CHAPTER 1

GENERAL PHYSIOLOGY: BLOOD, OXYGEN AND THE CIRCULATION

Key points

1. Blood is a complex organ system composed of:
   - red blood cells, whose primary function is to transport oxygen to tissues
   - white blood cells, whose primary function is to fight infection, provide immunity and destroy foreign material that has invaded the body
   - platelets, whose primary role is to promote coagulation at the site of vascular wall injury
   - plasma, which is noncellular fluid containing many important proteins, electrolytes and other nutrients essential to maintain health
   - vascular endothelium, which is in constant contact with the blood and is essential for nutrient transport and haemostasis.

2. Blood coagulation is a complex process consisting of:
   - primary haemostasis involving platelet activation and aggregation at the site of bleeding (vascular wall)
   - secondary haemostasis, which involves the activation of two cascading plasma protein pathways to produce fibrin and create a strong clot at the site of bleeding
   - fibrinolysis, which limits the final size of the clot to prevent thrombosis extending beyond the site of injury.

   An imbalance of these mechanisms can lead to excessive bleeding (coagulopathy) or clotting (thrombosis).

3. Blood oxygen transport to tissues is dependent on:
   - sufficient diffusion of oxygen from the atmosphere into the plasma and red blood cell haemoglobin
   - an adequate arterial oxygen content comprising red blood cell haemoglobin concentration and its saturation with oxygen
   - delivery of arterial oxygen content with a cardiac output that is adequate to meet the metabolic demands of the tissues to maintain aerobic metabolism.

   Failure to meet the oxygen-based metabolic demands of tissue results in shock, which can be fatal.

1.1 Introduction

The human body consists of an integrated aggregate of bony and soft tissue structures formed into various organ systems working under a coordinated control system. This allows for a remarkable number of functions, many of which are automated and designed to preserve life. No less complex than the others, blood is a sophisticated organ system consisting of several compartments, cell types and biochemical mediators, among others, to which all other organ systems are critically linked and are dependent on. A basic understanding of the composition and function of blood is critical to an overall understanding of health and the use of blood and blood products in the treatment of disease.

Learning outcomes

After studying this chapter, the reader will be able to describe:

1. the content and function of blood and its components
2. blood physiology
3. coagulation and haemostasis
4. supply of oxygen to the body

1.2 Body fluids and compartments

The critical role of blood in providing nutrients to tissues and removing waste is dependent on a remarkable connected network of fluid-filled compartments allowing for both passive and active diffusion.

Including its presence in blood, water is the major contributor to body mass, accounting for nearly 60% of adult body mass and upwards of 80% of the body mass of children. Proteins, fats, sugars and minerals account for the remaining body mass, with a large proportion of these being distributed and dissolved in body water *(1)*.

Body fluids exist in two main compartments:

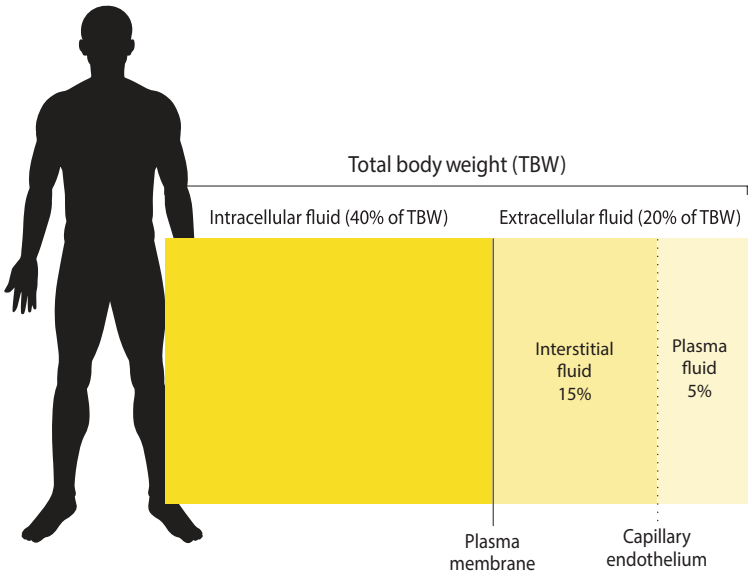
1. Intracellular fluid compartment (ICF): this is the fluid within the cells themselves, which accounts for approximately 40% of body weight.

2. Extracellular fluid compartment (ECF): the ECF is composed of two spaces:
   - intravascular space: blood and plasma confined to circulating within the vascular system, accounting for approximately 8–10% of body weight;
   - interstitial space: non-blood and non-plasma fluid existing outside the vascular system but within organs, which surrounds and bathes cells of the organs, accounting for approximately 15% of body weight.

Fig. 1.1 illustrates the structure of these compartments, including the proportions in which they generally exist and the mechanisms by which they are separated from each other.

The fluid in each of these compartments serves specific functions in maintaining health. The composition of these fluids together with differences in the membranes that separate them allow for the creation of forces that permit the essential movement of fluid constituents across membranes to meet the needs of the organs.

Figure 1.1. Structure of the body fluid compartments



These forces include:

1. Diffusion: This refers to the movement of discrete substances across compartments through concentration gradients (from high concentration to lower concentration).

2. Filtration: Hydrostatic pressure causes fluid to be filtered through a membrane.

3. Active transport: Mechanisms within a membrane exist to actively move a substance across the membrane.

4. Osmosis: This is the passive movement of water into a compartment that has a high concentration of impermeable substances, but which is freely permeable to water. The concentrations of these impermeable substances on each side of the membrane determine the extent of water movement.

Table 1.1 provides a comparison of the composition of electrolytes and the protein content within the major compartments.

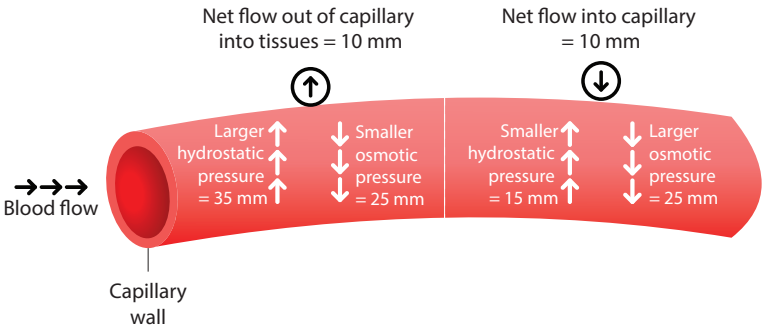
Although the plasma and interstitial compartments are quite similar, their protein content is very different. Also, as can be seen from Table 1.1, the ICF is significantly different from both components of the ECF. The major protein in the ECF is albumin. It exists mainly in the vascular space and is thus known as plasma protein. Albumin and other ECF proteins are relatively large, making cellular membranes impermeable to them. The ICF also contains high concentrations of a wider variety of proteins than are present in plasma and are for the most part too large to pass through the membrane.

Table 1.1. Composition of electrolytes and protein content within the major compartments

	Plasma (mmol/L)	Interstitial fluid (mmol/L)	Intracellular fluid (mmol/L)
Na^+	142	144	10
K^+	4	4	160
Ca^{2+}	2.5	1.25	1.5
Mg^{2+}	1	0.5	13
Cl^-	102	114	2
HCO_3^-	26	30	8
PO_4^{2+}	1	1	57
SO_4^{2-}	0.5	0.5	10
Organic acid	6	5	0
Protein	16	2	55

Oncotic pressure, or colloid osmotic pressure, is a form of osmotic pressure induced by proteins, notably albumin, in a blood vessel's plasma (blood/liquid). It displaces water molecules, thus creating a relative water molecule deficit with water molecules moving back into the circulatory system within the lower-pressure venous end of the capillaries. It has the opposing effect of both hydrostatic blood pressure pushing water and small molecules out of the blood into the interstitial spaces within the arterial end of capillaries and interstitial colloidal osmotic pressure. These interacting factors determine the partition balancing of total body extracellular water between the blood plasma and the larger extracellular water volume outside the bloodstream. Fig. 1.2 illustrates the balance of hydrostatic and oncotic forces in the capillaries, which contribute to fluid and nutrient transport to and from tissues.

Figure 1.2. Illustration of the balance of hydrostatic and oncotic forces in the capillaries



The ICF is also subject to water volume regulation, which again is mainly dependent on osmotic forces. However, unlike the ECF, which is largely protein-dependent, the ICF is mostly dependent on differences in the concentrations of sodium and potassium, which are actively controlled by pumps situated in the cell membrane.

1.3 Blood, platelets, plasma, endothelium and coagulation

Although it is not typically viewed as such, blood should be considered an organ system. Like other organ systems such as the central nervous and gastrointestinal systems, blood is made of a complex but integrated variety of cell types and has a distinct biochemistry. This allows it to provide critical nutrients to and remove waste from all other organ systems as well as to provide life-saving functions such as fighting infection and coagulation. Also, similar to other organ systems, it may malfunction for many reasons and can be subject to injury and failure.

Blood is composed of a number of cellular and acellular components including red cells, white cells, platelets and plasma proteins. Because it is in constant contact with the vascular lining and the role it plays in coagulation, the endothelium should also be considered a critical component of blood.

Red blood cells

Red blood cells (erythrocytes) account for the majority of the cellular population of circulating blood and for approximately 40–45% of total circulating blood volume. The major function of red blood cells is to take up oxygen from the lungs and carry it to tissues throughout the body. Produced in the bone marrow under the hormonal influence of erythropoietin, red blood cells have an approximate lifespan of 120 days after entering the circulatory system from the bone marrow. After this time, red blood cells are disposed of by the liver and spleen's reticular endothelial system. Red blood cells achieve their major function of uploading and offloading oxygen by making use of the iron-based molecule haemoglobin. Haemoglobin is a protein that has two pairs of peptide chains each containing an iron ring. For adult haemoglobin, one pair of these peptides is the alpha (α) chain and the other is the beta (β) chain. Each of the four chains or subunits is capable of reversibly binding with one molecule of oxygen giving a total of four molecules of oxygen for one molecule of haemoglobin.

Measured in grams per decilitre (g/dl), the typical amounts of haemoglobin in an adult male and female are approximately >13 g/dl and >12 g/dl, respectively.

White blood cells

White blood cells or leukocytes are also produced by the bone marrow, as well as the lymphatic tissue, and make up less than 1% of total circulating blood volume. However, they play the critical role of combating infection, identifying, destroying and removing invading or foreign material from the body. They also help to develop immunity and resistance in response to natural exposure to infection or from purposeful immunization.

These functions are carried out by a heterogeneous population of white blood cells. The types and percentage contribution to the white blood cell family are as follows:

- neutrophils (55–73%)
- lymphocytes (20–40%)
- eosinophils (1–4%)

- monocytes (2–8%)
- basophils (0.5–1%).

White blood cells are usually measured and reported in numbers per microlitre (µl) or cubic millimetre (mm^3).

Platelets

Produced as small fragments from megakaryocytes in the bone marrow, the major function of the platelets is to respond to damage to the vascular wall, especially damage that could result in haemorrhage. Platelets adhere to the damaged vascular wall and release a number of mediators and enzymes that participate in the coagulation process. Platelets are a major component of the resulting clot and are incorporated with fibrin where they are capable of contracting, as a mechanism to strengthen the clot. Platelets are measured as number per microlitre of blood.

The microcirculation and endothelium

An important but overlooked aspect of the blood is the role of the endothelium and microcirculation, which are critical to ensure the delivery of nutrients such as oxygen to tissues, as well as coagulation. The microcirculation with its endothelial lining is estimated to cover an area of up to 7000 m^2 *(2)*. The individual microcirculatory unit is composed of the arteriole, capillary bed and postcapillary venule. Its role is to ensure the delivery of oxygen and other nutrients to tissues in excess of their needs, as well as to remove products of metabolism. With an estimated 10^{13} endothelial cells in an adult, the endothelium is constantly exposed to blood. Thus, manipulation of the blood will inevitably affect the vascular system in some way. Injury to the endothelium can result in undesirable complications through three major mechanisms: paracellular permeability, dysfunctional haemostasis and inflammation *(3)*.

Coagulation

Coagulation is a complex but orchestrated process used by the body both to maintain vital blood flow within the vascular system to tissues and to prevent and reduce haemorrhage when the vascular system is injured. This process, which involves integrated cellular and noncellular components, is termed haemostasis. Imbalances in the system are major causes of a number of primary bleeding and clotting disorders as well as bleeding and clotting complications caused by a number of illnesses and injuries.

Coagulation and haemostasis can be divided into three major processes *(4)*:

1. *Primary haemostasis*: When injured and bleeding, the damaged endothelium of the blood vessels is the first to be involved in the process of haemostasis. This process includes vasoconstriction of the damaged vessels to reduce blood flow and the exposure of specific proteins and structures such as collagen, microfibrils and basement membranes that promote adhesion of platelets to the site. Platelet adhesion prompts the release of a number of mediators that promote further vasoconstriction and aggregation of additional circulating platelets at the site resulting in a primary platelet plug, which will grow to consist of trapped red cells.

2. *Secondary haemostasis*: Occurring in concert with primary haemostasis, the activation of an important acellular network and pathway of specific plasma proteins combined with phospholipids and calcium ions participate in clot formation. Known as the coagulation cascade, it consists of two pathways (intrinsic and extrinsic).

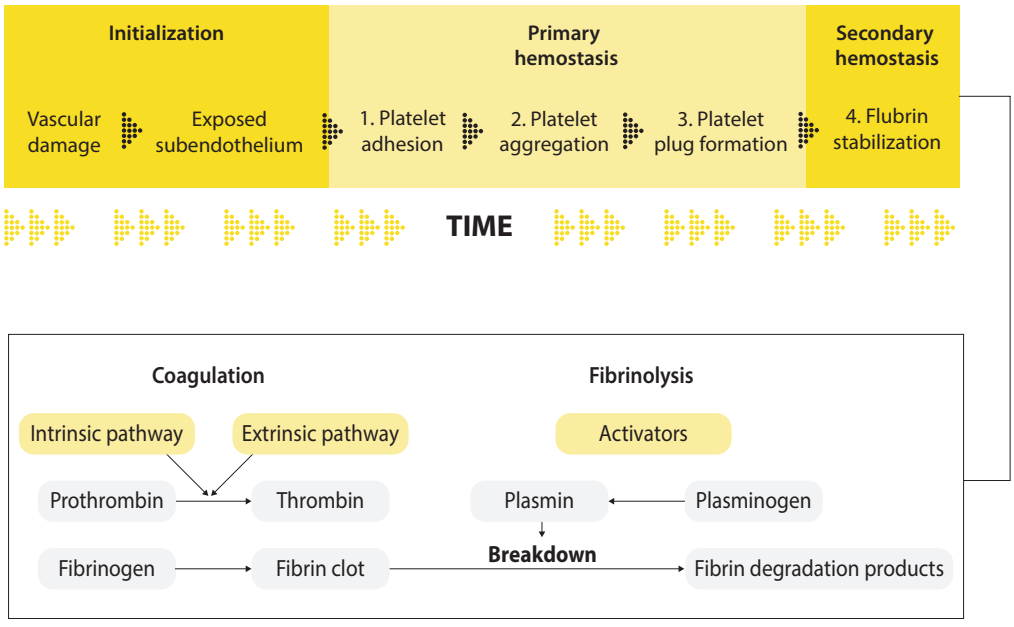
The intrinsic, or contact activation pathway, is triggered through the activation of several clotting proteins coming in contact with exposed collagen in the damaged vascular wall.

The extrinsic, or tissue factor pathway, is activated by the release of tissue factor from the damaged vascular wall. Activation of both pathways results in a cascade of enzymatic reactions leading to a final common pathway activating the protein thrombin. This causes the conversion of the soluble protein fibrinogen into insoluble fibrin, which is then incorporated into the platelet plug, strengthening it so that it becomes a fibrin clot.

3. *Fibrinolysis*: Although production of a fibrin clot is essential to produce haemostasis, it is also critical to have limitations to growth of the clot to prevent progressive thrombosis beyond the site of injury. This process of fibrinolysis or clot removal occursthrough several mechanisms including:
   - blood flowing past the clot to remove additional activated clotting factors;
   - activation of proteins designed to inactivate clotting factors; and
   - active degradation of the clot over time by specific enzymes such as plasmin.

Fig. 1.3 provides a high-level overview of the coagulation process. Although it is normally a very balanced process, major insults such as severe trauma with haemorrhage or severe inflammation, such as sepsis, can lead to drastic alterations resulting in extreme responses such as hyperfibrinolysis or thrombosis *(5, 6)*.

Figure 1.3. Overview of the coagulation process



1.4 The role of blood in supplying oxygen to the body

The primary purpose of blood and its components is to supply nutrients to tissues, remove waste from tissues, maintain haemostasis and assist in fighting infection. Critical to each of these functions is a constant supply of oxygen, which ensures life sustaining metabolism.

Basic oxygen transport

For tissues to receive oxygen, several fundamental processes must take place *(7)*.

- Oxygen is transferred from the lungs into the plasma.
- Oxygen is bound to haemoglobin in red blood cells.
- Oxygen is transported to the microcirculation where it is released to tissues for utilization.

Air contains mainly a mixture of oxygen, nitrogen and a small proportion of additional gases such as carbon dioxide. Each of these gases contribute to the total atmospheric pressure in proportion to their concentration. At sea level (760 mmHg or 101 kPA), air contains approximately 21% oxygen (160 mmHg or 21 kPA) with rest being mainly nitrogen (close to 79%).

Although the partial pressure of oxygen seems high, this level is reduced by the time air reaches the lung alveoli where diffusion of oxygen into the plasma occurs. Air humidification in the upper airways, transfer of air to the alveoli and diffusion of blood carbon dioxide from the blood plasma into the lung alveoli reduce the partial pressure of oxygen from 160 mmHg to 100 mmHg (13.3 kPa).

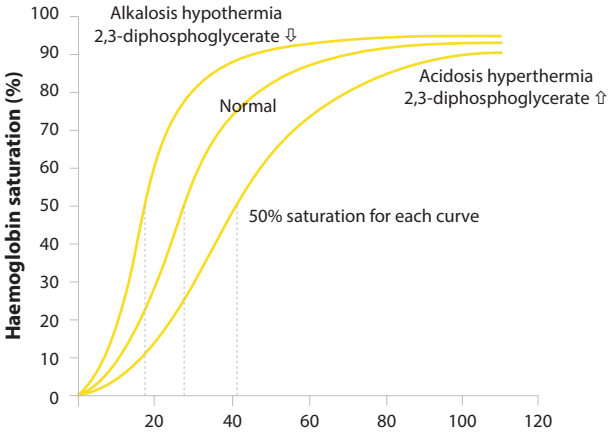
Although this is a significant drop, this partial pressure is still higher than the partial pressure of oxygen in the pulmonary capillary venous blood returning to the lung from the body, which in a resting state averages only 40 mmHg (5.3 kPA). This represents the main driving force, resulting in a rapid diffusion transfer into blood plasma from a higher-pressure gradient to a lower-pressure gradient.

In the absence of any alveolar barriers such as infection, oedema or other causes of damage, almost total equilibrium is achieved between the partial pressure of alveolar oxygen and the arterial capillary blood leaving the alveoli.

The main carrier of oxygen in the blood is the haemoglobin molecule present in red blood cells. As oxygen diffuses from the alveoli to the plasma, it rapidly crosses into the red cell, binding to haemoglobin until almost fully saturated (98 mmHg or 13 kPA). When fully saturated, each gram of haemoglobin can carry 1.36 ml of oxygen. Thus, blood would carry nearly 20 ml of oxygen in an individual with a haemoglobin level of 15 g/dl if the haemoglobin is fully saturated with oxygen. However, plasma is a very poor oxygen carrier. Only 0.3 ml of oxygen is dissolved in each 100 ml of plasma when breathing 21% oxygen.

The relationship between the partial pressure of oxygen in the plasma and haemoglobin oxygen saturation can be described using the oxyhaemoglobin dissociation curve (Fig. 1.4). This curve represents the unique cooperative oxygen binding properties of haemoglobin coupled with the concentration-driven diffusion gradients that exist between plasma and haemoglobin. The combination of these factors is responsible for the nonlinearity of the curve. Haemoglobin has a P50 of 26.7 mmHg. The P50 is the oxygen tension at which haemoglobin is 50% saturated with oxygen. Because oxygen is continuously being utilized at the tissue level, the partial pressure of oxygen in tissues is significantly lower than that entering the capillary. Oxygen will, therefore, diffuse down its pressure gradient from the capillaries into the tissue.

Figure 1.4. Oxyhaemoglobin dissociation curve



Several important factors including pH, partial pressure of CO_2, temperature and 2,3- diphosphoglycerate (2,3 DPG) can shift this curve to the left or to the right and play an important role in several disease processes. Shifting the curve to the left decreases the P50 of haemoglobin thus increasing the affinity of oxygen binding to haemoglobin. Shifting the curve to the right increases the P50 of haemoglobin thus decreasing the affinity of oxygen binding to haemoglobin, facilitating its release to tissues.

Oxygen transport to tissues

It is important to understand oxygen transport in the blood to tissues via the relationship between oxygen delivery (DO_2 in ml/min) to tissues and oxygen consumption (VO_2 in ml/min) by the tissues.

DO_2 is determined by the following equation:

arterial oxygen content (CaO_2) × cardiac output (CO)

Where CaO_2 (ml/dl blood) = (1.34 × [Hb] × SaO_2) + (0.003 × PaO_2)
1.34 = volume of oxygen bound to 1 gram of saturated haemoglobin (ml/g)
Hb = concentration of haemoglobin in g/L
SaO_2 = percentage of haemoglobin saturated with oxygen (expressed as a fraction)
0.003 = solubility coefficient of oxygen in plasma (ml/dl/mmHg or kPa). For every 1 mmHg of oxygen tension, 0.003 ml of oxygen is dissolved in 100 ml of plasma
PaO_2 = partial pressure of oxygen dissolved in arterial blood (mmHg or kPa)

Since plasma carries only 0.3 ml of oxygen per 100 cm^3 of plasma, its contribution to the total DO_2 is negligible and therefore it is often deleted from the equation.

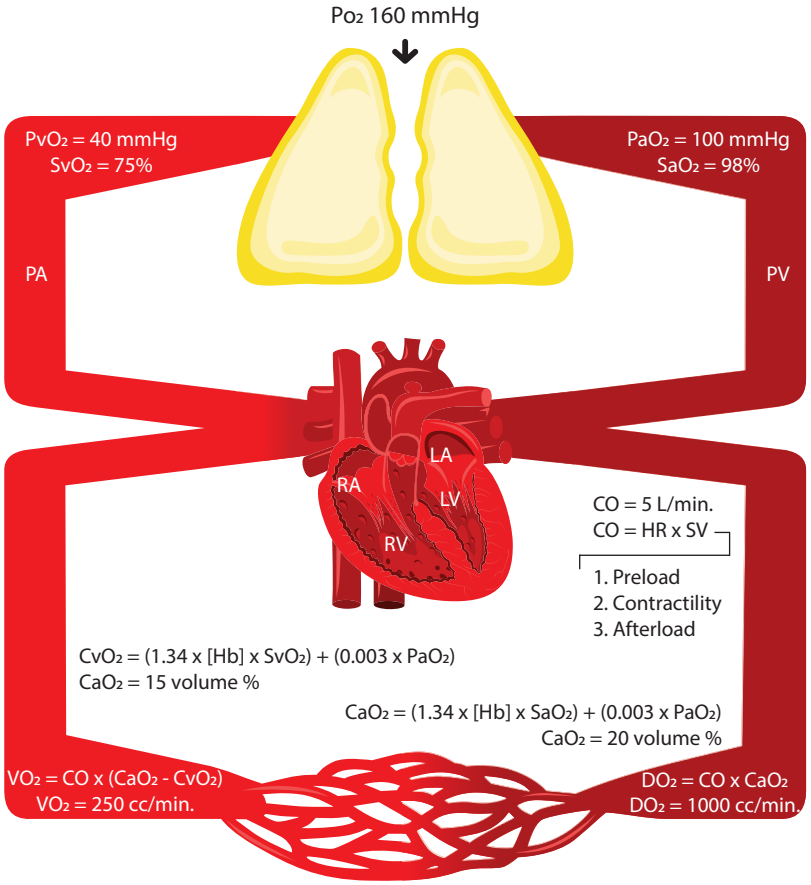
Cardiac output (cm^3 or litres per minute) is the product of heart rate and stroke volume, which are subject to a combination of mechanical, vascular and neurohormonal influences. In particular, stroke volume (the amount of blood pumped from the heart by each heartbeat) is determined by a combination of preload (amount of blood entering the heart), afterload (the arterial resistance the heart must pump against) and contractility (how forcefully the heart contracts).

VO_2 is determined by the following equation:

$CO \times (CaO_2 - CvO_2)$

where CvO_2 is calculated similarly to CaO_2 except that mixed venous haemoglobin saturation from the pulmonary artery (reflecting return from the body as a whole) is used in the calculation. On average and under resting conditions, the adult body will consume approximately 200–250 cm^3 oxygen per minute. This represents approximately 25–30% extraction of the available oxygen, resulting in a mixed haemoglobin oxygen saturation of 70–75% when arterial haemoglobin oxygen saturations are 95–99%. Fig. 1.5 shows an overview of whole-body oxygen transport.

Figure 1.5. Overview of whole-body oxygen transport



CaO_2: Arterial oxygen content
CvO_2: Mixed venous oxygen content
CO: Cardiac output
DO_2: Oxygen delivery
Hb: Concentration of haemoglobin
HR: Heart rate
PaO_2: Partial pressure of oxygen dissolved in arterial blood
PvO_2: Mixed venous oxygen pressure
SaO_2: Arterial oxygen saturation
SV: Stroke volume
SvO_2: Mixed venous oxygen saturation
VO_2: Oxygen consumption

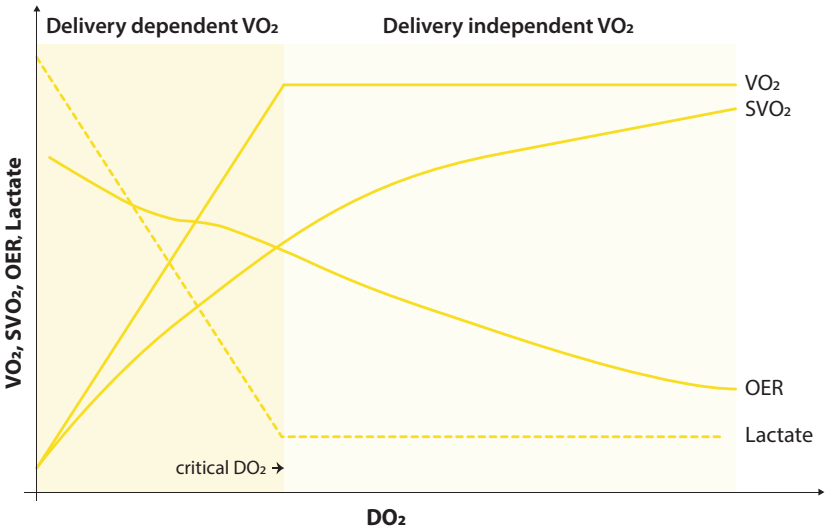
Using the equations above, it becomes clear how certain pathologies individually or in combination can contribute to detrimental decreases in DO_2. This is useful in determining which components can or should be manipulated using transfusion medicine. There are, of course, limits to how much each component of DO_2 can be altered. For example, increasing haemoglobin above 15 g/dl to increase CaO_2 will at some point reach a limit due to rheological challenges at the level of the microcirculation as well as how much volume the heart can handle before it fails. Table 1.2 lists major influencers of DO_2 and VO_2, which can alter the balance favourably or unfavourably depending on the situation.

Table 1.2. Major influencers of the balance of oxygen delivery (DO_2) and oxygen consumption (VO_2)

⇧ VO_2	⇩ DO_2	⇧ DO_2	⇩ VO_2
Stress	⇩ SaO_2	⇧ SaO_2	Hypothermia
Pain	⇩ Haemoglobin	⇧ Haemoglobin	Anaesthesia
Hyperthermia	⇩ Cardiac output	⇧ Cardiac output	
Shivering			

These principles form the basis for understanding shock, which is a major cause of death and frequently requires transfusion for its treatment. Shock is traditionally defined as tissue DO_2 below tissue oxygen metabolic needs or demands. Fig. 1.6 demonstrates the biphasic relationship between DO_2 and VO_2. As DO_2 decreases, VO_2 may remain constant due to an increasing ratio of oxygen that is extracted at the level of the tissue (oxygen extraction ratio, OER), which is mirrored by a decrease in haemoglobin oxygen saturation (SvO_2) in the tissues. However, as DO_2 continues to decrease, there will eventually come a point where the OER cannot meet tissue VO_2 demands resulting in a state of DO_2-dependent VO_2. At this point (critical DO_2), there is a transition from aerobic to largely anaerobic metabolism and VO_2 is directly dependent on DO_2. It is at this point that an oxygen deficit begins to accumulate, as signalled by increased levels of anaerobically produced lactate. Because oxygen deficit is the change in VO_2 from baseline, this deficit is equal to the difference between baseline VO_2 and the VO_2 at a particular time point after reaching critical DO_2. This quantified deficit over time is the oxygen debt *(8)*.

Figure 1.6. The biphasic relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2)



The degree (depth and duration) of oxygen debt has clear consequences, as oxygen debt has been linked to the degree of reperfusion injury, inflammation and acidosis. These events in turn are responsible for the development of endothelial injury and the coagulopathy that can occur in the setting of severe haemorrhagic and other forms of shock as well as the incidence of organ failure *(9)*.

References

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