“以器官系统为中心”原版英文教材
SYSTEMS OF THE BODY

心血管系统·第2版

The Cardiovascular System

SECOND EDITION

BASIC SCIENCE AND CLINICAL CONDITIONS

Alan Noble
Robert Johnson
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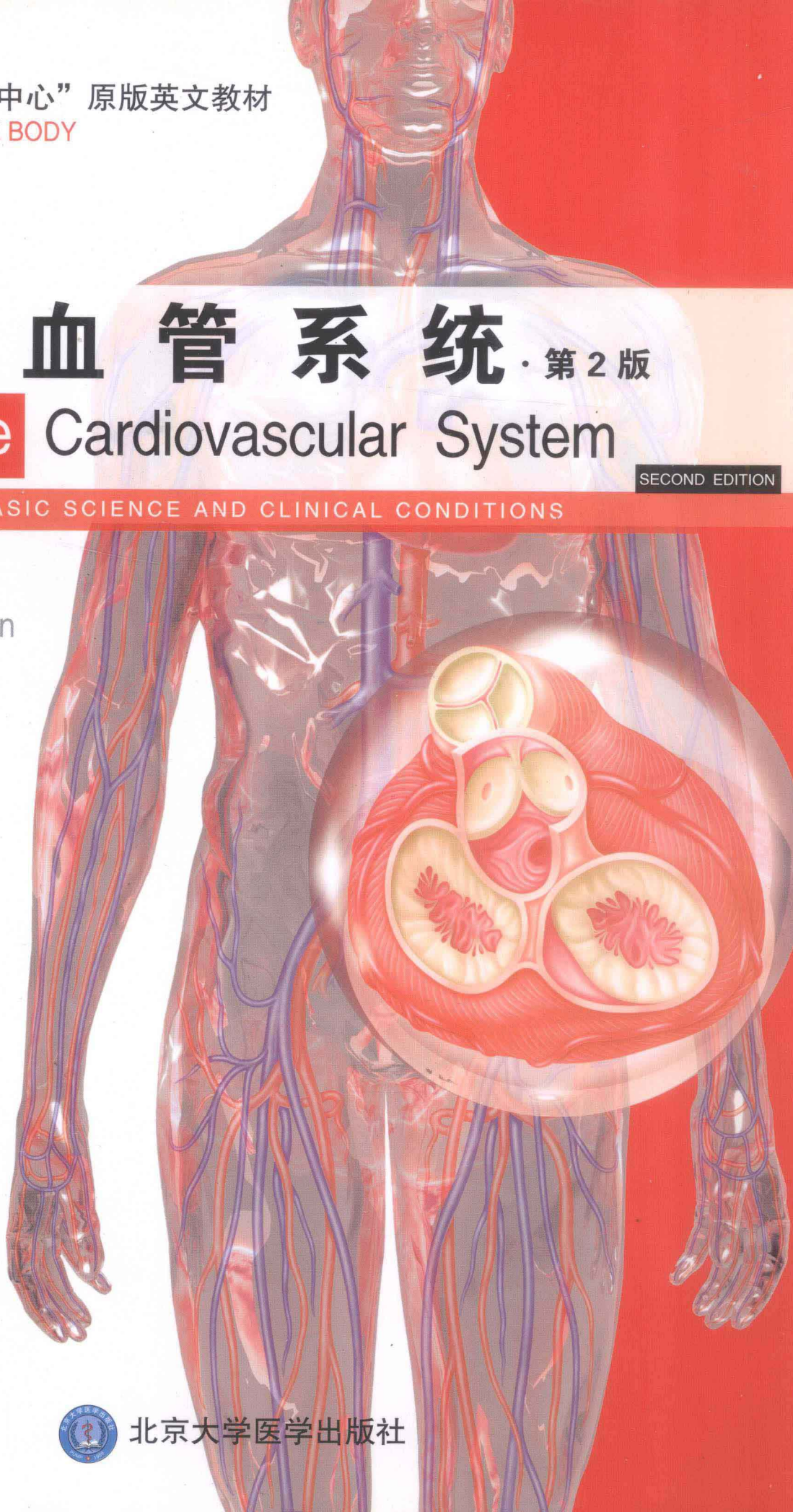
Paul Bass



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The Cardiovascular System SECOND EDITION

BASIC SCIENCE AND CLINICAL CONDITIONS

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出版说明

“以器官系统为中心”的医学教学模式是国际医学教育的趋势。本系列书是世界著名医药卫生出版集团爱思唯尔公司出版的一套“以器官系统为中心”的医学基础课程教材，共分为骨骼肌肉系统、心血管系统、呼吸系统、消化系统、泌尿系统、神经系统、内分泌系统七个分册。该套教材第1版出版后受到世界各地许多医学院校的欢迎，并被多家进行“以器官系统为中心”教学的医学院校选定为教材。第2版根据第1版出版后教师和学生的反馈意见，结合医学知识的更新进行了全新修订。在编写内容上，该系列教材强调基础与临床的整合。每一章节都是围绕着一个临床病例展开，通过对病人问题的呈现以及解决过程引出对相关知识的探究，从而使与器官系统结构、功能以及疾病相关的重要的基础医学知识得到了完善的整合。在版式安排上，图框中的病例资料与正文中的医学知识完美匹配，一步一步地激起读者的求知欲望。

当前，我国很多医学院校都在进行“以器官系统为中心”的医学课程教学改革，为了借鉴国外教材的经验，北京大学医学出版社通过版权引进影印出版了这套“SYSTEMS OF THE BODY”原版英文教材。该系列书可以作为医学院校“以器官系统为中心”教学的教材和教学参考书，也可以作为医学院校进行英语授课的教材或供学生自学使用。

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When we set about planning the First Edition of this book we were very conscious of the fact that medical education, in many centres, has moved on from traditional discipline-based curricula. The Systems of the Body series of books was conceived at Elsevier as being particularly suitable for integrated system-based or problem-based learning courses. In order to try to assist with this form of learning, our book on the cardiovascular system therefore includes relevant aspects of anatomy, physiology, pharmacology and pathology, all introduced in a 'whole-body' clinical context. We have included illustrative case histories which we hope will help to provide a framework for understanding the main content of each chapter.

In updating the book for the Second Edition we have included a series of "interesting facts" boxes which are scattered through the text. Some of these contributions identify particularly important concepts, some provide a historical context to the material in the Chapter concerned and others identify a more offbeat aspect of the topics discussed. A section of the book which demanded substantial modification was that concerned with the techniques currently in use to assess aspects of cardiac function. This reflects the remarkable technological advances which have been made in the only four year period between producing the two editions of this book.

All four of the co-authors of this book have been associated, in varying ways, with medical education programmes in the University of Southampton. In 1971 the Medical School was established with a systems-course basis and so it was a very early example of this type of course. The course has evolved steadily since its inception and the original educational concepts have been retained and developed.

A fundamental aspect of studying anything is to develop an understanding of the language that is used. In order to try to help with this, we have included a glossary of commonly used terms at the end of the book.

We do hope that you find this book useful and that you enjoy reading it.

We particularly wish to acknowledge the contribution of Sue Noble to the production of this book. She has been a major source of help and enthusiasm for both editions. Lynn Watt, the Project Development Manager at the publishers, Elsevier, was exceptionally helpful in producing the First Edition of this book and for the Second Edition Lulu Stader has been similarly outstanding.

Our colleague, Professor Geraldine Clough, provided very helpful and constructive criticism of a draft of Chapter 11: Capillary function and the lymphatic system.

Paul Bass acknowledges the patience and encouragement of his family, Paulina, Aaron, David and Abraham and Alan Noble would similarly like to acknowledge Sue, Kate, Liz and Han.

A DESIGN SPECIFICATION FOR THE CARDIOVASCULAR SYSTEM

1

Chapter objectives

After studying this chapter you should be able to:

1. Explain the necessity for our enormously profuse circulatory system.
2. Describe the limitations posed by diffusion as a way of delivering oxygen to tissues and removing carbon dioxide.
3. Outline the mechanisms whereby the pH of body fluids is kept within narrow limits.
4. Briefly outline the characteristic changes in cell structure and function associated with cell death.
5. Describe the gross structure and function of the major types of blood vessel within the circulation.
6. Define angiogenesis and outline its role in the mature cardiovascular system.
7. Explain the pattern of presentation of cardiovascular disease with peaks in the very young and in older members of society.

The gross structure and function of the cardiovascular system is dictated firstly by the need to deliver oxygen continuously to the 100 000 000 000 000 (10^{14}) cells which make up the 'textbook person'. Oxygen is used by cells to generate ATP, the metabolic energy source for all the functions of the body. Oxygen is not particularly soluble in water and will only diffuse quickly over short distances. Moreover, oxidative metabolism generates acidic products, particularly CO_2, and continuous removal of these sources of H^+ is essential for the maintenance of life. Marginal failure of either oxygen delivery or hydrogen ion removal will result in illness and tissue damage but total failure of either will end in death within a few minutes. For example, cessation of oxygen supply to the brain leads to a loss of consciousness in 8–10 seconds and permanent brain damage in 5–10 minutes.

As a consequence of these performance requirements we have evolved with a circulatory system which in the textbook person, if stretched out end to end, would measure 60 000 miles or 96 000 km. This is enough to encircle the world three times. This book is about the organization and control of this circulatory system, the causes and effects of failure and the basis for treatment regimens aimed at avoiding or minimizing the effects of circulatory failure. An example of a clinical history of a patient with developing circulatory problems is introduced in Case 1.1:1.

Some fundamental concepts in relation to these opening paragraphs need further explanation.

Textbook person

Textbooks of basic biomedical sciences are inherently sexist, ageist and do not recognize either relatively small or large individuals. They are written primarily about male, 70 kg subjects in the age range 20–25 years. Textbooks contain statements such as 'cardiac output is 5 L/min'. This is a figure which may well apply to the textbook person at rest, but there are wide variations which all represent perfectly normal values for a given individual within the population at large.

Oxygen consumption

Our textbook subject at rest consumes about 250 mL O_2/min and generates 200 mL CO_2/min. This gives rise to the concept of a respiratory quotient (RQ):

$$\text{Respiratory quotient (RQ)} = \frac{CO_2 \text{ produced}}{O_2 \text{ consumed}}$$

The precise value for RQ in any individual will reflect the composition of their diet but for a typical person consuming a mixed diet of carbohydrate, fat and protein the RQ would be about 0.8. This means that we normally consume more oxygen than we produce carbon dioxide. During exercise oxygen consumption may increase to

Case 1.1 A design specification for the cardiovascular system: 1

A young man with a history of insulin-dependent diabetes mellitus

Calvin was first diagnosed with diabetes when he was 10 years old. He had initially responded well to the need to comply with his treatment regimen of dietary control and regular doses of insulin given by self-injection. He was familiar with these problems as both his father and grandfather also had diabetes.

However, by the time Calvin reached 18 years old his diabetes did not fit well with his own self-image. He wanted to be out enjoying life with his friends and did not like to feel he was 'an invalid'. This led to him becoming lax with his medication and his blood glucose control became less rigorous.

There were a number of occasions on which Calvin felt unwell and over a period of 5 years there was a series of eight emergency hospital admissions. On one such occasion he had been drinking more water than usual (polydipsia) and had been producing greater than normal amounts of urine (polyuria) for about 3 weeks. He had become drowsy and lethargic and, for the 3 days prior to the hospital admission, he had been vomiting.

The doctor in the emergency room noted that he was underweight for his age and build. Initial observations included a pulse rate of 142 beats/min, a blood pressure of 100/60 mm Hg and abnormally deep breathing. A venous blood sample provided the following data:
[Glucose] = 37 mmol/L (3.5–5.5 fasting)
[Na^+] = 132 mmol/L (135–145)
[K^+] = 5.5 mmol/L (3.5–5.0)
[Haemoglobin] = 17.5 g/100 mL (13.5–18.0)
Normal reference values are shown in brackets.

A urine dipstick test also showed the presence of glucose and ketones.

This case history raises the following questions:

1. What evidence is there in this history of body fluid volume depletion?
2. What is the link between volume depletion, Calvin's low blood pressure and his fast heart rate?
3. What aspects of this history give immediate cause for concern and form the basis for clinical management strategies?

Aspects of the answers to these questions are discussed in Case 1.1:2 and in the text of this chapter.

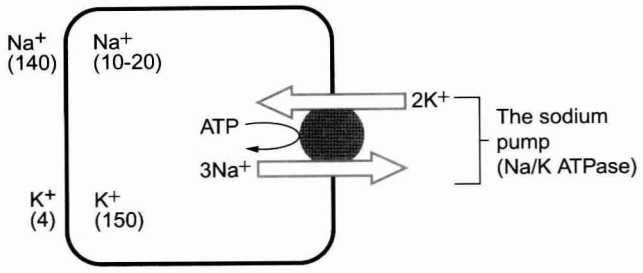

Fig. 1.1 The left hand side of this diagram shows typical concentrations of Na and K inside and outside cells. The right hand side depicts the sodium pump which uses ATP to maintain the ionic gradients across cell walls. Concentration units are mmol/L.

about 10 times the resting value and the RQ may move closer to a value of 1 due to preferential metabolism of carbohydrate.

Interesting facts

30–40% of all the food we consume in our lifetime is used to generate ATP to drive the sodium pump which maintains the sodium and potassium concentration gradients across cell membranes.

Oxygen is used within the mitochondria of cells to generate adenosine triphosphate (ATP). This provides the energy for movement, for the synthesis of macromolecules and to drive the movement of ions, particularly Na^+ ions, across cell membranes against a concentration gradient. The distribution of Na^+ and K^+ inside and outside cells is summarized in Figure 1.1. The ion gradients are maintained by the sodium pump which expels three Na^+ ions and pulls two K^+ ions into the cell each time it operates. As both of these ion movements are against a concentration gradient, an ATP molecule is hydrolysed to provide the energy. For some cells there may be about a million sodium pumps each operating at about thirty times a second. In the body as a whole the sodium pump accounts for about 30% of all of our energy intake over our lifetime. In this way, ionic gradients are maintained which are essential for the continuing function of nerves and muscles, including the heart. Failure to maintain ATP generation in hypoxic tissues leads to osmotic swelling of cells and to a loss of normal cellular function (see p. 7). To serve all the requirements, the quantities of ATP which must be synthesized are quite prodigious and amount to something roughly equivalent to an individual's body weight every day.

Diffusion

Diffusion is the movement of particles from an area of high concentration to an area of low concentration. The concentration of a gas in solution is actually the product of the partial pressure and the solubility coefficient (a constant at a given temperature). Two sets of units are in common usage for gas pressures. The appropriate conversion factors are as follows:

$$1\ \text{kPa} \equiv 7.5\ \text{mm Hg}$$

$$1\ \text{mm Hg} \equiv 0.133\ \text{kPa}$$

Some important parameters determining rate of diffusion are:

- the diffusive gradient (concentration difference between two points)
- the solubility of the particle in the solvent; if it is not very soluble the concentration will be low
- the size of the solute particle (small particles will diffuse faster than large particles)
- temperature: diffusion is faster at high temperatures than at low temperatures; body temperature is about 37°C in normal human subjects.

Most diffusion in living systems takes place in an environment in which water is the solvent, although molecules such as oxygen and carbon dioxide also have to diffuse through the lipid bilayer which makes up cell membranes. Special provision, in the form of transport proteins and ion channels, is made for ions which carry a charge and are therefore not lipid soluble.

Einstein (1905) showed that the time taken for a molecule to diffuse between two points varies as the square of the distance between the points. In physiological terms, diffusion is fine as a process for moving molecules short distances. A typical cell diameter in the body is about 10 μm and the time taken for an oxygen molecule to diffuse this distance would be a few milliseconds. Diffusion of oxygen over longer distances, however, such as the approximately 10 mm (a thousand times 10 μm) thickness of the ventricular wall of the heart, would take a million times as long, a time measured in hours. This would be inconsistent with maintaining life as, given the composition of the atmosphere, the diffusive gradients of oxygen available to us would be too small. The solution to these problems is to have an amazingly profuse circulatory system which delivers the oxygen and other nutrients very close to the cells where they will be used. Cells in the body are rarely more than 50 μm from a capillary and most are not more than 10–20 μm away.

The diffusive gradients concerned with loading of oxygen into pulmonary capillary blood at the lungs and the delivery of oxygen into the tissues are shown in Figures 1.2 and 1.3. Figure 1.2 shows the events at the interface between an alveolus and a pulmonary capillary. A typical Po_2 in the alveolus is 13.3 kPa (100 mm Hg). Blood returning to the lungs has a Po_2 of about 5.3 kPa (40 mm Hg) and so oxygen diffuses into the pulmonary capillary blood from the alveolus. The diffusive gradient for unloading CO_2 at the lungs is much smaller than for O_2. Mixed venous blood Pco_2 is about 6.1 kPa (46 mm Hg) whilst alveolar Pco_2 is typically 5.3 kPa (40 mm Hg).

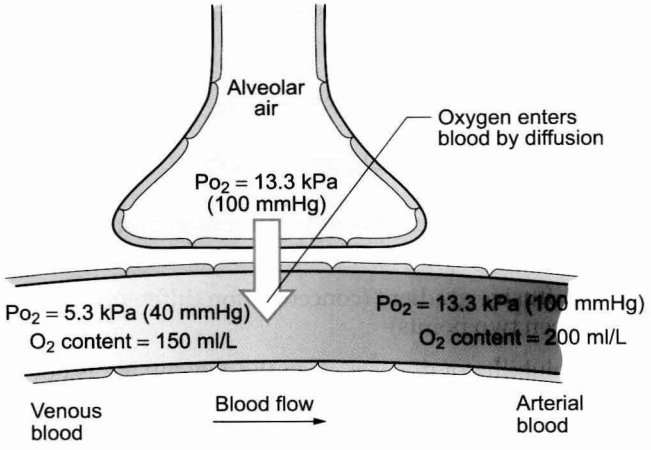

Fig. 1.2 Loading of oxygen by diffusion from the alveolae into pulmonary capillaries.

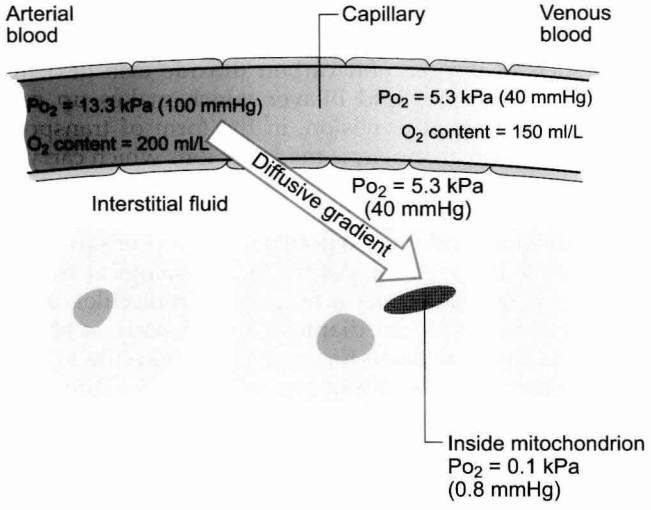

Fig. 1.3 Diffusive gradient. Diffusive gradient for oxygen from arterial blood to the mitochondrion of a cell where the oxygen is used. The interstitial fluid outside the cell is part of the way down this diffusive gradient. When blood leaves the tissue as venous blood it has equilibrated with the interstitial fluid.

The diffusive gradient for CO_2 (0.8 kPa) is 10% of the diffusive gradient for O_2 (8 kPa). Both diffuse at about the same rate because CO_2 is 20 times as soluble in water as O_2. The transit time for red blood cells through pulmonary capillaries at rest is about 1 second but the diffusive exchange of O_2 and CO_2 is normally complete in about 0.25 seconds.

Delivery of O_2 into the tissues (Fig. 1.3) starts with the arterial blood which has picked up O_2 in the lungs (Po_2 = 13.3 kPa; 100 mm Hg). Oxygen is used inside the mitochondria and the Po_2 here is of the order of 0.1 kPa (about 1 mm Hg). The interstitial fluid outside a cell is part of the way down a continuous diffusive gradient between the arterial blood and the inside of a mitochondrion. A typical Po_2 in the interstitial fluid is 5.3 kPa (40 mm Hg). Blood leaving a capillary has equilibrated with this fluid and so venous Po_2 is the same as in the interstitial fluid.

Interesting facts

Under normal circumstances, the lungs have spare capacity for several of their functions. For example, completion of the exchange of oxygen and carbon dioxide at the pulmonary capillary: alveolus interface only takes about a quarter of the approximately 1 second available for gas exchange. These safety factors mean that some degree of malfunction of the heart and lungs can be tolerated.

Carriage of oxygen in blood

A further consequence of the poor solubility of oxygen in water is that we have evolved with an oxygen-carrying pigment, haemoglobin (Hb). The oxygen-binding characteristics of haemoglobin are such that it is nearly fully saturated with oxygen at the partial pressure of oxygen normally present in the alveoli of the lungs. Figure 1.4 shows the oxyhaemoglobin dissociation curve. At a Po_2 of 13.3 kPa (100 mm Hg), a typical figure for the alveolus, Hb is 97–98% saturated with O_2. This information can be used to calculate the amount of oxygen carried bound to haemoglobin as follows:

$$\text{Amount } O_2 \text{ carried bound to Hb} = [\text{Hb}] \times 1.34 \times \% \text{ saturation Hb with } O_2 \ (\text{mL}O_2/\text{L blood}).$$

Typical values for [Hb] are 120 g/L (women), 140 g/L (men). The figure 1.34 mL/g is the volume (mL) of oxygen bound to 1 g Hb when it is fully saturated. These figures mean that arterial blood contains about 200 mL O_2 bound to Hb per litre blood. A small amount (0.3 mL/L) is carried as dissolved O_2

Reference to the oxyhaemoglobin dissociation curve (Fig. 1.4) shows that venous blood is about 75% saturated with O_2 at Po_2 = 5.3 kPa (40 mm Hg) and therefore about one quarter of the O_2 carried in arterial blood has moved into the tissues. One quarter of the 200 mL O_2/L present in arterial blood is 50 mL. If 50 mL of O_2 is typically deposited in the tissues from each litre of arterial blood, and the textbook person's cardiac output (volume of blood pumped per minute from each side of the heart—see Chapter 4) is 5 L/min, then 250 mL O_2/min is delivered to the tissues. This is the amount of oxygen identified previously as a figure for O_2 consumption rate for the textbook person at rest.

All tissues do not have the same oxygen consumption rate relative to blood flow. The figure quoted above, that 'venous blood is typically 75% saturated with oxygen', refers to 'mixed venous blood', i.e. the blood in the right side of the heart which is a mixture of all the venous drainages for the whole body. Venous blood from the kidneys, which have a high flow rate but relatively low O_2 consumption, has an oxygen saturation of about 90%. By contrast, the blood in the venous drainage from the

Case 1.1

A design specification for the cardiovascular system: 2

Calvin's acute circulatory problems

Calvin's fundamental problem was a lack of insulin, a hormone which moves glucose from the circulation into cells particularly in the liver and skeletal muscle. In addition, in the absence of insulin gluconeogenesis, the conversion of amino acids from the breakdown of protein into glucose is promoted. The high blood [glucose] leads to an osmotic diuresis, excessive urine production and hence body fluid volume depletion. Responses to volume depletion in the form of blood loss (haemorrhage) are discussed in Chapter 14.

The diuresis is the cause of a high [haemoglobin] due to loss of fluid from the extracellular compartment. An appropriate clinical test for volume depletion is to compare standing and lying arterial blood pressure measurements. Normally there will be no substantial difference but in the volume-depleted patient there is a drop in pressure (postural drop) on standing.

In Chapter 4 of this book the links between blood volume and cardiac output (the volume of blood pumped by the heart per minute) are discussed. Basically, the fall in blood volume (a decreased preload on the heart) leads to a decrease in cardiac output and, as a consequence, a fall in arterial blood pressure. The baroreceptor reflex (see Chapter 10) reacts to a fall in blood pressure with an increase in heart rate and constriction of peripheral blood vessels.

Body fluid replacement with a combination of 0.9% saline and 5% glucose is the first priority in order to avoid circulatory collapse. The apparent anomaly of giving extra glucose to a patient with an already high blood [glucose] is explained as follows.

The textbook person contains about 42 L of water. The factors which determine the distribution of this volume between different compartments are described in detail in Chapter 11. Basically, about 14 L is in the extracellular compartment, which includes blood plasma and 28 L is in the intracellular compartment. An increase in the osmotic strength of body fluids, due to high blood [glucose] combined with a decrease in capillary blood pressure associated with volume depletion, means that there is movement of water from the intracellular compartment to the extracellular compartment. As a consequence Calvin suffers both intracellular and extracellular volume depletion. There is a high [Na^+] in extracellular fluid and a low [Na^+] in the intracellular fluid. Infusion of saline into a patient will therefore selectively expand the extracellular compartment. Administration of 5% glucose solution initially does not substantially change the osmotic strength of body fluids but, once the glucose has become distributed around the body, insulin supplements will drive the glucose into cells where it can be metabolized to CO_2 and water. Giving 5% glucose is therefore equivalent to an infusion of pure water and will initially dilute the extracellular compartment. The osmotic gradient created will move water into the intracellular compartment. Infusion of 5% glucose will therefore expand both the intracellular and extracellular compartments. These ideas are explained in more detail in Chapters 11 and 14.

A further potential cause for concern is the increase in plasma [K^+]. This is likely to be a result of a ketoacidosis, a form of metabolic acidosis. At a level of 5.5 mmol/L this is not a significant problem, but further increases in potassium as a result of acidosis-induced movement of K^+ from inside to outside cells can lead to the development of cardiac arrhythmias and potentially cardiac arrest (see Chapters 2 and 7). Despite a raised plasma [K^+] there may be whole body depletion of K^+ as most of the K^+ is in the intracellular compartment.

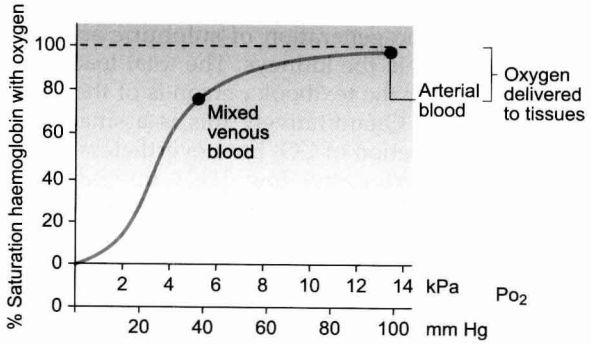

Fig. 1.4 Oxygen–haemoglobin dissociation curve.

heart is only 25% saturated with O_2. This is an important concept in relation to physiological control mechanisms and to the pathological consequences of disturbances of coronary blood flow (see Chapter 5).

Interesting facts

The task of working out the three-dimensional structure of haemoglobin was undertaken by Max Perutz in Cambridge. It took him 23 years but the answer taught us a huge amount about how the oxygen carriage mechanism works. He was awarded the Nobel Prize in 1962.

The shape and position of the oxyhaemoglobin dissociation curve (Fig. 1.4) shows one of the safety factors in relation to lung function. The top of the curve is nearly flat from 13 kPa (100 mm Hg), normal arterial Po_2, down to about 10 kPa (75 mm Hg). This means that a decrease in Po_2 within this range makes little difference to the % saturation of haemoglobin with oxygen, that is little change to the total amount of oxygen carried in arterial blood. Put another way, we can afford to have a certain degree of lung malfunction before it makes any significant difference to oxygen delivery to the tissues.

Cyanosis

Cyanosis is an important clinical sign. It refers to the blue colouration of the skin and mucous membranes produced by the presence of excessive amounts of deoxygenated haemoglobin in arterial blood. It is fundamentally classified into central and peripheral cyanosis.

Central cyanosis is often observed on the lips particularly but is conveniently looked for in a warm environment, the inside of the mouth. It represents a failure of the heart and lungs to ensure adequate oxygenation of the blood during passage through the lungs. There is no agreed quantitative standard for central cyanosis but the presence of 50 g of deoxygenated haemoglobin in 1 L of arterial blood is a commonly used definition. In some laboratories lower levels down to 20 g deoxygenated Hb in 1 L of blood are used to define central cyanosis. In a patient with 150 g Hb in 1 L of blood, 50 g/L as deoxygenated Hb is one third of the total, i.e. a % saturation of 67%. In anaemic patients, despite poor oxygenation of their tissues, a point is reached at which it would be impossible for them to become cyanosed. A patient with 70 g Hb in 1 L blood (about half normal) which is normally saturated with oxygen (97–98%) has enough oxygen delivery to the tissues to support life. However if 50 g Hb/L out of 70 g Hb/L in arterial blood was deoxygenated the patient would be dead not cyanosed.

Peripheral cyanosis which is visible in extremities such as fingers and ears is caused by impaired local blood flow and excessive local extraction of oxygen from the available blood supply. This occurs for example in cold environments (hence the expression 'blue with the cold') or in peripheral vascular diseases such as Raynaud's disease (see Chapter 9).

Interesting facts

Polymorphisms of the haemoglobin molecule are thought to be the most numerous naturally occurring genetically determined variations of any protein in the body.

The battle against the hydrogen ion: acid–base balance

Proteins play many important roles in the body, as structural proteins, membrane ion channels and transporters and as enzymes.

The amino acids which make up proteins have a number of side groups which can bind or release H^+ ions. These include carboxylic acid groups ($-COO^- + H^+ \rightleftarrows COOH$), amino groups ($-NH_2 + H^+ \rightleftarrows NH_3^+$) and the imidazole side group of histidine which can be protonated. Increasing $[H^+]$ will make it more likely that these sites bind an H^+ ion and, conversely, decreasing $[H^+]$ will make it more likely that H^+ ions are released. These anionic and cationic sites are involved in forming ionic bonds which stabilize the three-dimensional structure of proteins and therefore changes in $[H^+]$ will alter the shape of proteins and will modify their functional characteristics. For example, altering the shape of ion channels will alter ion permeability and hence bring about changes in the membrane potential of the conducting system of the heart (see Chapter 2), and in the nervous system, which can be lethal. Close regulation of extracellular and intracellular $[H^+]$ is therefore crucially important.

Under normal conditions extracellular fluid pH is maintained within the narrow range of 7.36–7.44. A pH of 7.4 corresponds to a $[H^+]$ of 40 nmol/L (40×10^{-9} M). This is a very low concentration, especially compared to the other constituents of body fluids. Typical $[Na^+]$ in plasma, for example, is 140 mmol/L, over three million times the free $[H^+]$, yet it is commonly changes in $[H^+]$ which ultimately lead to death. The extremes of pH which are compatible with human life are thought to be pH 6.8–7.8 ($[H^+] = 160$ to 16 nmol/L). It must be stressed however that these extremes could only be tolerated for a very short period of time and, clinically, very much smaller deviations from the normal range are a cause for concern.

Although we need to maintain $[H^+]$ in body fluids at a very low level, oxidative metabolism generates large quantities of H^+. The major source of this H^+ is carbon dioxide.

The textbook person generates about 14 moles of CO_2 per day. Failure of the circulation (as the transport system) and the lungs (as the site of excretion) to adequately get rid of this CO_2 leads to respiratory acidosis, a common feature of lung disease. Acutely, complete failure to excrete CO_2 for only a few minutes would lead to a rapid fall in pH and death. Overvigorous excretion of CO_2 (i.e. hyperventilation) leads to respiratory alkalosis, a pH above the normal range. Clinically, alkalosis is much less common than acidosis but is still potentially dangerous when it does occur.

The second form of acid to be excreted comes from the oxidative metabolism of dietary constituents. Complete metabolism of sulphur-containing amino acids, for example, will lead to the generation of sulphuric acid which must be excreted via the kidneys. The total load of such 'metabolic acid' for the textbook person is of the order of 50–100 mmol/day. Quantitatively this is a smaller challenge than the excretion of CO_2 but nevertheless it is very significant considering the low $[H^+]$ in body fluids. Failure to excrete H^+ adequately via the kidneys leads to metabolic acidosis. Examples of this are renal failure or the overproduction of keto acids which occurs in poorly controlled diabetes mellitus, as in the case history of Calvin described in this chapter. Depletion of metabolic acid, as in vomiting, leads to a metabolic alkalosis.

The roles of the circulatory system in relation to acid–base balance can be summarized as buffering and transport. Buffering of H^+ is essential to prevent substantial fluctuations in pH during the transport of H^+ from the site of generation in the cells to the site of excretion in the lungs or kidneys. The most important buffering systems in blood are proteins, especially haemoglobin, and the bicarbonate

Case 1.1

A design specification for the cardiovascular system: 3

Arterial blood gas measurements

Calvin provided an arterial blood sample for blood gas analysis, which gave the following results:
Pco_2 = 1.4 kPa (4.7–6.0) = 10.5 mm Hg (35–45)
Po_2 = 15.9 kPa (11–13) = 119 mm Hg (80–100)
pH = 7.15 (7.35–7.45)
$[HCO_3^-]$ = 3.5 mmol/L (24–30)
Base excess = −22 mmol/L (−2 to +2)
Normal reference values are shown in brackets.

Calvin has a ketoacidosis, a form of metabolic acidosis. This is shown by the large negative base excess. He is hyperventilating as a response to H^+ ions detected by his peripheral chemoreceptors. The CO_2 produced in his tissues is being diluted into a volume of alveolar gas about three to four times the normal volume and hence Pco_2 is a quarter to a third of normal values. The Po_2 is high as a result of the hyperventilation and there is no indication of lung malfunction. An increase in Po_2 at this level does not significantly increase the volume of oxygen carried in the blood as haemoglobin is already 97–98% saturated at normal arterial Po_2 (Fig. 1.4).

Base excess is a quantitative assessment of the metabolic component of the acid–base disorder. Thus in this case each litre of body fluids has been depleted of bicarbonate (HCO_3^-) by 22 mmol/L. This can be viewed as the result of bicarbonate binding to hydrogen ions and being excreted at the lungs as CO_2.

$$H^+ + HCO_3^- \rightleftarrows H_2CO_3 \rightleftarrows H_2O + CO_2$$

Clinical management of the acidosis may involve infusion of sodium bicarbonate but it will often be corrected just by administration of insulin. This will end the ketoacid production and hence help to normalize acid–base status. A danger in the management of the acidosis is the attendant fluctuations in plasma $[K^+]$. During an acidosis there is effectively an exchange of H^+ and K^+ across cell membranes such that acidosis results in hyperkalaemia. This may itself become life-threatening (see Case 1.1:2). Treatment of the acidosis however brings its own problems. K^+ ions re-enter cells when the acidosis is corrected but also one of the physiological roles of insulin is to move K^+ into cells. This happens normally for example after the intake of a K^+ load, such as a banana, chocolate or orange juice. The combination of a reversal of the acidosis and the effects of insulin administration may cause plasma $[K^+]$ to fall to dangerously low levels with consequent effects on the membrane potential of pacemaker cells in the heart (see Chapter 2).

buffer. Haemoglobin acts as a buffer because the protein component, globin, can absorb or release H^+ as described earlier. The bicarbonate buffer relies on the generation of HCO^-_3 by the kidneys each time a hydrogen ion is excreted into the urine. The transport function of the circulatory system is crucial in maintaining acid–base balance. It is essential to have a very profuse circulatory system with a blood capillary close to every cell in the body so that H^+ ions can be removed immediately they leave the cells where they are generated. Local circulatory failure will lead to local tissue acidosis. This concept is further discussed in relation to shock mechanisms in Chapter 14 of this book.

Apart from its general role as a nutrient delivery and waste collection system in the body, the circulatory system has other functions in relation to the immune system (see Chapter 11) and in thermoregulation (see Chapter 9).

Cell injury and cell death

Cell injury

Cell injury may be reversible or irreversible. Often a cell/group of cells will initially adapt to a given stimulus and there may be no cellular signs of injury. An example is the cardiac muscle cell in mild hypertension. However, if the stimulus persists or increases in amount/frequency as in severe, long-term hypertension, reversible and ultimately irreversible injury leading to apoptosis or necrosis may occur.

Causes of cell injury

There are numerous causes of cell injury. These include: hypoxia (lack of oxygen), infection (bacteria, viruses, fungi), physical agents (hot or cold temperatures, ultraviolet radiation), chemicals (acids, alkalis), and immunological stimuli such as autoantibodies against, for example, thyroid epithelium.

Cell injury occurs because a cell has to function outside its normal homeostatic capabilities. Thus, if acid is slowly added to the environment of a cell, initial adaptation may occur, but eventually a point of no return will be reached when the adaptive response can no longer protect the cell and cell death occurs.

Mechanisms of cell injury include:

- cell membrane damage such as that caused by complement pathway-related membrane attack complex or free radicals
- mitochondrial damage as seen in hypoxia and cyanide poisoning
- ribosomal damage as in the effect of alcohol on hepatocytes
- nuclear damage caused by radiation or viruses.

Although a particular agent may preferentially target one part of the cell, there is always a wide-ranging cascade of events. Thus, once the cell membrane is damaged, cell pumps such as the sodium pump described earlier will be compromised, also the cytoplasmic composition will change and this will affect mitochondria, the nucleus and other cell organelles.

The response to injurious agents will depend on both the type of cells involved and the type of agent.

Highly specialized cells with a cytoplasm rich in sensitive organelles, such as cardiac muscle cells or renal proximal tubular epithelial cells, may be more prone to cell injury from factors such as hypoxia or drugs than more simple cells such as fibroblasts. In addition, cells which are already compromised, by hypoxia for example, may be more prone to new or further injury than normal cells. The response of a cell population to injury is also dependent on the ability of the cells to divide. In this respect, the cells of the body can be categorized into three groups designated labile, stable and permanent.

- Labile cells divide continuously as they are maintained in the cell cycle (Fig. 1.5). They are often stem cells or precursor cells in a cell population such as basal epidermal or gut lining cells and bone marrow cells. A reduction in labile cell number can, potentially, be quickly reversed.
- Stable cells are usually excluded from the cell cycle and are found in G_0. They can be driven into the cell cycle, at G_1, by an appropriate stimulus. This usually involves growth factor production by the surviving similar or neighbouring different cells. Once in the cell cycle, they can divide and restore cell numbers. Examples of this include renal tubular epithelial cells after acute tubular necrosis or hepatocytes after viral hepatitis.

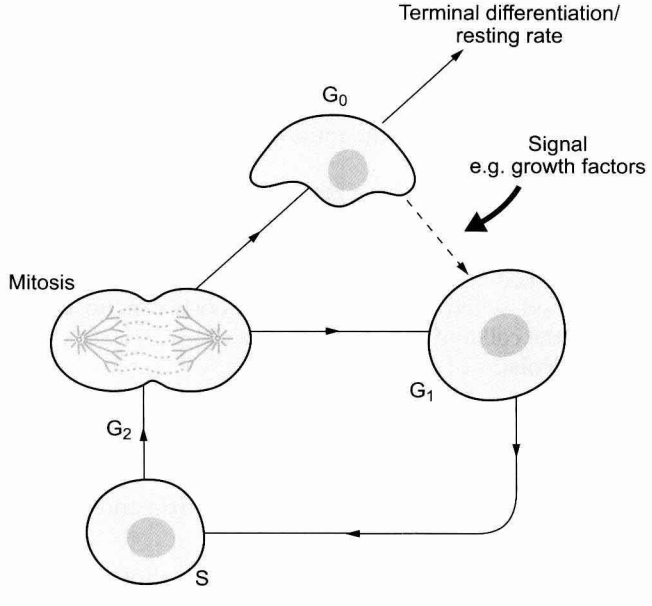

Fig. 1.5 The cell cycle. G_0, non-dividing (resting) state; G_1 and G_2, gap/preparation phases; S, replication of DNA. Source: Bass et al., 2009.

In both labile and stable cell populations there is a large potential 'reserve' for restoring cell numbers and therefore tissue/organ function. This replenishment of a cell population by exactly similar cells is known as 'regeneration'.

- Permanent cells have no ability to divide and are excluded from the cell cycle. The classic examples are neurones and cardiac myocytes. Thus, after the brain and heart have been fully formed in utero, no new neurones or cardiac muscle cells will appear. These cells cannot replicate when cells are lost as, for example, after significant hypoxia. The body therefore has an alternative strategy. 'Scarring' known as gliosis in the brain and fibrosis in the heart, occurs and the dead cells are replaced by inert, non-specialized, fibrous tissue composed mainly of collagen. This is laid down by myofibroblasts found in granulation tissue. The process whereby the cells of a tissue are replaced by scar tissue is known as 'repair'.

The type of agent causing the injury will also be important. Some cells, such as cardiac myocytes, are more prone to hypoxia than for example fibroblasts. The length of time cells are exposed to the injurious agent is also important, and after a significant time period even fibroblasts will be injured by hypoxia. A further critical variable is the severity of the exposure. Cardiac myocytes are more prone to injury in anoxic (no oxygen) conditions than mild hypoxic (relative lack of oxygen) conditions.

Cell death: apoptosis and necrosis

It is now well established that cell death is actually a spectrum of cellular events and changes. At one end of this spectrum is 'apoptosis', a recognized normal physiological event, and at the other is the pathological process of 'necrosis'.

Apoptosis occurs when cell populations need to be fine-tuned. Although essentially a physiological event, it can occur as part of pathological processes. Physiologically, during fetal development, the digits of the hands and feet develop from solid 'bars' of tissue and the interdigital webs are removed by apoptosis. Similarly, the lumen in many hollow viscera is produced by apoptosis of the central cells. Autoreactive T lymphocyte cells are deleted from the young thymus by apoptosis. During the apoptotic process, the cell itself switches on genes which code for new proteins and some of these proteins cause the cell to die. Hence the term 'cell suicide' is used to describe apoptosis. Endonucleases cause DNA fragmentation and caspases destroy proteins. The cell is effectively killed from within. Cell membrane pumps may remain viable until the very end of the process. Morphologically, the cell shrinks, the nuclear chromatin condenses and the cell breaks up into a number of apoptotic bodies, which are cleared up (phagocytosed) by macrophages or neighbouring cells. The apoptotic cells are recognized by novel surface signal molecules. The apoptotic process is extremely

quick, lasting a few minutes. It often only affects a relatively small number of cells and causes no lasting tissue damage.

At the other end of the cell death spectrum is necrosis. Necrosis is the sum of the morphological changes that result from cell death in a living tissue. Necrosis is pathological, involves large numbers of cells and, importantly, evokes a potentially damaging, inflammatory response. Table 1.1 shows a comparison between apoptosis and necrosis. There are five main types of necrosis and these are outlined in Table 1.2.

Overall, therefore, cell death usually results in cessation of function of a tissue or organ. In necrosis, the dead cells rupture and there is spillage of cell contents. Amongst the extruded material there may be enzymes/proteins from the cytoplasm or specific organelles that enter the blood stream. These enzymes/proteins can be used as clinical 'markers' to assess which cells are damaged, the extent of the damage and even the timing/duration of the process. Examples of this include enzymes released following myocardial necrosis (see Chapter 5).

Overall functional structure of the cardiovascular system

The gross structure of the cardiovascular system is that we have two populations of blood vessels, the systemic and pulmonary circulations, which are perfused by two pumps mounted in series (Fig. 1.6). The fact that the two pumps are joined together in the heart with a common control system is convenient but is not theoretically essential.

The relatively high pressure developed in the systemic arterial system, a result of the left ventricle pumping against the resistance to blood flowing through the rest of the systemic circulation, provides the driving force to perfuse all the tissues of the body with blood except the lungs (see Chapter 10). A series of arterial vessels branching from the aorta distribute the blood to the tissues of the body. Within these tissues, distribution of blood flow is primarily controlled at the level of the arterioles and precapillary sphincters but exchange of nutrients and waste

Table 1.1 Comparison of apoptosis and necrosis

Feature	*Apoptosis*	*Necrosis*
Type of process	Programmed cell death usually physiological	Pathological cell death
Purpose of process	Process used to 'fine tune' cell populations—individual cells/groups of cells involved (e.g. finger webs in embryogenesis)	Pathological event, often causing massive tissue destruction with numerous cells dying (e.g. myocardial infarction)
Progression of process	Complex 'triggered' series of intracellular biochemical events involving enzyme production and activation (DNA switched on)	Pathological insult tips cells out of limits of adaptability and irreversible cell death occurs
Rate of process	Very rapid	Usually slow
Final result	Ultimately cell shrinks, nucleus condenses and cell fragments into apoptotic bodies which are phagocytosed. No inflammation occurs	Ultimately the cells swell, burst and the intracellular contents often provoke intense inflammation

Table 1.2 Types of necrosis

Type	*Aetiopathogenesis*	*Morphology*	*Example*
Coagulative	Denaturation of intracellular proteins	Firm tissue. Cell 'ghosts' seen	Heart Kidney
Liquefaction (colliquative)	Enzymatic tissue dissolution (lysomes in neurones)	Soft semi-fluid tissue. Destroyed architecture	Brain
Fat	Damage to adipocytes (enzymatic or traumatic)	Firm yellowy tissue. Dead adipocytes seen±inflammation with giant cells	Pancreas Breast
Gangrenous	Coagulative necrosis and putrefaction as a result of infection particularly with clostridia	Black foul-smelling tissue	Limb Bowel
Caseous	Intracellular infection with *Mycobacterium tuberculosis*	Soft, white tissue. No cell 'ghosts' seen	Tuberculosis