr>
<tr>
<td>Trauma (including surgery and burns)</td>
<td>Hypovolaemia/shock states</td>
</tr>
<tr>
<td>Inflammation/sepsis/pyrexia</td>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Shivering</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Pain</td>
<td>Physiotherapy (quoad patients in critical care)</td>
</tr>
</tbody>
</table>

Oxygen extraction ratio \(^{2,11,12,14,18,20}\)

This is the fraction of oxygen delivered via the cardiovascular system that is actually utilized by the tissues, and is therefore the ratio of oxygen consumption to oxygen delivery:

\[
O_2ER = \frac{V_{O_2}}{D_O} \quad \text{(globally)}
\]

\[
O_2ER = \frac{C_{O_2} - C_{vO_2}}{C_{O_2}}
\]

or

\[
O_2ER = \frac{(O_2_{\text{in}} - O_2_{\text{out}})}{(O_2)_{\text{in}}}
\]

In health, only 20–30% of the oxygen delivered to the tissues is utilized (an \(O_2ER\) 0.2–0.3) and it can be seen that by substituting the figures presented earlier (namely \(V_{O_2}\) 254.5 ml min\(^{-1}\) and \(D_O\) 997.5 ml min\(^{-1}\)) an adult male has an \(O_2ER\) 0.26 at rest. Under these circumstances, oxygen consumption is said to be ‘supply independent’ and \(V_{O_2}\) is maintained even in the face of a decreasing \(D_O\). However, at a critical \(D_O\) (\(D_O\)crit) of ~4 ml kg\(^{-1}\) min\(^{-1}\) in humans, the \(O_2ER\) is maximal (\(O_2ER\) 0.6–0.8) and \(V_{O_2}\) is said to become ‘supply dependent’. If \(D_O\) continues to decrease further below the \(D_O\)crit, or if \(V_{O_2}\) increases for a given \(D_O\)crit, tissue hypoxia ensues with resultant anaerobic respiration and lactate production secondary to an imbalance between ATP supply and demand (producing a type A hyperlactataemia). \(^{21}\) While this theoretical framework underpins our understanding of oxygen physiology in the shocked patient, the empirical evidence supporting these phenomena is limited and the concepts remain controversial. It is also important to highlight that even if global oxygen consumption appears to be supply independent, it does not rule out pathological oxygen supply dependency at a regional or local level, which may only manifest clinically at a later stage. \(^{22}\)

Figure 2 illustrates the theoretical biphasic relationship between oxygen consumption and oxygen delivery. The solid line ‘ABC’ depicts what is seen in health, the broken line ‘DEF’ in critical illness. Points B and E depict \(D_O\)crit in health and critical illness, respectively. In health, \(V_{O_2}\) is ‘supply independent’ between B and C (\(D_O\) is above \(D_O\)crit) and ‘supply dependent’ between A and B. \(O_2ER\) is known to increase during exercise, peaking at maximal exercise at 0.8. This is because although \(D_O\) increases, it does not match the increase in \(V_{O_2}\) required by exercise. In critical illness, however, especially sepsis, \(V_{O_2}\) may continue to increase, even with increasing \(D_O\) (demonstrated by the line EF), and \(D_O\)crit may be greater than in health. This is termed a ‘pathological \(D_O\) dependency’ and \(O_2ER\) may not increase proportionately with \(V_{O_2}\). Slopes AB and DE represent the maximum \(O_2ER\). The gradient of slope DE is reduced in critical illness as the tissues are less able to extract oxygen.

Another method used clinically to assess \(D_O\) is to measure pulmonary artery mixed venous blood saturation (\(SV_{O_2}\)) using a pulmonary artery catheter (PAC) as this represents unused oxygen returned to the lungs from the tissues. Targeting an \(SV_{O_2}\) of >70% suggests adequate resuscitation of a critically unwell patient has been performed and \(D_O\) optimized. However, under these circumstances, consideration should be given to the possibility that a ‘normal’ \(SV_{O_2}\) may be an indication of inadequate oxygen utilization, be it through microcirculatory dysfunction or altered cellular oxygen uptake, rather than adequate oxygen delivery. In the absence of a PAC, central venous saturations can be used as a surrogate (\(Sv_{O_2}\)), with the normal range only marginally higher than the 68–77% range of \(SV_{O_2}\).

Section 2: diffusive oxygen transport

Diffusion

Within the lung, oxygen diffuses from the alveoli into the pulmonary capillaries, driven by the gradient between the partial pressure of oxygen in the alveolar space and that in the deoxygenated pulmonary capillary blood. In the tissues, oxygen diffuses down a gradient between oxygenated blood in the systemic capillaries and the oxygen-consuming cells.

Diffusion can be described by either a phenomenological approach using Fick’s laws or an atomistic approach applying the principle known as the random walk of the diffusing particles (another example of which is Brownian motion).

Fick’s laws of diffusion \(^{14}\)

Adolf Fick (1829–1901) derived two laws of diffusion in 1855. His first law states that at steady state, particles move from an area of high concentration to an area of low concentration, the rate of which is proportional to the difference in their concentrations (i.e. it relates flux to concentration gradient). Thus:

\[
J = -D \frac{\partial C}{\partial x}
\]
where \( J \) is the diffusion flux [(amount of substance) area\(^{-1}\) time\(^{-1}\)], \( D \) the diffusion coefficient or diffusivity of the diffusing species (length\(^2\) time\(^{-1}\)), \( C \) the concentration (amount of substance volume\(^{-1}\)), and \( x \) the position (diffusion length).

Fick’s second law describes how diffusion causes the concentration gradient to change with respect to time:

\[
\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}
\]

Fig 3 A diagram illustrating the importance of diffusion distance from capillary to cell and local oxygen tension in determining diffusive oxygen flow rate. Taken from Leach and Treacher\(^1\) with kind permission from BMJ Publishing Group Ltd.

Fig 4 A participant undergoing CPET. Reproduced with permission.
where $C$ is the concentration (amount of substance volume$^{-1}$), $t$ the time, $D$ is diffusion constant or diffusivity of the diffusing species (length$^2$ time$^{-1}$), and $x$ the position (length).

Therefore, adapting Fick’s first law to human physiology, it can be shown that the rate of diffusion (rate of flux) for a gas across a capillary wall is:

$$\text{Flux} = \frac{D A (C_1 - C_2)}{T}$$

where $D$ is the diffusion constant (or capillary permeability) for a specific gas at a specified temperature, combining the factors that affect diffusion of a substance such as molecular size, charge, and lipid solubility, $A$ the capillary surface area, $C_1 - C_2$ the concentration gradient (or difference in partial pressures) of the gas across the membrane (flow is from $C_1$ to $C_2$), $T$ the capillary wall thickness, $S_{ol}$ the gas solubility, and $MW$ the molecular weight.

Thus, although the global oxygen delivery (oxygen flux) may be manipulated through changes in cardiac output and oxygen content, at a tissue level diffusion distance and partial pressure gradients will have the greatest effect in altering the diffusive oxygen flux. This is shown in Figure 3.

**Section 3: clinical applications of oxygen transport**

Whole-body oxygen transport and utilization can be estimated using two principle approaches:

- Estimation of oxygen mass transport, through separate measurement of cardiac output and the elements of oxygen content. In combination with the latter approach, additional measurement of mixed venous oxygen content allows calculation of oxygen extraction and therefore oxygen consumption.
- Evaluation of oxygen consumption through measurement of steady state, or dynamically changing, oxygen uptake using expired gas analysis to measure gas flows and concentrations [cardiopulmonary exercise testing (CPET), metabolic cart].

It is worth noting that expired gas analysis, although less invasive, is more direct in its measurement of cellular oxygen consumption.
Cardiopulmonary exercise testing\textsuperscript{23,24}

In addition to its use in the physiological assessment of elite athletes, CPET has been developed as a tool to assess a patient’s pre-operative functional capacity, that is, their ability to do external physical work, before major surgery. Also determining \( V_{\text{O}_{2\text{max}}} \), a subject’s (ventilatory) anaerobic threshold (AT) may be calculated. The AT is the \( V_{\text{O}_{2}} \) (in \( \text{ml kg}^{-1} \text{min}^{-1} \)) at which, with increasing work, anaerobic metabolism commences. While this is often presented as being evidence of the demand for oxygen delivery to the tissues, it may in fact be more closely related to the recruitment of muscle fibres with different patterns of metabolism.

During CPET, anaerobic metabolism is shown when carbon dioxide production \((V_{\text{CO}_2})\) outstrips \( V_{\text{O}_2} \), whereas during aerobic metabolism, \( V_{\text{CO}_2} \) increases proportionately with \( V_{\text{O}_2} \) (see panel 1 in Fig. 5). A high level of functional capacity (physical fitness) is an index of a substantial physiological reserve over and above resting values. This in turn is inferred to provide benefit in withstanding the physiological challenge of major surgery. In patients undergoing major surgery, postoperative morbidity and mortality are consistently increased in individuals with lower values of AT and \( V_{\text{O}_{2\text{max}}} \). A standard CPET set-up is shown in Figure 4 and an example of a nine-panel plot in Figure 5. See the American Thoracic Society/American College of Chest Physicians Joint Statement\textsuperscript{25} and the American Heart Association Scientific Statement\textsuperscript{26} on CPET for more in-depth reviews.

Goal-directed hemodynamic therapy

In GDT, blood flow and/or oxygen delivery \((D_O)_2\) is augmented through the use of supplemental oxygen and fluids (both crystalloids and colloids), and in some cases, additional inotropes, vasopressors, and vasodilators are also used to achieve the stated goals. Blood flow measurements are obtained using haemodynamic monitoring equipment such as the oesophageal Doppler (Deltex Medical Ltd), LiDCO (LiDCO Ltd), and PiCCO (PULSION Medical Systems SE, Germany). A variety of physiological variables have been targeted including \( D_O_2 \), cardiac index \((C_I)\), stroke volume \((S_V)\), and indexed systemic vascular resistance \((S_VR)\). Originally, measurement of these variables required thermodilution techniques and a pulmonary artery (right heart) catheter.\textsuperscript{27} However, this modality has subsequently gone out of favour following concerns about its safety.\textsuperscript{28}

GDT is used perioperatively in anaesthesia and critical care. Theoretically, by improving \( D_O_2 \) (convection) to the tissues, the oxygen concentration gradient between the microcirculation and the cells increases, causing increased oxygen diffusion (or rather increased diffusive flux). However, although GDT may provide more oxygen at tissue level, this will not necessarily affect oxygen utilization (in the absence of supply-dependency). It is also assumed that capillary surface area and diffusion coefficient remain constant, which may not hold if tissue fluid status changes, for example, in the case of the tissue oedema often seen in critically unwell patients. A more in-depth review of GDT is beyond the scope of this article; however, see the clinical reviews by Lobo and de Oliveira,\textsuperscript{29,30} Ramsingh and colleagues,\textsuperscript{31} and Lees and colleagues,\textsuperscript{32} and also the Cochrane Review by Grocott and colleagues\textsuperscript{33} for further information.

Conclusion

The convective and diffusive transport of oxygen from the air into the tissues is clearly complex, with each step in the process affected by multiple factors. However, understanding how our respiratory and cardiovascular systems combine to facilitate the movement of oxygen from where it enters the circulation in the pulmonary capillary to where it is ultimately utilized in mitochondria within cells is fundamental for anaesthetists.

Declaration of interest

M.G.M. is Smiths Medical Professor of Anaesthesia and Critical Care UCL and a Consultant at UCLH. He is Director of the UCL Centre for Anaesthesia and The UCL Discovery Lab and a resident PI at the Institute of Spots Exercise and Health. He is a paid Consultant for Edwards Lifesciences (via UCL Consulting and independently) and Deltex in the USA. He was a National Clinical Advisor for the Department of Health Enhanced Recovery Partnership until May 2013; Stock holder and advisory board for Medical Defence Technologies LLC (\textsuperscript{2}Gastrostim\textsuperscript{2} patented); Director Bloomsbury Innovation Group a community interest company owned by UCLH Charity; Co-Inventor of \textsuperscript{2}QUENCH\textsuperscript{2} (fluid managementsystem) IP being exploited by UCL Business. His institution has also received charitable donations and grants from Smiths Medical Endowment, Deltex Medical and Fresenius-kabi. He was also co-author of the GIFTASUP guidelines on perioperative fluid management; Editor in Chief of Peri-operative Medicine; on the Editorial Board of the BJA and Critical Care; a member of the Improving Surgical Outcomes Group; Expert advisor to the NICE IV fluids guideline development group; Chair of the Board of The National Institute of Academic Anaesthesia; Co-Director Xtreme Everest; Co-Chair Evidence Based Perioperative Medicine (EBPOM). In the past 20 years he has also received honoraria and travel expenses from Fresenius-kabi, B Braun, Baxter, Cheetah, LiCo, ADIX, Hospira and Massimo. He does a small amount of Private Medical Practice.

M.P.G. serves on the Medical Advisory Board of Sphere Medical Ltd through a consulting contract via the University of Southampton. He also serves (no remuneration for any of these roles) as a director of Oxygen Control Systems Ltd, as a director of the Bloomsbury Innovation Group (a novel community interest group using an innovative low-cost open source IP model to drive innovation and development in medical devices in the areas of anaesthesia and critical care within the NHS) and is chair of the board of the Xtreme-Everest Community Interest Company (jointly owned by University of Southampton and UCL; maintenance, development and exploitation of the Xtreme Everest Bioresource). He also leads the Xtreme-Everest Oxygen Research Consortium which has received unrestricted research grant funding paid to his institution (UoS/UHS/UCL/UCLH) from BOC Medical (Linde Group), Ely-Lilly Critical Care, Smiths Medical, Deltex Medical, London Clinic, Rolex, UCLH Special Trustees, and the Royal Free Special Trustees. He has also received honoraria for speaking and/or travel expenses from Edwards Lifesciences (2009 and 2016), Fresenius-Kabi (2008), BOC Medical (Linde Group) (2008), Ely-Lilly Critical Care (2008) and Cortex GmBH (2008 & 2009).

J.-G.C.D. has no conflicts of interest to declare.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to BJA Education.

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