4 Renal physiology

Introduction to renal structure

The kidneys are primarily responsible for the maintenance of the internal environment of the human body. They share the following **structural features**:

- They are paired retroperitoneal organs.
- They weigh 110–170g each in the adult male, are 10–12 cm long, 5–7.5 cm wide and 2.5–3 cm thick.
- They receive 20%–25% of the cardiac output, which corresponds to 1000–1200 ml/minute, but only account for about 10% of the oxygen consumption of the body.
- The kidneys thereby receive the highest blood flow per gram of organ weight in the human body, while accounting for only 0.4% of the body weight. The entire plasma volume is cycled through the glomerular system 20 times per hour.
- Their internal structure consists of an outer cortex and an inner medulla. The medulla consists of ten pyramids, with their bases near the cortex and apices (papillae) which project into the calyceal sinuses. The pyramids are separated by columnar extensions of the cortex. Ninety per cent of the renal blood supply goes to the cortex.
- The cortex comprises glomeruli and proximal convoluted tubules, while the medulla comprises the loops of Henle, the distal convoluted tubules and the collecting ducts.

Functional components of the kidneys

The functional components of the kidney are the nephrons (each kidney contains one million nephrons), collecting ducts and the microvasculature.

A **nephron**, the structural and functional unit of the kidneys, demonstrates functional segmentation and consists of:

Renal corpuscle, which comprises Bowman's capsule and the glomerular capillary tuft. The glomerular tuft has three cell types: mesangial cells, capillary endothelial cells and podocytes (visceral epithelium of Bowman's capsule).

Renal tubule, which comprises:

Proximal convoluted tubule;

Proximal straight tubule (pars recta);

Descending thin limb of loop of Henle (in long-loop nephrons only);

Medullary thick ascending limb of loop of Henle;

Cortical thick ascending limb of loop of Henle;

Distal convoluted tubule.

The **collecting duct system** comprises the connecting tubule, cortical collecting duct, outer and inner medullary collecting ducts.

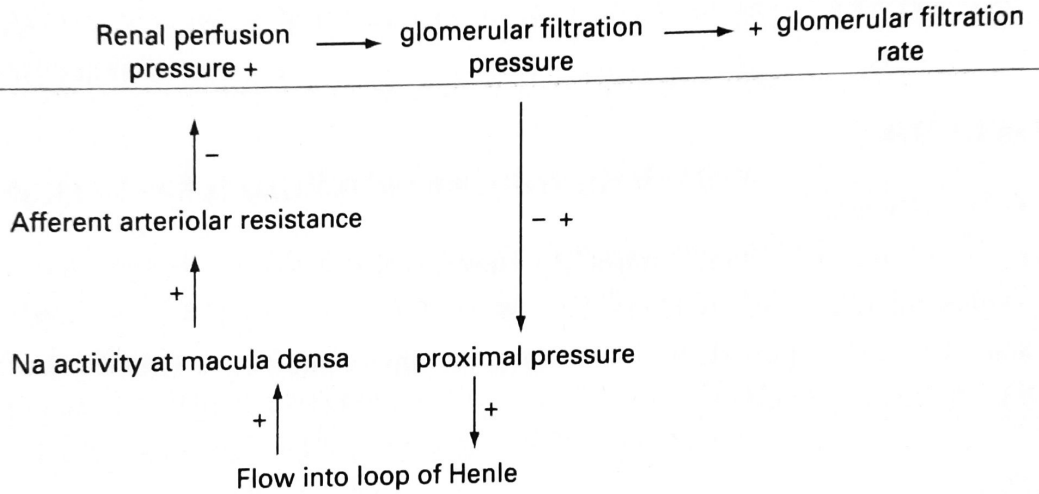

Figure 4.1 Pathway for glomerular feedback.

Types of nephrons

Superficial and mid-cortical nephrons, which comprise 85% of the total. They possess short loops of Henle and their peritubular capillaries carry nutrients to the tubules. Juxtamedullary, which possess long loops of Henle specialised for the concentration of urine. These loops extend into the medulla. The efferent glomerular capillaries form vasa recta, which function as counter-current exchangers.

Functions of the kidney

Excretory and regulatory

Removal of water-soluble nitrogenous waste products of metabolism (urea, creatinine, urate) and catabolic turnover of cells, and the elimination of drugs and toxins;
Maintenance of water, electrolyte (ion concentrations) and acid–base balance (pH of body fluids);
Regulation of extracellular fluid volume;
Maintenance of body fluid composition;
Maintenance of blood pressure.

Metabolic

Gluconeogenesis

Endocrine

Renin production;
Erythropoietin production: control of erythropoiesis;
Synthesis of 1,25-dihydroxycholecalciferol;
Catabolism of polypeptide hormones (e.g., parathyroid hormone, insulin);
Prostaglandin synthesis.

Characteristics of erythropoietin

This glycoprotein hormone of molecular weight 34 000 daltons is synthesised by renal cortical interstitial cells, which account for about 80% of the body's production. Production is stimulated by tissue hypoxia.

It is a major regulator of red blood cell production, binding to specific cell surface receptors and promoting erythroid differentiation.

The renal circulation

This consists of, in sequence, several orders of branches of the renal artery, including:

Interlobar arteries
Arcuate arteries
Cortical radial (interlobular) arteries
Afferent arterioles
Glomerular capillary tufts
Efferent arterioles
Descending vasa recta
Capillary plexus at medullary level
Ascending vasa recta
Arcuate veins
Interlobular veins
Arcuate veins
Interlobar veins

The kidney is unique in possessing two capillary networks in series, each with a preceding arteriole. These are the glomerular bed and the peritubular capillary bed. The glomerular capillary pressure is much higher than that of any other capillary bed in the body, this being a reflection of its interposition between two arteriolar systems.

Effects of renal circulation on urine production

The renal circulation affects urine formation in the following ways:

- The glomerular filtration rate is an important determinant of solute and water excretion.
- The peritubular capillaries in the cortex return reabsorbed solutes and water to the systemic circulation and can modulate the degree of proximal tubular reabsorption and secretion.
- The vasa recta capillaries return reabsorbed salt and water to the systemic circulation and participate in the counter-current mechanism.

Abnormalities of renal haemodynamics may be involved in the genesis of acute renal failure, associated with a reduction in total renal blood flow and with the redistribution of intrarenal blood flow away from cortical to juxta-medullary nephrons in order to protect the medulla.

Autoregulation

The renal circulation is subject to **autoregulation** by the following mechanisms:

- A myogenic response, with arteriolar smooth muscle contraction in response to increased vessel wall tension;

The intranephron tubuloglomerular feedback system, which describes the coupling of distal nephron flow with single nephron glomerular filtration rate.

Humoral influences on the renal vasculature

These are mediated by the following substances:

Vasoconstrictors:

- Angiotensin II
- Noradrenaline
- Thromboxane A2, B2
- Leukotrienes D4, C4
- Platelet-activating factor
- Endothelin-1
- Vasopressin

Vasodilators:

- Prostaglandins E1, E2, I2
- Acetylcholine
- Bradykinin
- ~~Nitric oxide~~
- Atrial natriuretic peptide (ANP)

Processes involved in urine production

- **Glomerular filtration**, which involves the passive formation of an ultrafiltrate (water and crystalloids) of the plasma, which is essentially blood cell and protein macromolecule free, at the glomerulus. Around 180 litres of glomerular filtrate is formed daily, of which 99% is reabsorbed by the tubules. The glomerulus functions as a size-selective, shape-selective and electrical charge-selective barrier for macromolecules. It is normally impermeable to molecules of the size of albumin (69 000 daltons) and larger. Cations are more readily filtered than anions for the same molecular radius.
- **Tubular secretion**, from the peritubular capillary blood to the tubular lumen, which may be active or passive.
- **Tubular reabsorption** from the tubular lumen to the blood, which is either active or passive. About two thirds of the glomerular filtrate is reabsorbed in the proximal tubule. The trans-tubular reabsorption or secretion of ions is facilitated by protein carriers or ion-specific channels.
- Tubular metabolism

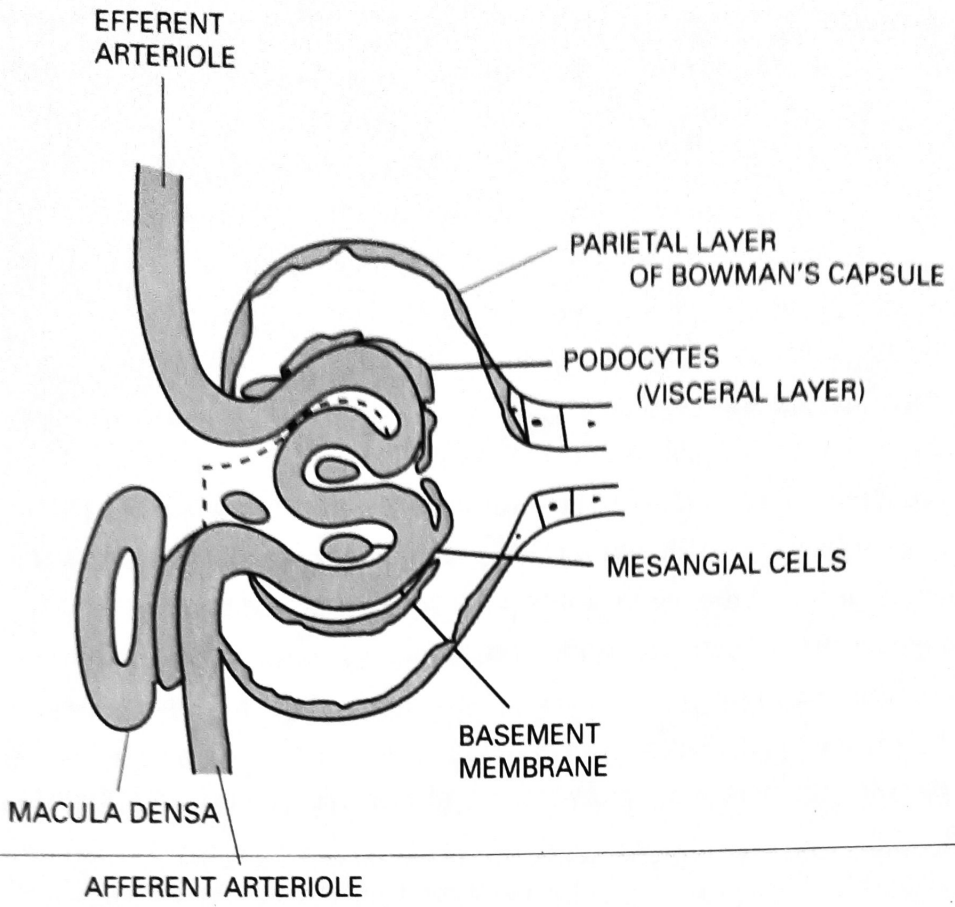

Figure 4.2 Glomerulus and glomerular capillary.

Glomerular filtration

The process of **glomerular filtration** is determined by:

- A balance of Starling forces, i.e. the hydrostatic and colloid osmotic forces acting across the glomerular capillary membrane. Glomerular capillary hydrostatic pressure, which is the main driving force, depends on the systemic arterial blood pressure, afferent arteriolar resistance and efferent arteriolar resistance.
- The capillary filtration coefficient.

Ultrafiltration from the glomerular capillaries into Bowman's membrane occurs through three **filtration barriers**:

Fenestrated **endothelium of the glomerular capillaries**. These are polygonal squamous epithelial cells with large open pores.

Basement membrane of Bowman's capsule. This comprises a lamina densa between two less dense cement layers.

Podocytes, or specialised epithelial cells of Bowman's capsule with numerous foot processes or pedicels that cover the basement membrane. The foot processes are separated by filtration slit diaphragms that contain pores.

Glomerular filtration rate

The **glomerular filtration rate** is determined by the number of functioning glomeruli, which is proportional to kidney size and relates to the glomerular capillary surface area, and by the filtration rate at each single glomerulus.

The determinants for the **single nephron glomerular filtration rate** are:

Mean trans-capillary hydrostatic pressure difference (glomerular capillary hydrostatic pressure minus the pressure in Bowman's space);

Systemic plasma colloid osmotic pressure;

Glomerular plasma flow rate;

Glomerular capillary ultrafiltration coefficient.

The glomerular filtration rate can be represented as the filtration coefficient x the filtration pressure. The **filtration coefficient** is a function of the total capillary surface area and of the permeability per unit of surface area.

The range for the glomerular filtration rate is

60–80 ml/min per m^2 or

100–140 ml/min per 1.73 m^2

The rate falls with increasing age by about 1 ml/min per year beyond the age of 40 years.

The glomerular filtration rate can be measured by **clearance techniques**. The clearance of a marker substance that is not metabolised by the kidneys is a hypothetical measure of the volume of arterial plasma completely cleared of the marker in unit time, usually in one minute. It is a virtual and not a real volume of plasma.

$$\text{Clearance} = \frac{(\text{Urine concentration} \times \text{urine volume per minute})}{\text{Plasma concentration}}$$

A **marker for measurement of glomerular filtration rate** should have the following properties:

Metabolically inert;

Free filtration at the glomerulus, with molecular weight compatible with unimpeded glomerular filtration;

No effect on the glomerular filtration rate;

Not reabsorbed, secreted or metabolised by the renal tubule;

No protein binding;

No extra-renal clearance;

Steady state level in plasma;

Easily measured in serum and urine;

Non-toxic.

Glomerular filtration rate in ml/min can be represented by the formula *UV/P* where

The **Cockcroft–Gault formula** allows calculation of creatinine clearance from plasma creatinine.

$$\text{Creatinine clearance} = \frac{(140 - \text{age in years}) \times \text{lean body weight in kilograms}}{\text{plasmacreatinine} \times 72}$$

In women, the result thus obtained is multiplied by 0.85.

The **filtration fraction** is the ratio of the glomerular filtration rate to the renal plasma flow, and represents the proportion of the renal arterial plasma flow removed by glomerular filtration. The normal value is around 0.2.

U = concentration of marker in urine (mg/ml)

V = flow rate of urine (ml/min)

P = plasma concentration of marker (mg/ml)

The clearance of either inulin or of endogenous creatinine is independent of the plasma concentration and of the rate of urine flow. Glomerular filtration rate can also be measured using chelating agents, such as ^{51}Cr-ethylene diamine tetra-acetic acid (EDTA) and ^{99}Tcm-diethylene triamine penta-acetate (DTPA).

Endogenous creatinine clearance can be measured following collection of a timed overnight urine collection and an early morning blood sample. A 24 hour clearance measurement eliminates errors due to period variable bladder emptying and wash-out effects. One to two per cent of the total muscle creatine pool is converted daily to creatinine. Creatinine clearance is increased in renal failure, leading to an overestimation of glomerular filtration rate.

The measurement of **inulin clearance** is achieved by administration of a bolus dose followed by a constant infusion, until the plasma concentration is almost steady, typically after 90–120 minutes. Moderate diuresis is induced by the regular administration of fluid before and during the test. Timed urine specimens are collected, with blood samples being taken at the mid-points of the collection periods for assay. The glomerular filtration rate is taken as the mean for each period.

Tubular function

The proximal convoluted tubules are lined with cuboidal cells, which possess an inner brush border with microvilli, and possess a high mitochondrial content. The distal convoluted tubules are lined with cuboidal cells, which possess many mitochondria but no microvilli. The tubular cells demonstrate polarity, whereby the apical or luminal membrane and the basolateral or peritubular membrane

Cardiovascular system

6

Introduction

The cardiovascular system comprises:

- A **pump**: the heart, which comprises two atria (reservoirs for blood and booster pumps to augment ventricular filling) and two ventricles (pumps). It consists of two pumps in parallel, with synchronised actions.
- A high pressure **distribution circuit**: the elastic arteries, i.e.the aorta and its major branches, serve a transport function. The muscular arteries serve a distributive function.
- **Exchange vessels**: the capillaries, which are 8–10 μ in diameter. Capillaries can possess either continuous endothelium (muscle, heart, liver), fenestrated endothelium (gastrointestinal tract, renal glomeruli), or discontinuous endothelium (liver, spleen).
- A low pressure **collection and return** circuit.

The system allows rapid transport of oxygen, nutrients, hormones and waste products throughout the body. The structure of the components is related to function across the vascular tree.

The fetal circulation

This has the following characteristics:

- The right and left ventricles function in parallel;
- The placenta provides for gas and metabolite exchange;
- The parallel circulation is maintained by shunts at the ductus venosus, foramen ovale and the ductus arteriosus.
- Oxygenated blood flows from the placenta via the ductus venosus and inferior vena cava into the right atrium, where it is deflected by the crista dividens and the eustachian valve across the foramen ovale into the left atrium and thence into the left ventricle. It is then ejected into the ascending aorta.

Distribution of blood volume

Systemic circuit 80%
Arteries 10%
Capillaries 5%
Veins and venules 65%
Pulmonary circuit 12%
Heart 8%

- Deoxygenated blood from the superior vena cava flows into the right atrium, being primarily directed into the right ventricle and ejected into the pulmonary artery.
- Mixing of the venous returns occurs.
- The pulmonary circulation is a high-impedance and low-flow system.
- The placental circulation is a low-impedance and high-flow system

At birth, a **transitional circulation** ensues, with the following changes:

A reduction in pulmonary vascular resistance secondary to expansion of the lungs and an increase in arterial pO_2.

An increase in systemic vascular resistance caused by removal of the low resistance placental circulation.

The systemic vascular resistance exceeds the pulmonary vascular resistance.

A left-to-right shunt through the ductus arteriosus, with progressive closure.

Functional closure of the foramen ovale as a result of raised left atrial pressure and volume.

Closure of the ductus venosus as a result of removal of the placenta from the circulation.

The adult circulation consists of two chambers, the right and left ventricles, in series, with two interposed vascular beds (systemic and pulmonary).

Control of blood volume

Blood volume control mechanism

Afferent limb

- **Volume sensors**

Low-pressure baroreceptors (venous side stretch receptors)

Cardiac atria

Roots of great veins

Cardiopulmonary receptors

Left ventricle
Pulmonary vascular bed
High-pressure baroreceptors (arterial side stretch receptors)
Carotid sinus (glossopharyngeal nerve)
Aortic arch (vagus nerve)
- Intrarenal baroreceptor system: juxtaglomerular apparatus
- Hepatic and central nervous system(CNS) sensors

Central control system

- Cardiovascular centre
  Pressor system: lateral pathway of descending reticular system
  Depressor system: medial pathway of descending reticular system
- Nucleus of the tractus solitarius
- Hypothalamus

Efferent mechanisms

Those regulating renal sodium excretion and controlling extracellular fluid volume

- Glomerular filtration rate
- Physical factors
  At proximal tubule level
  Beyond proximal tubule level
- Humoral effector mechanisms
  Renin–angiotensin–aldosterone system
  Vasopressin
  Catecholamines
  Prostaglandins: PGE2, PGI2, thromboxane
  Kinin–kallikrein system
  Atrial natriuretic peptide (ANP)
  Endothelium-derived factors
- Renal sympathetic nerves

Effects of blood loss

The effects of the rapid loss of one litre of blood (20% total blood volume) in an adult can be listed in sequence as consisting of:

- **Blood loss** leading to reduced venous return, reduced right atrial pressure and reduced cardiac output.
- **Immediate baroreceptor reflex activation**. A reduced discharge rate of baroreceptors in carotid sinus and aortic arch leads to reduced afferent input to

the medullary cardiovascular centre causing a reduction in parasympathetic, and increase in sympathetic, activity. This is manifested by tachycardia, increased myocardial contractility and arteriolar constriction.

- **A slower hypothalamic–pituitary–adrenal response**. Reduced renal blood flow stimulates intrarenal baroreceptors with renin release from the juxtaglomerular apparatus. Angiotensin II which results causes arteriolar constriction and stimulates aldosterone and arginine vasopressin (antidiuretic hormone; ADH) release. Arginine vasopressin release is also stimulated by reduced extracellular fluid volume acting via atrial stretch receptors.
- **Redistribution of cardiac output** from skin, muscle, viscera to heart and brain.
- **Starling forces**, which are responsible for tissue fluid reabsorption into the plasma compartment.

  Movement out of capillary:

  Capillary hydrostatic pressure

  Interstitial fluid colloid osmotic pressure

  Fluid retention within the capillary:

  Plasma colloid osmotic pressure

  Interstitial space hydrostatic pressure
- **Carotid chemoreceptor response**: reduced blood flow to the aortic and carotid bodies, with reduced oxygen in the peripheral chemoreceptor tissues, leading to hyperventilation.

Blood pressure

Systemic arterial blood pressure is related to cardiac output and to total peripheral resistance (in turn related to the number and calibre of small arteries and arterioles, and to blood viscosity). Arterial hypertension represents a disproportion between these two components.

Blood pressure comprises:

A steady component, **the mean arterial pressure**, which is related to small arterial and arteriolar resistance. This in turn depends on a combination of neural mechanisms (sympathetic and parasympathetic), hormonal mechanisms (renin–angiotensin–aldosterone mechanism) and local transmitters (nitric oxide), all of which affect arteriolar calibre.

A pulsatile component, the **pulse pressure**, which depends on arterial stiffness and the timing of reflected waves. It represents the oscillation around mean pressure, extending from systolic to diastolic pressures.

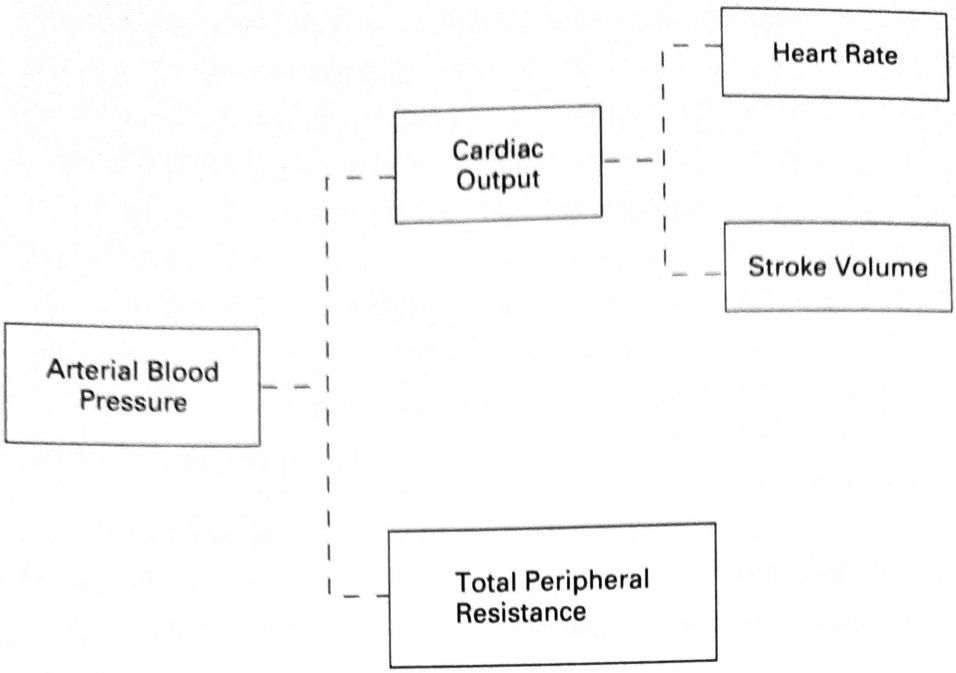

Figure 6.1 Determinants of arterial blood pressure.

Determinants of arterial blood pressure

Physical
- Blood volume in arterial system
- Elastic characteristics (compliance)

Physiological
- Cardiac output
- Peripheral resistance

Mean arterial pressure is equal to cardiac output multiplied by total peripheral resistance. Pulse pressure is equal to systolic minus diastolic pressure. It is directly proportional to stroke volume and inversely proportional to compliance. Pulse pressure increases with age due to reduced compliance.

Systolic blood pressure depends on myocardial contractility, the compliance of the great vessels and on diastolic blood pressure. Diastolic blood pressure depends on systemic vascular resistance, peripheral run-off and on heart rate.

Factors regulating blood pressure

Short-term regulation

Baroreceptors comprise a negative feedback system incorporating stretch receptors sensitive to both mean pressure and rate of change of pressure

(elevations in blood pressure increase the rate of firing). Under physiological conditions, baroreceptor firing exerts a tonic inhibitory influence on the sympathetic outflow from the medulla oblongata. High-pressure baroreceptors are found in the carotid sinus, at the bifurcation of the common carotid artery and in the aortic sinus in the arch of the aorta.

Hypothalamus.

Arterial chemoreceptors.

Vomiting centre.

Pulmonary stretch receptors.

Ventricular mechanoreceptors.

Atrial stretch receptors.

Longer-term regulation

Alterations in blood volume and osmolality.

Hormonal regulation of blood pressure

This is achieved by a balance of vasopressor and vasodepressor hormones, which include the following:

Vasopressor hormones:

- Renin–angiotensin–aldosterone system
- Arginine vasopressin
- Catecholamines
- Endothelins (ETs)

Vasodepressor hormones:

- Natriuretic peptides: ANP, brain type natriuretic peptide (BNP)
- Kinin–kallikrein system
- Prostaglandins (PGI2, prostacyclin)
- Medullipine system
- Adrenomedullin
- Nitric oxide

Endothelins

A family of peptides acting locally as autacoid or paracrine hormones. Three isoforms of the 21 amino acid peptide have been identified: ET-1, ET-2 and ET-3. They are produced by a variety of cells, including endothelial and epithelial cells, macrophages and fibroblasts. Endothelins are characterised by two intra-chain disulphide rings, leading to a hairpin loop configuration, along with six conserved amino acid residues at the C terminus.

Endothelins are synthesised by the proteolysis of large pre-proendothelins, which are cleaved to big endothelins, and then processed to the mature peptide by endothelin-converting enzyme.

Endothelins induce dose-dependent contraction in vascular smooth muscle, ET-1 being the most potent known endogenous vasoconstrictor. Two high affinity endothelin receptors have been recognised, ETA and ETB. They have been characterised as seven transmembrane domain G-protein receptors coupled to phospholipase C. The ETA receptor is the predominant type of receptor.

Valsalva manoeuvre

The **Valsalva manoeuvre** is a global test of cardiovascular responses. It involves forced expiration against a closed glottis

Effects of the resulting positive intrathoracic pressure include:

Compression of the lungs

Blood forced through the pulmonary veins to the left atrium and ventricle

Increased left ventricular stroke volume

Transient rise in systemic blood pressure

Reduced venous return to the heart

Reduced cardiac output

Reduced blood pressure

Measurement of arterial blood pressure

Indirect methods

Sphygmomanometer, using palpation and auscultation, the latter making use of the characteristic sequence of Korotkow sounds.

Oscillotonometry, which uses a double cuff system, the proximal cuff occluding the arterial pulsations and the distal cuff sensing pulsations. The pulsations are amplified by a pressure-sensitive aneroid chamber.

Direct methods

Intra-arterial cannula connected to a calibrated pressure transducer.

■ Renin-angiotensin mechanism

This integrated hormonal cascade system regulates arterial blood pressure, intravascular volume and electrolyte balance. More broadly, it is a complex autocrine system involved in diverse processes of cellular biology and pathophysiology.

Heart failure

Heart failure can be due to either:

Systolic dysfunction:

Impaired ejection (forward failure), due to reduced inotropy (contractility)

Diastolic dysfunction:

Impaired filling (backward failure), due to reduced lusitropy (relaxation)

The term **hibernating myocardium** refers to reversible LV dysfunction due to chronic coronary artery disease which responds positively to inotropic stress. This is associated with reduced coronary blood flow reserve.

Adaptive mechanisms that allow maintenance of cardiac output in the presence of factors predisposing to congestive heart failure

These include:

The Frank–Starling mechanism;

The inotropic state of the cardiac muscle;

Increase in heart rate;

Myocardial dilatation (with chronic volume overload) or myocardial hypertrophy (with chronic pressure overload);

Increased sympathetic nervous system activity;

Humoral mechanisms, mediated via ANP.

Pathophysiology of the failing myocardium

Mechanical alterations

Reduction in force development per unit cross-sectional area;

Reduction in maximum rate of force development;

Reduced velocity of shortening;

Reduced relaxation (lusitropy).

Biochemical alterations

Catecholamines: reduced synthesis and myocardial content;

Reduced myofibrillar actomyosin-ATPase;

Increased hydroxyproline (hypertrophy);

Variable reduction in adenosine 5′-triphosphate (ATP);

Reduced calcium binding by sarcoplasmic reticulum, with myocardial calcium overload;

Reduced adenyl cyclase activity.

Exogenous changes

Increased cortisol, catecholamines and free fatty acids.

Factors that regulate cardiac myocyte hypertrophy

Positive: insulin growth factor-1; angiotensin II; endothelin 1; PGF2alpha; cardiotrophin 1.

Negative: vitamin A; ATP.

Inotropic mechanisms

These can be broadly classified as being:

Adenosine 3′-5′-monophosphate (cyclic AMP)-dependent mechanisms:

Beta-adrenoreceptor stimulation. These are G-protein-coupled cell membrane receptors that activate adenyl cyclase to produce cyclic AMP. Agonists at these receptors include noradrenaline, adrenaline, dopamine, dobutamine, isoprenaline and dopexamine.

Inhibition of phosphodiesterase isoenzyme in the myocardium. Inhibitors include bipyridine derivatives (amrinone, milrinone) and the imidazole derivatives (enoximone).

Cyclic AMP-independent mechanisms:

Inhibition of membrane bound Na^+/K^+-ATPase, causing an increase in intracellular sodium and intracellular calcium. This increases calcium stores in the sarcoplasmic reticulum and also increases the slow inward current responsible for the phase 2 plateau of the action potential in cardiac myocytes.

Partial agonists at the dihydropyridine receptor on the L-type calcium channel.

Calcium sensitisers, which promote prolonged actin and myosin interaction.

Alpha-1-adrenoreceptor agonists, such as phenylephrine and methoxamine.

Myocardial oxygen consumption

Determinants of myocardial oxygen consumption

Myocardial oxygen consumption involves a balance between oxygen demand and oxygen supply.

Myocardial oxygen supply depends on:

Oxygen content of the coronary arterial blood.

Coronary vessel calibre (concentration of myocardial metabolic products and the pCO_2).

Coronary perfusion pressure, which is diastolic and dependent on the LVEDP. It is equal to the difference between the aortic diastolic blood pressure (driving pressure) and the LVEDP or coronary pressure (back pressure), whichever is greater.

Coronary perfusion time, which equates to 1/heart rate. With faster heart rates diastole is shorter.

Myocardial oxygen demand depends on:

Basal oxygen requirements.

External work (mean arterial pressure × stroke volume), which is determined by LV preload, myocardial contractility or inotropic state (measured by the velocity of contraction), and LV afterload (dependent upon aortic contractility and arteriolar run-off).

Internal work (during isovolumetric contraction), which is pressure generated and dependent on the ventricular radius.

Myocardial mass.

Heart rate: tachycardia increases demand.

Coronary circulation

The **coronary circulation** consists of:

Arteries: The two coronary arteries arise from the coronary ostia just above the respective cusps of the aortic valve.

Left coronary artery, which gives off the following branches:

Left circumflex artery supplies posterior free wall of left ventricle

Left anterior descending artery supplies the anterior free wall of the left ventricle; a septal branch supplies the upper inter-ventricular septum

Right coronary artery supplies the free wall of the right ventricle and right atrium and the posterior free wall of the left ventricle.

Veins: epicardial veins; coronary sinus; Thebesian veins.

Features of coronary blood flow

The epicardial arteries give rise to small vessels that supply the outer third of the myocardium. They also give off penetrating vessels that anastomose with the subendocardial capillary plexus, which functions as an **end-arterial system**. There is no significant collateral circulation at the microcirculatory level, explaining the discrete nature of ischaemic lesions following myocardial infarction.

Flow is phasic, predominantly in diastole, owing to the aortic pressure wave and to intramural coronary vessel compression by cardiac muscle contraction in systole. During tachycardia, when myocardial oxygen demand is increased, the duration of diastole is reduced, thereby reducing coronary flow. The flow at rest

in an adult with a cardiac output of 5 l/min is around 60–70 ml per 100 grams of myocardium per minute. The normal myocardium weight is 300 grams.

Maximal oxygen extraction takes place. Myocardial oxygen extraction ranges between 11 and 12 ml/100 ml per minute.

Coronary flow is subject to **autoregulation**. The difference between autoregulated flow and maximal flow constitutes the coronary vascular reserve. Flow is controlled by:

Myogenic response to change in luminal pressure (arterial smooth muscle contraction occurs in response to increased intraluminal pressure).

Metabolic vasodilatation (coronary arteriolar tone depends on the balance of myocardial oxygen supply and demand). Potential mediators for metabolic regulation include oxygen, carbon dioxide and adenosine. Adenosine is a product of ATP utilisation, and increased adenosine concentrations reflect an imbalance between energy demand and supply.

Autonomic innervation may play a role but the effects of sympathetic or parasympathetic activation on the coronary circulation may be difficult to isolate owing to concomitant changes in heart rate, blood pressure and contractility.

■ Cardiac cells

There are five functionally and anatomically separate types:

Sino-atrial node
Atrio-ventricular node
His-Purkinje system
Atrial muscle
Ventricular muscle

The properties of cardiac muscle

These are:

Automaticity (chronotropy): the ability to initiate an electrical impulse.
Conductivity (dromotropy): the ability to conduct an electrical impulse.
Contractility (inotropy): the ability to contract.
Lusitropy: the ability to relax and to fill.

Cardiac muscle cells form a structural and functional **syncytium** (a complex three-dimensional network), being linked by low-resistance intercalated disks. The cells measure 16–100 μm in length and 12–20 μm in diameter.

The **intercalated discs** serve the following functions:

The connection of adjacent cells via desmosomes.

The connection of actin filaments of adjacent cells.

Tight intercellular coupling through low-resistance gap junctions. Each gap junction consists of a cluster of several ion channels. Each channel comprises two hemi-channels or connexons. Each connexon is made up of six connexin molecules that traverse the lipid bilayer and form a central pore. Isoform-specific determinants of conductance, selectivity and gating are located in the cytoplasmic domains of the connexins.

Blood vessels

Types of blood vessels

- **Damping vessels**: arteries. The conduit and large distributing arteries offer little resistance to blood flow and help in the propagation of the arterial pulse. They have a windkessel or air cushion effect by virtue of partial accommodation of the stroke volume with ventricular systole. They offer dynamic resistance to the oscillatory components of pulsatile flow, constituting vascular impedance. This damps the pressure oscillations caused by intermittent ventricular ejection. With distal movement of the arterial pressure pulse, there is a rise in systolic pressure, a fall in diastolic pressure and a widening of the pulse pressure. The peak systolic pressure is amplified with passage down the lower limbs.
- **Resistance vessels**: small arteries; arterioles. These vessels are largely responsible for vascular resistance and the maintenance of blood pressure. A microcirculatory unit is a collection of vessels taking origin from an arteriole.
- **Exchange vessels**: capillaries, which are concerned with the transfer of nutrients and waste products between the blood and tissues. They are thin-walled, consisting of a single layer of endothelial cells (with no muscle or connective tissue) and have a large surface area. The endothelial cells are surrounded by a basement membrane and a fine network of reticular collagen fibres. Capillaries form branching networks and have a high density in metabolically active tissues such as glands, and cardiac and skeletal muscle. Capillary endothelial cells possess the property of forming new capillaries (angiogenesis).

  Capillaries may vary in structure according to functional needs as follows:

  Fenestrated or visceral capillaries (glomerulus, choroid plexus, intestinal epithelium, ciliary bodies of the eye) with fenestrations or pores, 60–80 nm in diameter, with or without a thin diaphragm.

Continuous or somatic capillaries (muscle; skin; lungs; brain; thymus; bone): with tight junctions and a continuous basal lamina.

Discontinuous capillaries (liver, bone marrow, spleen), with wide intercellular gaps.

- **Capacity vessels** (collecting and reservoir system): veins and venules, vena cavae, right atrium. Two thirds of the blood is contained within the venous system, which performs a reservoir function.

Arterio-venous shunts connect arterioles and venules and are common in the skin in certain parts of the body, including the fingertips and ear lobules. They are involved in thermoregulation.

Capillary exchange

The capillary acts as a selective filter. The movement of fluid across the capillary wall by filtration, between the capillary and the interstitial fluid, is governed by **Starling forces**. The Starling forces define water movement between the intravascular and extravascular spaces as the difference between hydrostatic forces forcing water out of the capillaries and osmotic forces drawing water into the intravascular space. The net fluid flux is directly proportional to the net driving pressure, which is outward at the arteriolar end and inward at the venous end of the capillary. This forms the basis of the plasma-interstitial fluid balance.

$$Qi = k((Pc - \pi i) - (Pi - \pi p))$$

Where

Qi = fluid movement across the capillary wall.

k = filtration constant for the capillary membrane (rate of filtration of fluid/min per mm Hg per 100 grams of tissue). It is a measure of the leakiness of the capillary wall to water.

πp = plasma osmotic pressure.

πi = interstitial fluid osmotic pressure.

Pc = capillary hydrostatic pressure.

Pi = interstitial fluid hydrostatic pressure.

The **mechanisms of tissue oedema** can be considered in the light of the Starling forces as follows:

Increased capillary hydrostatic pressure, secondary to venous obstruction;

Reduced capillary plasma osmotic pressure, due to low plasma albumin levels as in liver disease or starvation;

Reduced interstitial hydrostatic pressure;

Increased interstitial fluid osmotic pressure, secondary to lymphatic vessel obstruction;

Alteration in the capillary filtration coefficient, i.e. increased capillary permeability due to local inflammation, hypoxia or local toxins as in anaphylaxis.

Light pressure on the skin can lead to a white response, caused by pre-capillary sphincter constriction. Harder pressure produces the **triple response**, which consists of a red reaction (dilatation of pre-capillary sphincters), a weal (raised capillary hydrostatic pressure and increased capillary permeability to proteins) and a flare (arteriolar dilatation).

Lymphatic vessels

These are thin-walled endothelial-lined vessels that aid in the return of tissue fluid to the venous system. They form a complex network of blind-ended permeable capillary vessels which are present in all organ systems except the CNS and the bone marrow. The volume of fluid transported through the lymphatics in 24 hours approximates the total plasma volume. The lymphatic vessels eventually drain into the great veins – the thoracic duct and right lymphatic duct draining into the junction of the internal jugular vein and the subclavian vein on the left and right sides respectively.

Flow of fluid through lymphatics is aided by:

The skeletal muscle pump: intermittent skeletal muscle activity;

Unidirectional valves;

Contractions of large lymphatic vessels;

The thoracic pump.

Functions of the lymphatic system

These include:

An in-line filter function of the lymph nodes;

Return of protein from the interstitial space to the venous system;

The transport of lipoproteins, long-chain fatty acids and cholesterol that has been absorbed in the small intestine;

Contributing to the maintenance of renal concentrating ability.

Factors determining smooth muscle tone

Intrinsic myogenic tone.

Locally produced vasoactive substances: metabolic products, including lactic acid, carbon dioxide, potassium, adenosine diphosphate (ADP), AMP and adenosine.

Circulating blood substances: adrenaline, vasopressin, angiotensin II, ANP.

Vascular endothelium

The endothelium is the confluent mono-cellular lining of blood vessels, which separates the blood from the extravascular tissues. It forms the structural and functional interface between the blood and the vessel wall. The endothelium constitutes the largest endocrine, paracrine and autocrine organ in the body, with a surface area of around 600 square metres in an average adult. It is responsible for the regulation of vasomotor tone (vasodilatation and vasoconstriction), vessel growth, platelet aggregation, monocyte adhesion and fibrinolysis. The endothelium plays a major role in the pathogenesis and progression of atherosclerosis and thrombotic disease.

Properties of endothelium

- Functions as a selective permeability barrier (permeability regulator: filter function).
  Large molecules: vesicular transport; passage through intercellular junctions
  Small molecules: vesicles; junctions; and through cytoplasm
- Forms a blood compatible container with a non-thrombogenic surface, which is achieved by the balance between the prothrombotic and the antithrombotic and fibrinolytic characteristics of the endothelial cell.
- Synthesis/metabolism/secretion of:
  Vasoactive (vasorelaxing and vasoconstricting) autacoids: prostacyclins; leukotrienes; nitric oxide; endothelin; angiotensin-converting enzyme.
  Connective tissue components: laminin, fibronectin, vitronectin.
  Chemokines: monocyte chemoattractant protein-1.
  Adhesion molecules: von Willebrand factor, E-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1.
- Binding and internalisation of lipoproteins: modify low density lipoproteins (LDLs)- LDL receptor; lipoprotein lipase.
- Synthesis of stimulating or inhibitory mitogens, with autocrine and paracrine effects.
- Regulator of vascular tone (regulation of smooth muscle contractility)
  Smooth muscle relaxation: nitric oxide.
  Smooth muscle contraction: endothelin; angiotensin II
- Regulator of haemostasis and inflammation: secretes procoagulant factors and inflammatory mediators:
  Platelet adhesion and activation: von Willebrand factor; P-selectin; E-selectin; platelet-activating factor
  Coagulation: thrombomodulin; heparin sulphate

Respiratory system

7

Introduction

The respiratory system allows oxygen delivery to, and carbon dioxide removal from, the bloodstream, which are mediated via the conducting airways and a gas-exchange region. The exchange of gases is termed respiration.

Functional components of the respiratory system

- The **pump** that drives ventilation: chest wall and pleura; respiratory muscles (intercostals and diaphragm). These can be supplemented by the accessory muscles of respiration (sternomastoids, scaleni, pectorals, latissimus dorsi) in situations where the work of breathing is increased. **Inspiration** is an active process, being brought about by negative intra-pleural pressure generated by contraction and descent of the diaphragm and rib cage elevation by the intercostal muscles. The contraction of the diaphragm expands the chest wall laterally (bucket handle effect) and antero-posteriorly (pump handle effect). The phasic action of the intercostal muscles helps in stabilisation of the chest wall. **Expiration** is mainly passive and dependent on the elastic recoil of the lungs and chest wall. Active expiration occurs during exercise and in hyperventilation states and primarily involves the anterior abdominal wall musculature, assisted by the internal intercostal muscles.
- The **distribution of ventilation**: upper respiratory tract, conducting airways, respiratory bronchioles. Apart from air conduction, these air passages are involved in the humidification and warming of inspired air.
- **Perfusion**: pulmonary arteries and veins, capillaries.
- **Bronchial clearance**: muco-ciliary escalator; macrophages.
- **Alveolar clearance and defence**: alveolar macrophages; pulmonary lymphatics; humoral mediators.

The process of **gas exchange** itself involves:
Ventilation of the lungs;
Capillary perfusion of ventilated alveoli;
Diffusion across the alveolar-capillary membrane.

The upper respiratory tract

This comprises:

- The **nose**, which serves the following functions:
  Air conduction.
  Particle and micro-organism clearance by the muco-ciliary mechanism, which comprises the pseudostratified ciliated epithelium, mucous blanket and the mucus-producing glands. The inspired air is thereby cleaned and filtered. In general, particle diameter requires to be greater than 10 μm to allow nasal filtration.
  Humidification and warming of inspired air by a counter-current heat and fluid exchange mechanism.
  Perception of smell, via the olfactory neuroepithelial receptors.
  Contributes to more than 50% of total airway resistance normally.
- The **pharynx**, which is involved in swallowing, while simultaneously preventing aspiration of food into the lungs.
- The **larynx**, which is involved with:
  The production of speech, which comprises the three components of phonation, resonance and articulation.
  Providing a sphincter for protection of the lower airway from soiling, especially during swallowing and vomiting.
  Acting as a sphincter in cough and expiration.
  Regulating airflow in and out of the lungs. When open, ventilation of the lungs is allowed.
  The Valsalva manoeuvre, of forced expiration against a closed glottis, which is involved in the control of venous return and also facilitates defaecation.
  Providing sensory input for respiratory control.

The **paranasal sinuses** are lined by ciliated stratified or pseudostratified columnar epithelium. They may subserve the following functions:
Humidification and warming of inspired air;
Regulation of intra-nasal pressure;
Provision of resonance to the voice;
Increase in the surface area of the olfactory mechanism;
Lessening the density and weight of the skull;

Providing an air buffer to the concussive effects of blunt trauma.

Nasal function testing

This can be carried out by:

- **Airflow measurements**
  Rhinomanometry: simultaneous trans-nasal pressure and airflow recording; which can be anterior, posterior or post-nasal;
  Peak nasal airflow;
  Acoustic rhinometry;
  Radiological imaging to assess the cross-sectional area of the nasal passages (computed tomography or magnetic resonance imaging).
- **Ciliary function testing**: saccharin taste test, which measures the time taken to taste saccharin in the back of the throat after application to the anterior tip of the inferior nasal turbinate. A time greater than 30 minutes is abnormal. Ciliated epithelium can be obtained by nasal brush biopsy of the inferior nasal turbinate and the sample is processed at 37 °C to determine ciliary beat frequency, and to assess the ciliary beat pattern by slow motion analysis. Ciliary ultrastructure can be assessed by transmission electron microscopy.
- **Tests of olfaction** using smell bottles.

Functional anatomy of the lower respiratory tract (Weibel)

The tracheo-bronchial tree can be described as a symmetrical dichotomous branching system of airways, comprising around 23 generations of airway from the trachea to the alveolar sacs. It comprises:

- Trachea: generation 0. This is 25 cm long in the adult and supported by 15–20 horseshoe-shaped cartilaginous rings that are joined posteriorly by smooth muscle.
- Main, lobar and segmental bronchi: generations 1–4. The major site of airways resistance to gas flow is at the level of the 3rd and 4th generation airways, contributing 60%–70% of total airways resistance.
- Small bronchi: generations 5–11. Bronchioles: generations 12–14. There is no cartilage in the wall at this level, and the air passages are held open not by structural rigidity but by elastic recoil.
- Respiratory bronchioles: generations 15–18.
- Alveolar ducts: generations 19–22.
- Alveolar sacs: generation 23. The 23rd generation airways possess a total cross-sectional airway diameter much greater than that of the trachea.

Airway calibre is determined by the coupling of airway wall elasticity and airway transmural pressure.

The topological unit of the lung is the **bronchopulmonary segment**, which is supplied by a principal branch of a lobar bronchus and its accompanying pulmonary artery.

Features of the pulmonary acinus (or terminal respiratory unit)

- The functional gas exchanging unit of the lung.
- The zone supplied by a first order respiratory bronchiole.
- Includes the respiratory bronchioles, alveolar ducts and alveolar sacs distal to a single terminal bronchiole, typically representing generations 15–23.
- A human lung contains between 30 000 and 50 000 acini, each with a diameter of about 3.5 mm and containing about 10 000 alveoli.
- This provides a total gas volume of 2500 ml and a surface area of between 50–80 square metres, through which gas exchange by diffusion can occur.
- The acini are connected by channels in the alveolar walls known as pores of Kohn, which act as portals for collateral ventilation and the transit of macrophages.

Respiratory epithelium

The **functions of respiratory epithelium** include:

Humidification of inspired air;

Chemical barrier and particle clearance;

Defence against infection.

Respiratory (bronchial) epithelium consists of the following cell types:

- Pseudostratified columnar ciliated epithelial cells, with 200–300 cilia per cell.
- Mucus-secreting (goblet) cells.
- Basal cells, which anchor the goblet and ciliated cells to the extracellular matrix.
- Mast cells, which secrete histamine, lysosomal enzymes, leukotrienes, platelet-activating factor, neutrophil and eosinophil chemotactic factors and serotonin.
- Non-ciliated bronchiolar epithelial (Clara) cells, which are specialised secretory cells in the terminal bronchioles. These cells synthesise, store, and secrete specialised lipids, proteins and glycoproteins.
- APUD (amine precursor uptake, decarboxylase) cells, which have a high content of amine and peptide hormones including serotonin, dopamine, noradrenaline and vasoactive intestinal peptide.
- Dense-core granulated cells (Kulschitzky cells)

Classification of alveolar cell types

Capillary endothelial cells with loose junctions.

Alveolar epithelial cells:

Type I: squamous lining cells, which comprise 90%–95% of the alveolar surface.

Type II: secretory cells: synthesise, secrete and store surfactant; cuboidal; microvilli; osmophilic inclusion bodies.

Alveolar macrophages, which are responsible for the phagocytosis of particles, viruses and bacteria.

Neutrophils.

Pulmonary defence mechanisms

These can be categorised as:

Mechanical

Filtration in the upper airways, especially the nose.

Humidification of the inspired air.

Epiglottic function.

A competent larynx allowing an effective cough reflex.

Ciliary action of respiratory epithelial cells, which allows upward clearance of mucus from the tracheo-bronchial tree – the muco-ciliary escalator. This characterises epithelial cells to the 17th generation of airways. There are over 200 cilia per cell.

Mucus blanket. Mucus is a mixture of water, electrolytes and macromolecules (lipids, mucins and enzymes) secreted by the goblet cells and mucosal glands.

Surfactant preventing alveolar atelectasis.

Glycoproteins (Fibronectin).

Immune defences

Immunoglobulins, especially IgA and IgG;

Complement factors, classical and alternative;

Cellular defence mechanisms (alveolar level): alveolar macrophages and T-lymphocytes; polymorphonuclear cells.

■ Diffusion

The **air–blood barrier** is about 2 μm thick and comprises:

The capillary endothelium;

The fused basement membranes of the endothelial and epithelial layers;
The epithelial type I and II pneumocytes.

The **pulmonary interstitium** separates the linings of the alveoli and of the capillaries. It comprises:

A fibrous scaffold of collagens and elastic fibres;
Extracellular matrix of vessel wall;
Fibroblasts, smooth muscle cells and macrophages;
Lymphatic vessels.

The rate-limiting steps for oxygen diffusion

These are:

The rate of passage of oxygen across the alveolo-capillary membrane;
The rate of combination of oxygen with haemoglobin in the red blood cells;
The driving pressure for diffusion, i.e. the differences in pressures between pO_2 in the alveolus and pO_2 in the red blood cell.

Diffusing capacity

This is measured using carbon monoxide as a tracer gas. The single breath-hold method involves the following steps:

- A single breath-hold for 10 seconds is followed by rapid inspiration from the residual volume to the total lung capacity of a gas mixture of 0.3%–0.4% carbon monoxide, helium, oxygen and nitrogen. This represents a vital capacity breath of gas from a reservoir bag.
- Slow even exhalation back to the residual volume follows. The first portion of the expired gas (750 ml) represents the anatomical and system dead space. The second portion (the last 75–100 ml) of the expired gas (the end-tidal gas) is collected and taken as representing alveolar gas.
- Carbon monoxide and helium concentrations are measured in alveolar gas.
- The carbon monoxide tension in pulmonary capillary blood is close to zero, owing to the long time required for the plasma to equilibrate with alveolar gas.
- The rate at which carbon monoxide leaves the alveoli depends on the rate of diffusion through the alveolar-capillary membrane.
- The diffusing capacity for carbon monoxide is equal to the volume of carbon monoxide transferred into the blood per minute per mm Hg of carbon monoxide partial pressure, i.e. the rate of uptake of carbon monoxide.

In the steady state method, the patient rebreathes the gas until equilibrium is reached.

8 Blood

Introduction

Blood is a suspension of cellular elements in an aqueous solution. Forty-five per cent of this volume comprises cellular elements (the haematocrit), the remainder being plasma. About 8% of the plasma volume consists of solutes, the remainder being water.

Plasma proteins

Most plasma proteins are synthesised in the liver. They are generally synthesised as pre-protein on membrane-bound polyribosomes and initially contain amino-terminal signal peptides. Almost all are glycoproteins. Many exhibit polymorphism. They are mainly anions. Each plasma protein has a characteristic half-life in the circulation.

Functions of plasma proteins

- Maintenance of colloid osmotic pressure, of about 25 mm Hg across capillary wall, and thereby control of extracellular fluid volume. This is mainly due to

Cellular composition of human blood

Red blood cells	4 500 000–5 000 000/cu mm
Platelets	150 000–400 000/cu mm
White blood cells	5000–10 000/cu mm
Neutrophils	63.5%
Lymphocytes	30.0%
Monocytes	4.0%
Eosinophils	2.0%
Basophils	0.5%

albumin. Human albumin is a single chain polypeptide of 584 amino acids, with 17 disulphide bonds. The plasma half-life is around 20 days.

- Carrier proteins for lipids, hormones, drugs and excretory products (transport functions). Albumin, in particular, binds a range of physiologically important ligands, including various hydrophobic molecules and metal ions.
- Defence reactions: immunoglobulins, complement system.
- Buffering of hydrogen ions. Plasma proteins provide about 15% of the total buffering capacity of the blood.
- Coagulation (haemostasis) and fibrinolysis.
- Specialised functions: protease inhibitors, haemoglobin binding, renin–angiotensin system, lipoprotein metabolism.

The plasma proteins can be considered to include five **interactive systems**:

Coagulation proteins
Fibrinolytic enzymes
The complement system
The kinins
Inhibitors to the preceding four systems

Electrophoresis

Electrophoretic separation of plasma proteins yields the following fractions:

Albumin	
Alpha 1-globulins	alpha 1-antitrypsin
	alpha 1-acid glycoprotein
Alpha 2-globulins	alpha 2-macroglobulin

Functions of transport proteins

Pre-albumin	Retinol, thyroxine (T4), triiodothyronine (T3)
Albumin	Inorganic plasma constituents (e.g. calcium)
	Free fatty acids
	Hormones
	Excretory products
	Drugs
Hormone-binding proteins	Corticosteroids: cortisol-binding globulin
	Sex hormones: sex-hormone-binding globulin
	Thyroid hormones: thyroxine-binding globulin
Metal-binding proteins	Copper (caeruloplasmin)
	Iron (transferrin)
Apolipoproteins	Lipids

Protease inhibitors of human plasma

Antithrombin III (ATIII) (heparin cofactor)
Heparin cofactor II
Alpha 2-macroglobulin
Alpha 1-antitrypsin
Alpha 2-antiplasmin (alpha 2-plasmin inhibitor)
C1-inactivator (C1-esterase inhibitor)
Extrinsic pathway (tissue factor pathway) inhibitor
Activated protein C inhibitor

Beta globulins	haptoglobin
	caeruloplasmin
	transferrin
	low density lipoprotein
	C3 fraction of complement
Gamma globulins	immunoglobulins

Acute phase reactants

The levels of certain plasma proteins increase during acute inflammatory states or secondary to certain types of tissue damage. Acute phase reactants are serum proteins that are produced by hepatocytes in the liver in response to pro-inflammatory cytokines (tumour necrosis factor-alpha, interleukin-1 and interleukin-6). Their synthesis constitutes a normal response to tissue inflammation or injury. These reactants help in minimising local tissue damage and participate in tissue repair, as well as aiding microbial killing. They include:

C-reactive protein: binds bacterial, fungal and parasitic polysaccharides and peptidopolysaccharides; activates complement; acts as opsonin to facilitate phagocytosis
Anti-protease inhibitors: alpha 1-antitrypsin
Caeruloplasmin
Alpha 1-acid glycoprotein
Fibrinogen
Haptoglobin
Serum amyloid A
Complement proteins
Metallothionein.

The acute phase response allows the detection, diagnosis and therapeutic monitoring of diseases that involve tissue damage and inflammation.

Causes of an acute phase response

These include:

- Bacterial infections
- Rheumatic diseases: rheumatoid arthritis; seronegative spondarthritis
- Vasculitis
- Crohn's disease
- Trauma including burns and surgery
- Malignancy

Cytokines

Cytokines are a group of soluble, low molecular weight glycoproteins, which are involved in cell proliferation, immunity and inflammation. They regulate both the amplitude and duration of the systemic inflammatory response, and may be either pro-inflammatory or anti-inflammatory. They may act on cells in a paracrine and autocrine manner. The systemic inflammatory response syndrome appears to result from excessive, inappropriate and/or prolonged release of cytokines into the systemic circulation. They are synthesised *de novo* and released in response to tissue damage.

Classification of cytokines

Interleukins: IL-1 to IL-13;
Interferons: alpha-interferon, beta-interferon, gamma-interferon;
Colony-stimulating factors: macrophage-colony stimulating factor (M-CSF), granulocyte-macrophage-colony stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CTF).

Plasma lipoproteins

These include:

- Chylomicrons: dietary triglyceride transport.
- Very low density lipoproteins (VLDL): endogenous triglyceride transport to adipose tissue.
- Intermediate density lipoproteins (VLDL remnants).
- Low density lipoproteins (LDL): contain a high concentration of cholesterol and cholesterol esters and are involved in the transport of dietary and endogenous cholesterol. Cholesterol is delivered from the liver to peripheral tissues, especially adipose tissue and the adrenal glands, and also returned to the liver.
- High density lipoproteins (HDL): HDL2 and HDL3: involved in the return of cholesterol from peripheral tissues to the liver (reverse transport).

Enzymes involved in lipid transport

Lecithin cholesterol acyltransferase (LCAT)
Lipoprotein lipase
Hepatic lipase
Mobilising lipase

Lipoproteins consist of a core of hydrophobic non-polar triacylglycerol, surrounded by a shell of polar lipids (phospholipids and cholesterol), in turn surrounded by a shell of protein, which together constitute a hydrophilic complex. Apolipoproteins, the protein components of the lipoproteins, are named ApoA, ApoB, ApoC and ApoE. The density of lipoproteins is inversely proportional to their lipid/protein ratio.

The low density lipoprotein supergene family of receptors

These possess four major structural characteristics:

Cysteine-rich C-type repeats;
Epidermal growth factor precursor-like repeats;
A cytoplasmic domain;
A transmembrane domain.

The low density lipoprotein receptor is an 839 amino acid transmembrane protein. It includes an N-terminal extracellular domain which binds apoB-100, and a C-terminal cytosolic domain that binds adapter proteins involved in modulation of clathrin coat formation (receptor-mediated endocytosis).

Normal lipoprotein metabolism

This involves three major pathways mediating:

The transport of exogenous dietary triglyceride and cholesterol;
The transport of endogenous triglyceride and cholesterol synthesised in the liver;
Reverse cholesterol transport, i.e. transfer back from peripheral tissues to the liver, in which HDL plays a major role.

Haemoglobin

Structure of haemoglobin

Haemoglobin consists of four polypeptide chains, two alpha chains of 141 amino acid residues each and two beta chains of 146 amino acid residues each. Each

chain harbours one haem, a cyclic tetrapyrrole. A single polypeptide chain combined with a single haem is called a subunit of haemoglobin or monomer of the molecule. In the complete molecule the four subunits are closely joined by hydrogen bonding to form a tetramer. Functions of haem proteins include oxygen binding, oxygen transport and electron transport.

Each polypeptide chain is divided into helical and non-helical areas. The helical areas are designated A to H. Amino acids can be designated by number or according to helical region. Each haem consists of protoporphyrin IX, with four nitrogen atoms co-ordinated to a ferrous ion, Fe^{2+}. The Fe^{2+} is also co-ordinated to a nitrogen atom in a histidine residue of the globin part of the molecule. Oxygen binding causes alterations in the plane of the Fe^{2+}, triggering a sequence of intermolecular rearrangements that are transmitted to the other subunits.

Haemoglobin is structurally adapted to bind strongly to oxygen in the lungs and to release it in oxygen depleted tissues. It can also transport some carbon dioxide back to the lungs for release.

Determinants of oxygen-carrying capacity of blood

Partial pressure (kPa) of oxygen: pO_2.

Haemoglobin concentration. Each gram of haemoglobin can combine with 1.34 ml of oxygen. One millimole of haemoglobin (64.5 grams) can carry up to 4 milllimole of oxygen if all binding sites are occupied, i.e. if haemoglobin is fully saturated.

Oxygen saturation of haemoglobin present: p50.

Tissue oxygen delivery depends on:

- Blood oxygen content, which is determined by:
  - PO_2
  - Haemoglobin level
  - Haemoglobin function
- Blood flow, which is determined by:
  - Cardiac output
  - Peripheral perfusion

Oxyhaemoglobin dissociation curve

The curve consists of an X axis representing the percentage saturation of haemoglobin and a Y axis representing pO_2. The sigmoid shape of the curve comprises:

- The **loading region**: oxygen-free molecules (deoxyhaemoglobin) are reluctant to take up the first oxygen molecule but their appetite for oxygen grows with the eating (Perutz).

Blood cells

Stem cells

Stem cells are the precursor of all blood cells as well as of further stem cells. They comprise about 1 in 10 000 of cells in the bone marrow. They possess the properties of lacking specialised function yet being able to transform to specialised cells, self-renewal over long periods of time and pluripotentiality (the ability to develop into many different cell types).

Pluripotential haematopoietic stem cells maintain haematopoiesis by clonal proliferation. Stem cells express CD34, a surface protein.

Red blood cells

Features

Each red cell is a non-nucleated biconcave disc 7.5 × 2 μm. This shape maximises the surface area/volume ratio, allowing more effective gas exchange. The discs are also deformable, allowing passage through small blood vessels such as capillaries.

There are a total of about 3×10^{13} cells in the body, containing 1 kg of haemoglobin. The average lifespan of a red blood cell is 120 days. Normal development takes 7–10 days. It comprises 90% haemoglobin by dry weight. Red cells are derived from reticulocytes, which are also non-nucleated, but possess ribosomes for globin synthesis, and mitochondria to allow oxidative metabolism and haem synthesis. They mature in 24–48 hours to red cells.

The red cell uses anaerobic metabolism as an energy source. It does not possess any mitochondria or ribosomes. Glucose is metabolised anaerobically primarily by glycolysis (Embden–Meyerhof pathway) and secondarily by the pentose phosphate pathway (hexose monophosphate shunt). The glycolytic pathway converts 90%–95% of the glucose metabolised in red cells to lactate. This generates one mole of ATP per mole of glucose metabolised. Five per cent to ten per cent of glucose is metabolised by the pentose phosphate pathway, generating one mole of nicotinamide adenine dinucleotide phosphate dehydrogenase (NADPH) for each mole of glucose metabolised. This is a cofactor for glutathione reductase, which maintains glutathione in the reduced state to protect against the toxic effects of free oxygen radicals, which are generated by intracellular haem oxidation.

The functions of red cells consist of oxygen transport, carbon dioxide transport and regulation of extracellular fluid pH.

ATP is used by the red cell for:
- The provision of energy for Na^+/K^+ -ATPase (sodium pump) and Ca^{2+}-ATPase (calcium pump);
- Protein phosphorylation;
- The maintenance of cell shape;
- Reduction of the oxygen affinity of haemoglobin.

Red cell membrane

The **red cell membrane** is composed of:

Lipids:
- Phospholipids: phosphatidylcholine; phosphatidylethanolamine; sphingomyelin; phosphatidylserine)
- Cholesterol

Proteins:
- Integral membrane proteins:
  - Band 3 or anion exchange protein
  - Glucose transporter GLUT 1
  - Glycophorins, which have a high sialic acid content
- Cytoskeletal proteins (which form a dense two-dimensional fibrous network):
  - Spectrin protein family: alpha and beta spectrins; spectrin deficiency is a hallmark of red cells in hereditary spherocytosis
  - Ankyrin
  - Short filaments of F-actin
  - Proteins 4.1, 4.2 and 4.9
  - p55
  - Adducins

White blood cells

White blood cells can be classified as:

Granulocytes:
- Neutrophils: 12–15 μm in diameter; nucleus with clumped chromatin and 2–5 lobes; drumstick in normal females; acidophilic cytoplasm. A right shift refers to an increase in lobe count.
- Eosinophils: 12–17 μm in diameter; nucleus with 2–3 lobes; spherical granules; weakly basophilic cytoplasm. They are phagocytic cells with a special

affinity for antigen–antibody complexes. The granules contain four cationic proteins: eosinophilic cationic protein, major basic protein, eosinophil derived neurotoxin and eosinophil peroxidase.

Basophils: 10–14 μm in diameter; purple black granules.

Mononuclear cells:

Lymphocytes: small: 10–12 μm in diameter; large: 12–16 μm in diameter.

Monocytes.

Functions of white blood cells

These depend on the cell type:

- Neutrophils phagocytose bacteria, fungi, protozoa, viruses, foreign cells, tumour cells and toxins. Chemotaxis occurs in response to activated complement proteins, cytokines and microbial products.
- Eosinophils phagocytose antigen–antibody complexes and larval forms of helminthic parasites. They inactivate mediators of anaphylaxis.
- Basophils possess IgE receptors and release mediators from granules in inflammatory and allergic reactions.
- Lymphocytes.

  B lymphocytes synthesise antibodies (immunoglobulins), contributing to humoral immunity. In response to a specific antigen they give rise to a monoclonal proliferation of plasma cells, which produce specific antibodies. T lymphocytes, which comprise 65%–80% of circulating lymphocytes, are responsible for cell-mediated immunity. They mediate the cell-mediated response to intracellular parasites, viruses, bacteria and fungi; delayed hypersensitivity; graft-versus-host reactions; and organ transplant rejection. They include subpopulations, which can be distinguished by cell surface markers.

  Helper (CD4 marker): enhance antibody production by B cells and stimulate the activity of other T cells.

  Cytotoxic (CD8 marker): kill virus infected and tumour cells, based on previous experience.

  Suppressor: block helper T cells.
- Monocytes are phagocytic and become macrophages in the tissues.

Macrophages occur in the following locations:

Connective tissues: histiocytes

Liver: Kupffer cells

Lungs: alveolar macrophages

Lymph nodes: free and fixed macrophages

Spleen: free and fixed macrophages

Bone marrow: fixed macrophages
Skin: Langerhans cells; histiocytes
Serous fluids: pleural and peritoneal macrophages

Blood groups

Blood group antigens are polymorphic, genetically inherited, structural characteristics of the outer surface of the red cell membrane.

The red cell phenotype depends on two classes of antigens:

- Carbohydrate moieties attached to membrane proteins or lipids (glycoproteins or glycolipids): e.g., ABO, Lewis and P systems. The A and B antigens are defined by a terminal sugar attached to a carbohydrate chain in membrane glycolipids and glycoproteins. A, B and H antigens may also be found in secretions such as saliva in secretors.
- Membrane proteins, e.g. Rhesus(Rh), Duffy, Kell, Kidd, MNSs systems. The Rh blood group system comprises 45 antigens, of which 5 are routinely identified, D, C, c, E and e.

The clinical importance of antigens depends on the degree of antigenicity, the frequency of occurrence of the antigen in the population and the activity of antibodies to the antigen at 37° C.

Blood transfusion principles

The recipient plasma must not contain antibodies corresponding to donor A and/or B antigens.

Rhesus D positive individuals may receive either RhD positive or RhD negative red cells.

Rhesus D negative individuals should only receive RhD negative red cells.

Table 8.1 ABO blood groups

Blood type	Genotype	Antigens (agglutinogens)	Antibodies (agglutinins)
O	OO	none	anti-A, anti-B
A	OA, AA	A	anti-B
B	OB, BB	B	anti-A
AB	AB	A, B	none

Blood components used for transfusion

Whole blood
Packed red blood cells
  Leukocyte added
  Adenine-saline added
Fresh frozen plasma
Cryoprecipitate: the portion of plasma remaining insoluble after thawing
Cryosupernatant
Platelet concentrates
Granulocytes
Platelet-rich plasma
Platelet-poor plasma

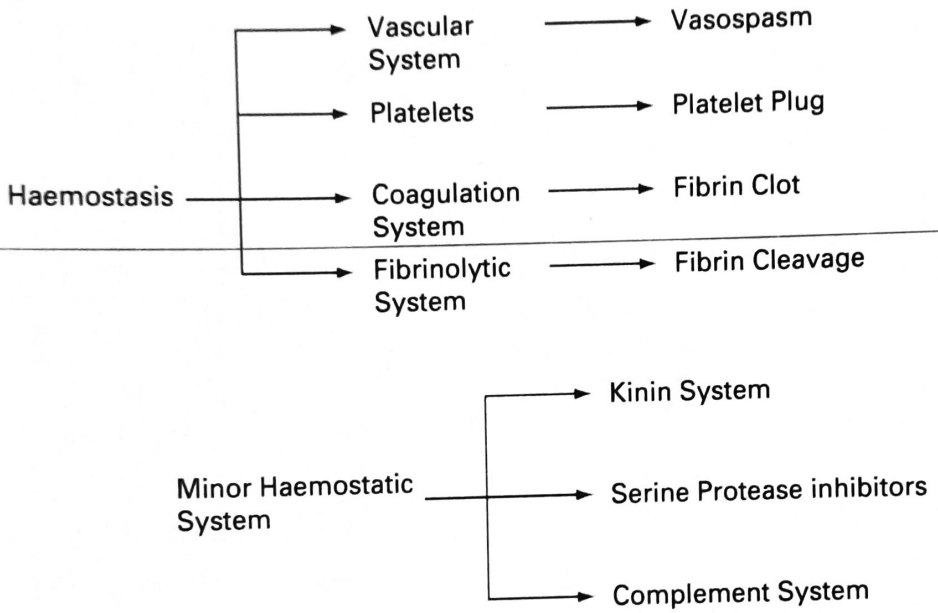

Figure 8.2 Components of haemostasis.

Haemostasis

Normal haemostasis is a balance between the simultaneous, opposing processes of clot formation and fibrinolysis. For a clot to form normally, there must be functioning vascular endothelium, platelets with adequate number and function, and sufficient plasma coagulation factors. Primary haemostasis refers to the formation of the platelet plug, a process that occurs within 1–3 minutes of injury. This involves platelet activation, platelet–vessel wall and platelet–platelet interaction. Secondary haemostasis refers to the action of the coagulation cascade to form clot. Normally haemostasis involves a sequence of vasoconstriction, platelet aggregation (adhesion, activation and aggregation) and blood coagulation.