

# The Cardiovascular System at a Glance

## Fourth Edition

### Key Points Revision

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#### Chapter 1 Overview of the cardiovascular system

- The cardiovascular system comprises the heart, the blood vessels and the blood.
- The key functions of the cardiovascular system are: distribution of O<sub>2</sub>, water, electrolytes and nutrients to all body tissues; transportation of CO<sub>2</sub> and metabolic waste products from the tissues to the lungs and kidneys; and thermoregulation.
- The systemic and pulmonary circulations are perfused in series, with the left side of the heart pumping oxygenated blood it receives from the lungs into the systemic circulation and the right side of the heart pumping the de-oxygenated blood it receives from the body into the lungs.
- Perfusion of the systemic circulation requires a much higher pressure (mean arterial pressure ~90 mmHg) than does perfusion of the pulmonary circulation (pulmonary arterial pressure ~15 mmHg).
- In both circulations, blood leaving the heart first enters the arteries, from which it passes successively through arterioles, capillaries, venules and veins before re-entering the heart via the venae cavae.

#### Chapter 2 Gross anatomy and histology of the heart

- The cardiac valves operate according to the pressure difference across them (i.e. they are passive).
- The AV valves are prevented from everting into the atria by the chordae tendineae.
- The annulus fibrosus provides a skeleton for attachment of muscle and valves, and prevents electrical conduction between atria and ventricles except at the atrioventricular node.
- Cardiac muscle cells are striated and roughly rectangular, and are linked physically at intercalated discs by desmosomes, and electrically by gap junctions (connexons).
- The membrane of cardiac muscle cells (sarcolemma) has tubular invaginations into the cell called the transverse (T) tubular system; the walls of T tubules are a continuation of the sarcolemma.
- In contrast to skeletal muscle, the T tubules of cardiac muscle cells do not physically touch the sarcoplasmic reticulum.

#### Chapter 3 Vascular anatomy

- The major arteries supplying blood to the head, arms and heart arise from the aortic arch and the major arteries supplying the visceral organs branch from the descending aorta.
- The aorta bifurcates at its inferior end into the left and right iliac arteries, which supply blood to the legs.
- The aorta and its major branches, termed elastic arteries, branch to give rise to thick-walled muscular arteries, which in turn give rise to the resistance vessels (small arteries and arterioles) which provide the bulk of the resistance of the system to the flow of blood.

- The arterioles, capillaries and venules comprise the microcirculation, which functions to transfer gases, water, nutrients and other substances between the blood and the body tissues.
- The veins of the limbs, particularly the legs, contained paired semilunar valves which ensure that the blood cannot move backwards.
- Although the various organs and regions of the body are perfused in parallel via the arteries of the systemic circulation, the liver receives most of its blood from the portal vein, which carries venous blood that has passed through capillary beds of the digestive system; this is termed a portal circulation.

#### Chapter 4 Vascular histology and smooth muscle cell ultrastructure

- Arteries and veins share a common three-layer structure, consisting of an inner layer (tunica intima) containing endothelial cells; a middle layer (tunica media) containing vascular smooth cells embedded in a connective tissue matrix; and an outer layer (tunica adventitia) containing collagen, nerves and fibroblasts.
- Capillaries and postcapillary venules lack smooth muscle and nerves, and are tubes formed of overlapping endothelial cells supported by a fibrous layer of proteins, termed the basal lamina.
- There are three types of capillaries: in ascending order of permeability these are termed continuous, fenestrated and sinusoidal.
- Vascular smooth muscle cells are 'smooth' because the actin and myosin filaments they contain are not aligned into sarcomeres but instead run roughly parallel to the long axis of the cell.
- The cytoplasm of vascular smooth cells contains the sarcoplasmic reticulum, a network of tubes and flattened sacs which stores – and can release and re-accumulate – a high concentration of  $\text{Ca}^{2+}$ .

#### Chapter 5 Constituents of blood

- Blood accounts for ~8% body weight, depending on body fat.
- Plasma is blood without cells; serum is plasma without clotting proteins (e.g. plasminogen).
- The ionic constituents of plasma are vital for cell function and are tightly controlled; normal values of  $[\text{K}^+]$  and  $[\text{Na}^+]$  are ~4mmol/L and ~140mmol/L respectively.
- Plasma osmolality is mostly due to dissolved ions and small diffusible molecules (glucose and urea) and is normally ~290 mosm/kg  $\text{H}_2\text{O}$ ; the major determinants of plasma osmolality are sodium and chloride ions.
- Osmolality reflects crystalloid and oncotic osmotic pressures. Crystalloid osmotic pressure is due to dissolved ions and small diffusible molecules; there is no difference between the crystalloid osmotic pressure of plasma and interstitial fluid because the capillaries are permeable to both water and these small molecules.
- Oncotic or colloidal osmotic pressure is due to dissolved proteins, and is much smaller than the crystalloid osmotic pressure. Oncotic pressure is important for capillary fluid filtration because it differs between plasma and interstitial fluid, as capillary walls have a low permeability to protein.

- Red cells are the most numerous cell type in blood, accounting for 45% of blood volume (haematocrit, packed cell volume). Packed cell volume is less in females because of blood loss in menstruation.

### Chapter 6 Erythropoiesis, haemoglobin and anaemia

- Erythropoiesis occurs in bone marrow of adults, and spleen and liver of the fetus and adults with bone marrow damage.
- Erythropoiesis is regulated by erythropoietin (EPO) released mainly from kidney in response to hypoxia. EPO stimulates transformation of stem cells into colony-forming unit erythroid cells (CFU-E) and proerythroblasts. Corticosteroids and growth hormones may also stimulate erythropoiesis.
- Reticulocytes, formed when late erythroblasts lose their nuclei, comprise ~1–2% of total blood red cell numbers. As they mature into erythrocytes they lose residual reticulum and develop a biconcave shape.
- Erythrocytes are destroyed after ~120 days by macrophages in liver and spleen. Iron is conserved and recycled via transferrin, haem converted to bilirubin and excreted.
- Haemoglobin is formed of four subunits, each containing a globin chain and a haem group with one ferrous ( $\text{Fe}^{2+}$ ) atom, and binds four  $\text{O}_2$ . Adult Hb has two  $\alpha$  and two  $\beta$  chains, fetal Hb two  $\alpha$  and two  $\gamma$  chains.
- Anaemia is low blood haemoglobin, as a result of reduced red cell count (e.g. haemorrhage) or less haemoglobin per cell content, most commonly due to iron deficiency.

### Chapter 7 Haemostasis

- Primary haemostasis initially involves vasoconstriction in response to vascular damage which limits blood loss, and then platelet adhesion and activation due to exposure of and binding to subendothelial matrix.
- Platelet activation stimulates production of thromboxane  $\text{A}_2$  ( $\text{TXA}_2$ ) by cyclooxygenase (COX), and consequent release of dense granules containing 5-hydroxytryptamine (5-HT) and adenosine diphosphate (ADP). Aggregation of platelets is stimulated by ADP via P2Y receptors, and involves activation of glycoprotein IIb/IIIa receptors which bind fibrinogen, which sticks the platelets together.  $\text{TXA}_2$  and 5-HT also contribute to the vasoconstriction.
- Clotting is initiated by exposure of tissue factor bearing cells to plasma clotting factors, leading to activation of factor Xa and formation of small amounts of thrombin. This activates the amplification and propagation phases by forming tenase and prothrombinase on the surface of platelets, leading to a massive thrombin burst that cleaves fibrinogen to fibrin.
- Fibrin monomers spontaneously polymerise and then are cross-linked by factor XIIIa, which is activated by thrombin.
- Fibrin is broken down by plasmin, which is activated by tissue plasminogen activator (tPA) when bound to fibrin.
- Binding of thrombin to thrombomodulin prevents it cleaving fibrinogen, but causes it to activate protein C (APC), which inhibits plasminogen activator inhibitor (PAI) and so promotes fibrinolysis. APC with protein S inhibits clotting by inhibiting factors Va and VIIIa, involved in the propagation phase of clotting.

## Chapter 8 Thrombosis and anticoagulants

- Virchow's triad of endothelial damage (primarily arterial), blood stasis (primarily venous) and hypercoagulability predispose to thrombosis. A common cause of arterial thrombosis is atherosclerotic plaque rupture in acute coronary syndromes. Embolism is the main danger of venous thromboses such as deep vein thrombosis (DVT).
- Arterial clots are primarily platelet-initiated (white clots) due to endothelial damage, and are best treated with antiplatelet drugs. Venous clots are primarily initiated by accumulation of clotting factors (red clots), and are best treated with anticoagulants.
- Aspirin irreversibly inhibits cyclooxygenase (COX) and therefore production of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) and platelet activation. Although it also inhibits production of prostacyclin by endothelial cells, unlike platelets these contain a nucleus and can generate more COX protein, so the prostacyclin : TXA<sub>2</sub> ratio is increased.
- Antiplatelet drugs suppress platelet activation (aspirin, P2Y receptor antagonists) and aggregation (GPIIb/IIIa receptor antagonists).
- Heparin is a highly effective anticoagulant but can only be given by injection. Unfractionated heparin activates antithrombin, which inactivates thrombin and factors IXa and Xa. Low molecular weight heparin and fondaparinux act similarly, but are only effective against factors IXa and Xa.
- Warfarin, the most common oral anticoagulant, inhibits vitamin K reductase and prevents proper formation of factors VII, IX, X and prothrombin in the liver. It is therefore only effective *in vivo*, and slow in effect. It has many drug interactions and must be titrated over weeks to give normally a prothrombin time international normalized ratio (INR) of ~3. Novel direct thrombin and factor X antagonists, which can be given orally, may eventually replace warfarin.

## Chapter 9 Blood groups and transfusions

- Transfusion of incompatible blood groups can cause agglutination of red cells and haemolysis when plasma antibodies react with antigens on the red cell membrane.
- The ABO system depends on the presence of A and B antigens on red cells, and  $\alpha$  and  $\beta$  antibodies in the plasma. Group A blood contains antigen A and antibody  $\beta$ , group B contains antigen B and antibody  $\alpha$ , group O contains neither antigen but both antibodies, and group AB both antigens but neither antibody.
- People of group O are therefore universal donors, and people of group AB universal recipients.
- The Rh (Rhesus) blood group is related to D antigen on red cells, present in 85% of the population (Rh+).
- Antibody to D antigen can be raised in Rh- individuals by transfusion of Rh+ blood or when red cells from a Rh+ fetus enter the circulation of a Rh- mother. This can cause haemolytic disease of the newborn in subsequent pregnancies as maternal antibodies cross the placenta.
- Transfusion of an inappropriate blood type causes a haemolytic transfusion reaction; breakdown of the released haemoglobin can cause accumulation of bilirubin (haemolytic jaundice) and renal failure.

## Chapter 10 Membrane potential, ion channels and pumps

- The equilibrium potential of an ion across a semipermeable membrane is the potential at which the electrical forces on that ion in one direction exactly balance the forces due to the concentration gradient in the other direction. The electrochemical gradient is the sum of the

electrical and concentration forces, and by definition is zero at the equilibrium potential, which is calculated from the Nernst equation.

- The cell membrane is a semipermeable membrane that at rest is most permeable to  $K^+$ , so the resting membrane potential is primarily dependent on the ratio of extracellular to intracellular [ $K^+$ ], and in cardiac muscle is close to the  $K^+$  equilibrium potential ( $\sim -90$  mV).
- During an action potential  $Na^+$  channels open so that  $Na^+$  permeability becomes much greater than that for  $K^+$ , so the membrane potential moves towards the equilibrium potential for  $Na^+$ . There are no significant changes to the intracellular concentrations of  $K^+$  or  $Na^+$ .
- Ions move through ion channels by passive diffusion down their electrochemical gradient. Ions are actively transported by ion pumps. Primary active transport uses ATP as an energy source (e.g. the  $Na^+$  pump), secondary active transport uses the electrochemical gradient of another ion (often  $Na^+$ ) as the energy source (e.g.  $Na^+-Ca^{2+}$  exchanger).
- Ion channels are either open or closed; transition between these states is called gating. Voltage-gated channels are regulated by membrane potential (e.g. fast inward  $Na^+$  channel). Receptor-gated channels are regulated by second messengers from activated receptors.
- Ions carry charge, so movement of ions through a channel causes an ionic current. An inward current means movement of positive charge into the cell (or negative charge out), and tends to depolarize the cell. An outward current means movement of positive charge out of the cell, and tends to repolarize or hyperpolarize the cell (make it more negative).

## Chapter 11 Electrophysiology of cardiac muscle and the origin of the heart beat

- In all regions of the heart except the sinoatrial node (SAN) and atrioventricular node (AVN), the fast upstroke of the action potential arises when the membrane is depolarized to threshold ( $\sim -65$  mV), causing activation of voltage-gated  $Na^+$  channels and thus a fast inward (depolarizing)  $Na^+$  current.
- The larger the  $Na^+$  current the faster the upstroke and speed of conduction through and between cells. The large cells of the cardiac conduction system have a large surface area therefore a large current, and thus a very rapid conduction speed.
- The inward  $Na^+$  current terminates because the  $Na^+$  channels start to inactivate when the membrane potential reaches  $\sim 0$  mV. They can only be reactivated when the cell repolarizes again.
- The action potential of cardiac muscle is  $\sim 300$  ms due to the plateau region, caused by  $Ca^{2+}$  entry via L-type voltage-activated  $Ca^{2+}$  channels.
- Repolarization occurs when the L-type channels close and delayed rectifier  $K^+$  channels open, causing an outward repolarizing current. These channels close soon after resting membrane potential is reached.
- Cells in the SAN and AVN have a slow action potential upstroke caused by opening of voltage-gated L-type  $Ca^{2+}$  channels, not  $Na^+$  channels. Repolarization is initiated by activation of delayed rectifier  $K^+$  channels.
- The resting membrane potential of SAN and AVN slowly depolarizes (pacemaker potential) after repolarization because the delayed rectifier  $K^+$  outward current slowly declines, uncovering an increased inward depolarizing current  $I_f$  (mostly  $Na^+$ ), and a steady background inward current  $I_b$ . Another action potential is initiated when the potential reaches threshold for L-type channels.

- Heart rate is regulated by altering the size of  $I_f$  and speeding up or slowing down the rate of depolarization of the pacemaker potential, so it reaches threshold sooner or later. The SAN normally has the fastest rate, so determines heart rate.

### Chapter 12 Cardiac muscle excitation–contraction coupling

- Contractility refers to the ability of cardiac muscle to generate force independent of changes in length. Positive inotropic agents increase contractility, negative inotropes reduce it.
- Cardiac muscle contraction is initiated when cells are depolarized sufficiently through gap junctions for an action potential (AP) to be elicited. During the AP plateau,  $Ca^{2+}$  enters the cell via voltage-gated L-type  $Ca^{2+}$  channels. However, this only accounts for 20–30% of the rise in intracellular calcium; the remainder comes from  $Ca^{2+}$ -induced  $Ca^{2+}$  release (CICR).
- $Ca^{2+}$  entering via L-type channels in the walls of T tubules causes an increase in  $Ca^{2+}$  concentration in the narrow space between the sarcoplasmic reticulum (SR) and T tubule. This activates  $Ca^{2+}$  release channels in the SR through which stored  $Ca^{2+}$  enters the cytosol (CICR).
- On termination of the AP relaxation occurs as  $Ca^{2+}$  is rapidly sequestered back into the SR by the sarcoendoplasmic reticulum calcium ATPase (SERCA).
- $Ca^{2+}$  that entered the cell is more slowly removed by the membrane  $Na^+Ca^{2+}$  exchanger (NCX), driven by the  $Na^+$  electrochemical gradient.
- Partial inhibition of the  $Na^+$  pump (e.g. with digoxin) reduces the  $Na^+$  electrochemical gradient, thus impeding NCX so more  $Ca^{2+}$  remains in the cell to support the next beat. Similarly, an increased heart rate reduces the time during which  $Ca^{2+}$  can be removed from the cell by the NCX. Both therefore have a positive inotropic effect, and increase contractility.
- Positive inotropes such as  $\beta_1$ -adrenergic agonists (e.g. noradrenaline) and phosphodiesterase inhibitors (e.g. milrinone) increase the second messenger cAMP, which promotes enhanced  $Ca^{2+}$  entry via L-type channels. This increases the elevation of intracellular  $Ca^{2+}$  during systole and therefore force development.

### Chapter 13 Electrical conduction system in the heart

- Electrical conduction between cardiac cells is via gap junctions (formed of connexons) within intercalated discs. Rate of conduction is dependent on the size of depolarizing current (and thus on cell size) and resistance of the gap junctions.
- The heart beat is initiated in the sinoatrial node (SAN), and the wave of depolarization subsequently sweeps across the atria; it can only cross the annulus fibrosus which separates atria from ventricles at the atrioventricular node (AVN).
- Conduction through the AVN is very slow, providing a delay between atrial and ventricular systole. This corresponds to the PR interval of the ECG.
- The impulse is carried from the AVN via the bundle of His, and thence the left and right bundle branches either side of the septum which lead to Purkinje fibres that spread out over the endocardium. Conduction is rapid through these specialized, large cardiac muscle cells, ensuring that that systole is initiated at the same time throughout the ventricles.
- Finally, the wave of depolarization spreads more slowly from endocardium to epicardium through gap junctions between cardiac myocytes.
- First-degree heart block: delayed conduction through the AVN, with prolonged PR interval.  
Second-degree heart block: only a proportion of impulses are conducted through the AVN (e.g. 2 : 1 block), or the PR interval progressively lengthens until a beat is missed. Third-degree heart

block: no transmission through the AVN, P waves are independent of the QRS which have a much slower rate. Bundle branch block: no transmission through a bundle branch; broad misshapen QRS.

## Chapter 14 The electrocardiogram

- The ECG, surface recording of cardiac electrical activity, is a vector quantity (i.e. both amplitude and direction). It reflects currents between resting and depolarized cells, and so is measurable only when the wave of depolarization or repolarization is sweeping through the heart.
- The largest deflection on any ECG lead is where the wave of depolarization is directly towards or away from the sensing (positive) electrode.
- The limb leads measure voltages between right arm (RA), left arm (LA) and left leg (LL), corresponding to the corners of an equilateral triangle centred on the heart (Einthoven's triangle). The classic bipolar leads measure the voltage between: lead I LA–RA, lead II RA–LL, lead III RA–LL.
- The three bipolar and three augmented limb leads give a view of the electrical activity of the heart every 30° (hexaxial reference system). A standard clinical 12-lead ECG also includes the six chest leads.
- The P wave reflects atrial depolarization, QRS ventricular depolarization, and T wave ventricular repolarization. Atrial repolarization is too small and diffuse to be detected. The cardiac conduction system is too small to cause a measurable voltage.
- Cardiac axis: direction of maximum ECG amplitude calculated from relative amplitudes of QRS deflections in the limb leads. Reflects the direction of maximum current and therefore muscle mass. Cardiac axis deviation may be due to left or right ventricular hypertrophy.
- The P-R interval reflects delay in the AVN, the Q-T interval the duration of ventricular activation; as the latter is dependent on heart rate, it is normally corrected by the Bazett formula.
- A wide and misshapen QRS may reflect bundle branch block or ventricular origin of the heart beat. S-T segment elevation is normally transient and indicative of recent MI. T wave inversion may reflect myocardial infarction and delayed conduction.

## Chapter 15 Vascular smooth muscle excitation–contraction coupling

- Vascular smooth muscle (VSM) contraction, like that of other types of muscle, is controlled by the intracellular  $\text{Ca}^{2+}$  concentration  $[\text{Ca}^{2+}]_i$  – an elevation of  $[\text{Ca}^{2+}]_i$  from its basal level of  $\sim 100$  nM causes contraction.
- As  $[\text{Ca}^{2+}]_i$  rises,  $\text{Ca}^{2+}$  binds to the cytoplasmic regulatory protein calmodulin, causing it to activate the enzyme myosin light chain kinase which phosphorylates myosin, allowing it to initiate the process of actin–myosin crossbridge cycling which causes contraction.
- Physiologically important vasoconstrictors such as noradrenaline and angiotensin II constrict VSM cells mainly by activating  $G_q$ , causing the production of the second messengers inositol 1,4,5 triphosphate and diacylglycerol which act through multiple pathways to raise  $[\text{Ca}^{2+}]_i$ .
- As well as raising  $[\text{Ca}^{2+}]_i$ , vasoconstrictors also promote contraction by causing  $\text{Ca}^{2+}$  sensitization, a process that is unique to smooth muscle and is due to inhibition of myosin phosphatase caused mainly by rho kinase.
- Smooth muscle relaxation is generally caused by stimuli that raise the intracellular concentrations of cyclic GMP or cyclic AMP: these are second messengers that act through their cognate protein kinases to reduce  $[\text{Ca}^{2+}]_i$  via largely common mechanisms.

## Chapter 16 Cardiac cycle

- Stroke volume: volume of blood ejected per beat; cardiac output: volume per minute. The ejection fraction is stroke volume as a proportion of end diastolic volume; normally ~60%, it is always reduced in systolic heart failure due to an increase in end diastolic volume.
- Atrial systole completes the last ~15–20% of ventricular filling, and is associated with the A wave of atrial and venous pressures.
- At the start of ventricular systole the rise in ventricular pressure causes the atrioventricular (AV) valves to shut, producing the first heart sound ( $S_1$ ). This is followed by a short period of isovolumetric contraction before the ventricular pressure rises sufficiently to open the semilunar valve. The rise in pressure causes the AV valves to bulge into the atria, causing the C wave of atrial and venous pressures. Opening of the semilunar valve initiates rapid ejection, followed by reduced ejection.
- When ventricular activation terminates, ventricular pressure falls below arterial pressure causing the semilunar valve to shut, producing the second heart sound ( $S_2$ ). This is followed by a short period of isovolumetric relaxation before the ventricular pressure falls below the atrial pressure, when the AV valve opens and rapid ventricular filling begins. The v wave of atrial and venous pressures reflects the build-up of venous pressure immediately before the AV valve opens.
- The ventricular pressure–volume loop is the plot of pressure versus volume; its area represents work done in a single beat. It is affected by ventricular contractility and compliance, and factors that alter refilling or ejection (e.g. CVP, afterload).
- The third heart sound ( $S_3$ ) is associated with rapid ventricular filling, and is commonly heard in the young and during exercise, or when the filling pressure is high (e.g. heart failure).  $S_4$  is only heard during atrial systole when filling pressure is high. Cardiac murmurs are caused by turbulence in the blood, due to either valve stenosis (narrowing) or regurgitation (leaks).

## Chapter 17 Control of cardiac output

- Cardiac output (CO) is influenced by filling pressure (preload), cardiac muscle force and afterload, which are modulated by the autonomic nervous system (ANS). The heart and vasculature are in series and interdependent; except for transient differences venous return *must* equal CO.
- Ventricular filling pressure (end-diastolic pressure, EDP) determines end-diastolic volume (EDV), and hence stretch of the ventricular wall. This influences the force of contraction (Starling's law of the heart). The relationship between EDP and stroke volume is the ventricular function or Starling curve. At normal EDP the curve is steep, so small changes in EDP cause large changes in force.
- The key importance of Starling's law is that it allows the outputs of the right and left ventricles to be matched. An increase in the right ventricular filling pressure (or central venous pressure, CVP) will consequently affect both ventricles and increase cardiac output.
- The ANS regulates CO by actions on heart rate and cardiac muscle contractility, arterial vasoconstriction (increases peripheral resistance and afterload) and venoconstriction (decreases venous compliance, mobilizes blood and increases CVP).
- An increase in CVP impedes venous return because it reduces the arterial–venous pressure difference. The vascular function curve shows the relationship between CVP and venous return.



- However, CO must equal venous return. By plotting the vascular function curve on the same axis as the ventricular (or cardiac) function curve, it can be seen that equilibrium can only occur where the lines cross, i.e. where CO = VR (Guyton's analysis). This can be used to show how the function of the heart and vasculature are integrated, and how perturbations (e.g. inotropes, vasodilators, increased CVP) lead to a new equilibrium.

## Chapter 18 Haemodynamics

- Haemodynamics is the study of the relationships between pressure, resistance and flow in the cardiovascular system.
- The cardiac output is equal to the difference between the mean arterial blood pressure and the central venous pressure divided by the total peripheral resistance:  $CO = (MABP - CVP)/TPR$ .
- Resistance to flow is caused by frictional forces within the fluid, and can be described by Poiseuille's law:  
resistance =  $8VL/\pi r^4$ , so that flow =  $\Delta P(\pi r^4/8VL)$   
where  $V$  is the fluid viscosity,  $L$  is the tube length,  $r$  is the inner radius of the tube and  $\Delta P$  is the pressure head driving the flow.
- The implication of Poiseuille's law is that flow through a tube, for example the flow of blood in an arteriole, is very sensitive to changes in the diameter of the tube.
- The vascular beds for the various organs and regions of the body are arranged in parallel, such that  
 $1/R_{Total} = 1/R_1 + 1/R_2 + 1/R_3 \dots 1/R_n$ .
- The implication of this parallel arrangement is that the blood flow in one region of the body can be altered (by adjustment of its arterial/arteriolar resistances) without greatly affecting pressures and flows in the rest of the system.
- Laminar flow and the Fåhræus–Lindqvist effect help to minimize blood viscosity.
- The wall tension in a blood vessel is defined by the LaPlace/Frank law, which states that wall tension =  $P_t(r/u)$ , where  $P_t$  is the transmural pressure,  $r$  is the vessel radius and  $m$  is the wall thickness.

## Chapter 19 Blood pressure and flow in the arteries and arterioles

- Systolic blood pressure is mainly influenced by the stroke volume, the left ventricular ejection velocity and aortic/arterial stiffness.
- Diastolic pressure is mainly influenced by the total peripheral resistance.
- Blood ejected from the left ventricle strikes the column of blood already in the aorta, creating a pressure wave which is rapidly conducted towards the arterioles.
- This pulsatile pressure wave propels the blood forward, causing a pulsatile flow wave.
- The pressure wave also causes the walls of the elastic arteries to bulge out; their rebound drives the blood forward during diastole (Windkessel effect).
- Part of the pressure wave is reflected back towards the heart at arterial branch points, and summates with the forward going wave, increasing its amplitude in the major arteries.
- The smallest arteries and arterioles create the greatest resistance to the flow of blood, so that the blood pressure declines sharply across this resistance.

- Constriction of the resistance vessels in a region of the body directs the flow away from that region and also promotes fluid reabsorption by the microcirculation in that region; vasodilatation has the opposite effects.
- The degree to which a blood vessel is constricted is termed vascular tone, and is determined by the balance of vasodilating and constricting influences acting on it.

## Chapter 20 The microcirculation and lymphatic system, and diapedesis

- The microcirculation comprises the smallest arterioles and the exchange vessels, including the capillaries and the postcapillary venules.
- Water, gases and solutes cross the walls of exchange vessels mainly by diffusion, a passive process by which substances move down their concentration gradients.
- O<sub>2</sub> and CO<sub>2</sub> and other lipophilic substances can easily diffuse across lipid bilayers, and so cross the walls of exchange vessels extremely quickly.
- Hydrophilic substances such as electrolytes and glucose cross the walls of exchange vessels much more slowly, because they must diffuse through the intercellular clefts which separate adjacent endothelial cells.
- Large proteins cross the walls of exchange vessels very slowly, and are thought to move through endothelial cells via temporary channels formed by vesicles.
- The blood–brain barrier tightly controls the movement of ions and solutes across the walls of the continuous capillaries in the brain, thereby maintaining the stable composition of its extracellular fluid.
- The lymphatic system collects fluid and substances filtered into the tissue spaces from the microcirculation into the lymph nodes – allowing activation of lymphocytes by antigens – and thence back into the venous system.
- Neutrophils and macrophages are able to enter tissues through diapedesis, a process by which they cross the walls of postcapillary venules by moving between or through endothelial cells.

## Chapter 21 Fluid filtration in the microcirculation

- The net movement of water across the walls of capillaries and postcapillary venules is determined by the balance between the hydrostatic and colloid osmotic pressure gradients across these walls.
- The hydrostatic pressure gradient ( $P_c - P_i$ ) tends to drive water out of capillaries (filtration), and the oncotic or colloidal osmotic pressure gradient ( $\pi_p - \pi_i$ ) tends to draw water into capillaries (absorption).
- The Starling equation describes the relationship between net flow ( $J_v$ ) and these gradients, where
 
$$J_v \propto [(P_c - P_i) - \sigma(\pi_p - \pi_i)].$$
- The osmotic gradient is determined by the difference in protein concentrations in the plasma and the tissue spaces because osmotic force is generated by substances that are relatively impermeant (i.e. have a reflection coefficient,  $\sigma$ , close to 1;  $\sigma$  is typically  $\sim 0.9$  for proteins but is zero for electrolytes and small molecules).
- Averaged over the entire body, these two gradients are very well balanced, such that although  $\sim 4000$  L of plasma enters the capillaries in a day, net filtration is only about 8 L.
- An imbalance between the transcapillary hydrostatic and colloidal osmotic pressure gradients that favours filtration causes oedema, an accumulation of fluid in tissues.

## Chapter 22 The venous system

- As a result of its large cross-sectional area relative to that of the arteries, the venous system offers little resistance to the flow of blood.
- The pressure gradient required to drive the blood through the venous system (~15 mmHg) is therefore much smaller than that needed in the arterial system.
- The veins contain most (~70%) of the blood in the cardiovascular system and therefore serve as reservoirs from which blood can be mobilized into the rest of the cardiovascular system by venoconstriction during exercise and haemorrhage.
- During standing, the increased pressure within the veins of the lower extremities causes them to distend so that their volume increases by ~500 mL.
- Standing causes a downward displacement into the spinal column of the cerebrospinal fluid, creating a negative pressure within the cranium that prevents the lowered pressure within cerebral veins from collapsing them.
- Rhythmic contraction of the muscles of the legs occurs even during quiet standing, and works with one way valves in leg veins to drive blood back to the heart (the skeletal muscle pump).

## Chapter 23 Local control of blood flow

- Mechanisms arising locally from within blood vessels or from surrounding tissues act to regulate flow through resistance vessels.
- These mechanisms act to stabilize flow in resistance vessels in many organs (autoregulation) and also cause local changes in vascular diameter which enable blood flow to be matched to local metabolic needs (metabolic vasodilatation or hyperaemia).
- Autoregulation involves the myogenic response and effects of vasodilating metabolites.
- Increased tissue metabolism causes the local increase of various extracellular factors cause metabolic vasodilation/hyperaemia.
- Important metabolic factors include adenosine,  $K^+$  ions and hypercapnia.
- Local changes in vascular tone in selected vascular beds can also be mediated by a host of other substances under specific conditions.

## Chapter 24 Regulation of the vasculature by the endothelium

- The endothelium exerts an important control over vascular tone by releasing a number of substances that cause vasodilatation or constriction, and also by regulating the membrane potential of adjacent vascular smooth muscle cells.
- The most important endothelium-derived vasodilator is nitric oxide (NO), a gas synthesized by the endothelial enzyme eNOS, which diffuses into adjacent smooth muscle cells and relaxes them by stimulating their synthesis of cyclic GMP.
- eNOS is stimulated by agonists that raise endothelial  $[Ca^{2+}]_i$ , and also by stimuli such as blood flow-induced shear, which cause its phosphorylation.
- Rises in endothelial cell  $[Ca^{2+}]_i$  also cause the opening of endothelial  $K^+$  channels, leading ultimately to the hyperpolarization and relaxation of adjacent smooth muscle cells.
- Endothelial cells also release prostacyclin ( $PGI_2$ ), which inhibits haemostasis, and endothelin, which causes vasoconstriction.

- Damage to the endothelium, for example as a result of oxidative stress or diabetes, is thought to be an important factor in driving the development of cardiovascular diseases such as atherosclerosis and systemic and pulmonary hypertension.

### Chapter 25 The coronary, cutaneous and cerebral circulations

- The vascular beds supplying the different organs of the body are structurally and functionally specialized, allowing an optimal matching of blood flow with their individual requirements.
- Blood flow to the left ventricle occurs mainly during diastole because coronary arteries within the cardiac wall are compressed by high intramural pressure during systole.
- Increases in heart rate decrease the duration of diastole more than that of systole and so reduce left ventricular perfusion time; this can cause cardiac ischaemia if coronary flow is compromised by coronary artery disease.
- Coronary arteries dilate markedly during exercise to allow a pronounced increase in blood flow which provides for the greatly increased oxygen demand of the heart.
- Apart from supplying the modest metabolic needs of the skin, the main function of the cutaneous vasculature is thermoregulation.
- Neural and local mechanisms control cutaneous vascular tone, allowing thermoregulation by causing blood flow to the skin to increase and decrease under hot and cold conditions, respectively.
- The brain has a very high capillary density, allowing it to receive a >10-fold higher blood flow per tissue weight than the rest of the body.
- Regional increases in neural activity in the brain increase local blood flow via the vasodilating effects of substances released by neurones and astrocytes.

### Chapter 26 The pulmonary, skeletal muscle and fetal circulations

- The right ventricle is able to drive its entire output through the pulmonary circulation utilizing a pressure head of only 10 mmHg because the resistance of the pulmonary circulation is only 10–15% that of the systemic circulation.
- Pulmonary vascular resistance is low because the vessels of the pulmonary microcirculation are short, relatively wide-bore and highly branching.
- Hypoxic pulmonary vasoconstriction, a process by which pulmonary vessels constrict to alveolar hypoxia, helps to maintain high blood oxygen levels by channelling pulmonary blood flow to normoxic alveoli.
- Blood flow through the skeletal muscle vascular beds is mainly regulated by sympathetic nerves at rest, but increases dramatically in working muscle during rhythmic exercise due to reactive hyperaemia.
- The fetus exchanges blood gases, nutrients and metabolic waste products with the maternal circulation via the placenta.
- In the fetus, the right and left ventricles pump the blood in parallel rather than in series.
- This arrangement allows the heart and head to receive more highly oxygenated blood, and is made possible by three structural shunts unique to the fetus.
- These shunts are the ductus venosus, the foramen ovale and the ductus arteriosus.
- At birth, the fetal circulation quickly assumes a quasi-adult pattern due to a large fall in pulmonary vascular resistance and the tying off of the umbilical cord; both events cause functional closing of the fetal circulatory shunts.

## Chapter 27 Cardiovascular reflexes

- Autonomic reflexes provide central regulation of blood pressure and volume, and allow maintenance of adequate coronary and cerebral perfusion. They involve: (i) receptors that sense a change in state and signal via afferent nerves to the brain, which (ii) integrates this information and implements a response via (iii) efferent nerves that regulate cardiac, vascular and renal function.
- Afferent nerves from cardiovascular receptors terminate in the nucleus tractus solitarius (NTS) of the medulla. Neurones from the NTS project to brainstem areas that control parasympathetic and sympathetic efferent outflow. Activity modulated by descending inputs from cortex and hypothalamus.
- Baroreceptor reflex acts rapidly to minimize acute fluctuations in mean arterial BP. Baroreceptors (stretch sensitive nerve endings) in carotid sinus and aortic arch increase or decrease firing rate as BP increases or decrease respectively. Sensitive to pressures between 80 and 150 mmHg, and show partial adaptation.
- Decreased BP and baroreceptor firing leads to reduced vagal activity to the sinoatrial node (SAN), causing tachycardia, and increased sympathetic activity to heart and blood vessels, causing increased cardiac contractility, vasoconstriction and activation of the renin–angiotensin–aldosterone axis and so salt and water retention. Increased BP and baroreceptor firing does the opposite.
- Cardiopulmonary reflexes are diverse cardiovascular reflexes originating in the heart and lungs, that exert a tonic depression of heart rate and vascular tone. Stretch receptors in low pressure areas such as veno-atrial junction and atria provide a measure of blood volume. Decreased activity due to decreased blood volume leads to increased sympathetic mediated vasoconstriction and activation of renin–angiotensin–aldosterone system, and if severe increased ADH release.
- Chemoreceptor reflexes: the carotid (and aortic) body chemoreceptors detect hypercapnia, hypoxia and acidosis, and are also activated by severe hypotension. Main function in control of ventilation, but strong activation causes vasoconstriction of skeletal and splanchnic circulations. Important for maintaining cerebral blood flow at BP too low to activate baroreceptors.

## Chapter 28 Autonomic control of the cardiovascular system

- The autonomic nervous system (ANS) provides the effector arm of cardiovascular reflexes designed to maintain an appropriate blood pressure, and also enables specific patterns of cardiovascular adjustments allowing the body to cope with stressful situations.
- The sympathetic branch of the ANS acts mainly through noradrenaline released by postganglionic fibres, but during stress its effects are supplemented by those of the blood-borne hormone adrenaline.
- Catecholamines act via  $\alpha_1$  and  $\beta_1$  (noradrenaline and adrenaline) and  $\beta_2$  (mainly adrenaline) adrenergic receptors.
- Sympathetic activation causes positive inotropic and chronotropic effects (mainly  $\beta_1$ ).
- Sympathetic activation constricts most arteries and veins ( $\alpha_1$  effect), but dilates coronary and skeletal muscle blood vessels ( $\beta_1$  and  $\beta_2$ ).
- The parasympathetic nervous system, acting via muscarinic receptors stimulated by acetylcholine released by postganglionic nerve fibres, slows sinoatrial node pacemaking,

decreases the speed of impulse conduction through the atrioventricular node, and dilates selected vascular beds, including those of the penis, the pancreas and the salivary glands.

### Chapter 29 The control of blood volume

- Long-term control of blood pressure requires regulation of blood volume, the key mechanisms for which are control of plasma osmolality and  $\text{Na}^+$ .
- Plasma osmolality is detected by osmoreceptors in the hypothalamus. Increased osmolality leads to thirst and release of antidiuretic hormone (ADH). ADH acts on principal cells of the renal collecting duct by increasing membrane aquaporins (water channels), promoting reabsorption of water. The system is highly sensitive to small changes in plasma osmolality.
- Because plasma osmolality is tightly controlled, blood volume can be controlled by regulating  $\text{Na}^+$ , the main determinant of extracellular fluid (ECF) osmolality. Any change in  $\text{Na}^+$  content will elicit rapid changes in water homeostasis to maintain osmolality.
- Blood volume is detected via its effects on central venous pressure (CVP) and arterial blood pressure via veno-atrial stretch receptors and the baroreceptors, respectively. Blood pressure also directly affects renal function via pressure natriuresis.
- Pressure natriuresis is an intrinsic renal process whereby increases in arterial blood pressure strongly promote diuresis and natriuresis ( $\text{Na}^+$  excretion in the urine).
- Increased atrial stretch ( $\uparrow$  blood volume) causes both release of atrial natriuretic peptide (ANP) which promotes diuresis and natriuresis, and a reduction in sympathetic stimulation to heart, vasculature and kidney. The latter suppresses activity of the renin–angiotensin–aldosterone system, leading to reduced  $\text{Na}^+$  reabsorption. The converse would apply to reduced blood volume.
- In emergency, a large fall in blood volume or pressure can cause water retention by increasing ADH release, at the expense of osmolality.

### Chapter 30 Cardiovascular effects of exercise

- Dynamic exercise necessitates an increase in cardiac output (CO) which rises almost linearly with the rate of muscle  $\text{O}_2$  consumption and results from increases in both heart rate and stroke volume.
- The increased CO is channelled mainly to the active muscles, which may receive  $\sim 85\%$  of CO, compared with 15–20% at rest, and to the heart.
- This redistribution of CO is due to a profound arteriolar dilatation in the heart and active muscles, and to constriction of the arteries and arterioles in the splanchnic and renal vascular beds and in non-working muscle.
- The diastolic arterial blood pressure does not change much because these opposite changes in vascular resistance in different vascular beds balance each other out; however, systolic pressure rises due to the more forceful ejection of blood from the heart.
- In anticipation of exercise, and during its initial stages, a process termed central command decreases vagal tone, raises the set point of the baroreceptor reflex, and increases plasma adrenaline levels, causing the cardiovascular adaptations required for increased effort.
- The cardiovascular adaptation during exercise is then sustained by autonomic reflexes dependent on receptors in muscle and also by dilatation of muscle arterioles due to reactive hyperaemia.

- Athletic training enhances exercise capacity by causing cardiac structural changes that increase maximum cardiac output, by decreasing total peripheral resistance, and by increasing capillary density in skeletal muscle.

### Chapter 31 Shock and haemorrhage

- Cardiovascular shock refers to an acute inadequacy of cardiac output (CO), caused by low blood volume (hypovolaemic shock), profound vasodilatation (low-resistance shock), acute heart failure (cardiogenic shock) or blockage of the cardiopulmonary circuit (e.g. pulmonary embolism).
- Haemorrhage is the most common cause of hypovolaemic shock. Shock may be induced if more than 20% of blood volume is lost; 20–30% loss may reduce blood pressure (BP) but death is uncommon; 30–50% loss causes profound falls in BP and CO and may become irreversible, severity depends on both extent and rate of loss. Death is generally inevitable for >50% blood loss.
- Immediate compensation: fall in BP detected by baroreceptors, with consequent increased heart rate, venoconstriction and vasoconstriction of splanchnic, cutaneous, renal and skeletal muscle circulations, leading to pallor, reduced urine production and lactic acidosis. Increased sympathetic discharge causes sweating and clammy skin.
- Increased renal sympathetic activity and reduced renal artery pressure activates the renin–angiotensin–aldosterone system. Angiotensin II is a powerful vasoconstrictor that has an important role in recovery of BP and stimulates thirst. Severe blood loss stimulates release of adenosine diphosphate (ADH) and adrenaline, both of which contribute to vasoconstriction. These mechanisms may prevent any large fall in BP or CO even though shock is severe.
- Longer term compensation: over hours, interstitial fluid may re-enter the blood as an internal transfusion, causing haemodilution. Over days, blood volume is restored by increased fluid intake, decreased urine production, increased Na<sup>+</sup> reabsorption caused by angiotensin II and aldosterone and reduced ANP, and increased ADH-induced water reabsorption.
- Blood loss >30% can lead to progressive shock, where an initial improvement in CO is followed by a steady decline. Caused by a vicious circle of hypoxia–ischaemia and multiple mechanisms including depressed cardiac function, which can lead to multi-organ failure. If transfusion is not performed in 1 hour, the patient may enter irreversible shock primarily due to irretrievable cardiac damage.

### Chapter 32 History and examination of the cardiovascular system

- It is essential to take a full history and make a full physical examination of the patient.

### Chapter 33 Cardiovascular investigations

- The main cardiac abnormalities to note on the chest X-ray include cardiomegaly (heart failure), peri-hilar shadowing indicating pulmonary oedema, prominent pulmonary vessels (pulmonary hypertension), fluid in the pleural space (pleural effusion).
- The echocardiogram provides information on chamber size and function including ejection fraction of the left ventricle, and information on valve abnormalities.
- Right heart catheterization with a Swan–Ganz catheter is used to measure mean pulmonary artery pressure and thus formally diagnose pulmonary hypertension.
- A thallium scan combined with an exercise test is used to diagnose coronary artery disease.

- Cardiac magnetic resonance imaging is a non-invasive imaging modality providing accurate assessment of global and ventricular function, myocardial perfusion and myocardial scar.

### Chapter 34 Risk factors for cardiovascular disease

- Cardiovascular risk factors increase the probability that an individual will develop coronary heart disease and/or other cardiovascular disease.
- Important fixed risk factors include age, gender and family history.
- Important modifiable risk factors include hypertension, dyslipidaemias, smoking, diabetes mellitus, obesity, physical inactivity and psychosocial stress.
- Removal or reduction of the severity of such modifiable risk factors decreases cardiovascular morbidity and mortality, and has assumed a central role in the management of cardiovascular disease.

### Chapter 35 $\beta$ -Blockers, ACE inhibitors, ARBs and $\text{Ca}^{2+}$ channel blockers

- $\beta$ -Blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and  $\text{Ca}^{2+}$  channel blockers stand out as being useful in treating multiple disorders of the cardiovascular system.
- The usefulness of  $\beta$ -blockers, which are used to treat angina, cardiac arrhythmias, myocardial infarction, hypertension and chronic heart failure, derives mainly from their blockade of cardiac  $\beta_1$  receptors.
- Overactivity of the renin–angiotensin–aldosterone system has multiple deleterious effects on the cardiovascular system, and as a result ACE inhibitors and ARBs are used to treat hypertension and to both prevent and treat chronic heart failure.
- $\text{Ca}^{2+}$  channel blockers, which block L-type voltage-gated  $\text{Ca}^{2+}$  channels in both vascular smooth muscle and cardiac cells, are used to treat angina pectoris, hypertension and cardiac arrhythmias (particularly supraventricular tachycardias).

### Chapter 36 Hyperlipidaemias

- Lipids are transported in the blood as lipoproteins, small particles consisting of a core of triglycerides and cholesteryl esters, surrounded by a coat of phospholipids, cholesterol and apoproteins.
- Hyperlipidaemias are abnormalities of lipoprotein levels which promote the development of atherosclerosis, coronary heart disease and stroke.
- Primary hyperlipidaemias are caused by genetic abnormalities affecting apoproteins, apoprotein receptors or enzymes involved in lipoprotein metabolism, and occur in about 1 in 500 people.
- Secondary hyperlipidaemias can be caused by conditions or drugs affecting lipoprotein metabolism, although hypercholesterolemia, the most widespread hyperlipidaemia, is usually due to consumption of a diet high in saturated fat.
- Drugs that reduce plasma levels of low-density lipoprotein, and particularly statins, which do so by blocking the rate limiting enzyme in cholesterol synthesis, reduce the risk of developing coronary artery disease and its sequelae.

### Chapter 37 Atherosclerosis

- Atherosclerosis is a disease of larger arteries which is characterized by focal lesions of the arterial wall, termed plaques.



- Atherosclerotic plaques demonstrate a number of features: vascular thickening due to intimal smooth muscle cell proliferation (termed the fibrous cap) and deposition of connective tissue, accumulation of a pool of extracellular lipid and cell debris under the intima, loss of endothelium and degeneration of the media.
- Atherosclerosis is thought to be initiated by endothelial dysfunction at sites of variable haemodynamic shear stress.
- This promotes the adhesion and penetration into the arterial wall of monocytes which subsequently mature into macrophages and take up oxidized low-density lipoprotein (LDL), thereby becoming foam cells.
- Cytokines and other factors released by foam cells, by T lymphocytes, which also penetrate the arterial wall, and by platelets adhering to the damaged endothelium cause progressive changes in the vascular wall culminating in the plaque.
- In coronary arteries, lesion with a thick fibrous cap can cause focal thickening of the arterial wall (stenosis) which can lead to stable angina, whereas if the fibrous cap is thin it can rupture leading to formation of a thrombus which can lead to an acute coronary syndrome.
- Atherosclerotic plaque in cerebral and renal arteries constitutes the major cause of stroke and renovascular hypertension, respectively.

### Chapter 38 Treatment of hypertension

- Hypertension is defined pragmatically as the level of blood pressure (BP) above which therapeutic intervention can be shown to reduce the risk of developing cardiovascular disease.
- Risk increases progressively with both systolic and diastolic BP levels.
- The goal of antihypertensive therapy is to reduce the blood pressure to below 140/90 mmHg (or to below 130/80 mmHg in diabetics and those with renal disease).
- Adequate control of BP usually requires the lifelong use of antihypertensive drugs, which act to reduce cardiac output (CO) and/or total peripheral resistance (TPR).
- The major classes of antihypertensive drugs in current use include angiotensin-converting enzyme (ACE) inhibitors, ARBs and Ca<sup>2+</sup> channel blockers, all of which reduce CO, and diuretics which reduce both CO and TPR.
- Less widely used antihypertensives include antagonists of  $\beta$ -receptors,  $\alpha_1$ -receptors, renin and the aldosterone receptor, as well as imidazoline receptor agonists.
- Most patients will require simultaneous treatment with drugs from at least two classes of antihypertensive drug for adequate BP control.

### Chapter 39 Mechanisms of primary hypertension

- Hypertension is an important risk factor for the development of coronary heart disease, stroke and renal failure, partly by virtue of causing endothelial cell damage.
- In the vast majority of cases, hypertension has no apparent cause and is termed primary or essential.
- Primary hypertension is a complex genetic disease, in which the inheritance of a large number of commonly occurring gene alleles predisposes an individual to developing high BP, particularly when combined with certain environmental and lifestyle factors.
- Multiple theories seek to explain the development of hypertension; none is universally accepted and because high BP likely arises through a variety of mechanisms each may be more or less relevant to individual cases.

- Because the kidneys have a central role in stabilizing long-term BP by virtue of their regulation of salt excretion, most theories of hypertension envision that high BP pressure arises when this function is compromised.
- This could occur due to abnormalities of renal function per se, or could be due to abnormalities in the regulation of renal function by the sympathetic nervous system or the renin–angiotensin–aldosterone system.
- Whatever the initial cause, in the long term primary hypertension is sustained and amplified by vascular remodelling and renal damage.
- In <10% of cases, hypertension is secondary to an identifiable condition or factor, in which case it is termed secondary.

#### Chapter 40 Stable and variant angina

- Angina describes the crushing and/or squeezing sensation in the centre of the chest that is caused by reversible myocardial ischaemia. It is most often due to atherosclerotic coronary heart disease.
- Three forms of angina are recognized: stable angina, unstable angina and variant angina. Unstable angina is one of the acute coronary syndromes. Variant angina is also known as Prinzmetal’s angina and is caused by vasospasm of a coronary artery.
- First-line pharmacological treatment of angina is  $\beta$ -blockade, which reduces myocardial oxygen demand. Nitrovasodilators are given to terminate an attack of angina.

#### Chapter 41 Pharmacological management of stable and variant angina

- The treatment of angina is twofold: first to control the symptoms of anginal pain and, secondly, to prevent the progression of cardiovascular disease.
- First-line agents in angina are  $\beta$ -blockers or calcium-channel blockers.  $\beta$ -Blockers work by decreasing myocardial oxygen demand and thus ischaemic pain. Calcium-channel blockers are effective because they cause vasodilatation.
- Short-acting nitrates are used to terminate an attack of angina. Long-acting nitrates are used in some patients whose angina is inadequately controlled on a  $\beta$ -blocker or calcium-channel blocker.
- All patients with angina should receive low-dose aspirin, which suppresses platelet aggregation.
- Calcium-channel blockers and nitrovasodilators are effective in treating variant angina.  $\beta$ -Blockers must not be used in variant angina.
- Ivabradine is a new anti-anginal agent which acts by reducing the heart rate, thus prolonging diastole and allowing more time for the left ventricle to be perfused with blood.

#### Chapter 42 Acute coronary syndromes: unstable angina and non-ST segment elevation myocardial infarction

- Unstable angina and non-ST segment elevation myocardial infarction (NSTEMI) are two of the three acute coronary syndromes (ACS). The third, which is the most serious, is ST segment elevation MI (STEMI).
- All of the ACS involve myocardial ischaemia secondary to a sudden decrease in the flow of blood through a coronary vessel.
- The ECG and troponin level are vital investigative tools in ACS. In unstable angina, the ECG is usually normal and the troponin will not be elevated, as the ischaemic episode has not been sufficient to cause myocardial damage. In NSTEMI, the ECG may be normal, or there may be

non-specific changes (e.g. T-wave inversion), or ST segment depression, indicating acute ischaemia. The troponin in NSTEMI is raised.

- If the patient presenting with symptoms suggestive of ACS has an elevated troponin but no ST segment elevation, they will be started on the ACS protocol of drugs. These are dual antiplatelet therapy with aspirin and clopidogrel and a low molecular weight heparin.
- Patients at high risk of a repeat ACS should undergo imaging of their coronary arteries (angiography). If necessary, a stent can be inserted.

### Chapter 43 Revascularization

- Revascularization refers to the process during which a new or augmented blood supply is provided to an area of ischaemic myocardium. Two main interventions are performed: coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).
- CABG involves the grafting of either a vein or an artery onto a coronary artery so that an atherosclerotic narrowing can be circumvented. The most frequently used vein is the greater saphenous vein and the most frequently used artery is the left internal mammary artery (LIMA). Use of the LIMA is associated with a much lower restenosis rate than use of the saphenous vein.
- PCI involves the introduction of a catheter into one of the coronary arteries, usually accessed via the femoral artery. A balloon is then introduced to the site of stenosis and inflated. During the majority of PCI, drug-eluting stents are inserted to maintain the patency of the vessel. Following stenting, patients must take dual antiplatelet therapy (aspirin for life and clopidogrel for 1 year) to help prevent restenosis.
- CABG is more effective than PCI in multivessel disease. Compared with medical therapy, CABG has a positive effect on survival in patients with severe coronary artery disease. On the other hand, PCI does not improve survival compared with medical therapy, but does result in greater improvement of anginal symptoms and decreases the need for drugs.

### Chapter 44 Pathophysiology of acute myocardial infarction

- Myocardial infarction describes the irreversible death of cardiac muscle secondary to prolonged ischaemia.
- The prolonged ischaemia is most often caused by plaque rupture followed by formation of a thrombus. These events occur in one of the coronary arteries.
- Rupture of an atherosclerotic plaque uncovers collagen, which results in: (i) platelet aggregation; and (ii) activation of the clotting cascade. These events result in the production of the ischaemia-inducing thrombus.
- If the ischaemia is severe and prolonged enough, the entire thickness of the heart wall may become infarcted. This is shown on the ECG as ST segment elevation and is an indication for percutaneous coronary intervention to enable reperfusion of the myocardium.
- After 2–3 months the infarcted area heals, leaving a non-contractile area of myocardium.

### Chapter 45 Acute coronary syndromes: ST segment elevation myocardial infarction

- STEMI is the most serious of the three acute coronary syndromes (ACS). In STEMI, there is by definition elevation of the ST segment in at least two leads of the ECG, and the troponin is elevated. The most important intervention in STEMI is urgent revascularization of the blocked coronary, preferably by percutaneous coronary intervention (PCI).
- If it is not possible to transfer the patient with acute ST segment elevation to a centre with the capacity for PCI in less than 2 hours, thrombolysis should be instituted, providing the patient

fulfils the requisite ECG criteria.

- Following a STEMI, patients should be started on antiplatelet therapy, a  $\beta$ -blocker if not contraindicated, an ACE inhibitor and a statin. Counselling regarding modifiable risk factors such as diet and smoking status is of paramount importance.
- Complications of acute myocardial infarction include cardiogenic shock, which has a very high mortality, arrhythmias and ventricular septal defect.

### Chapter 46 Heart failure

- Chronic heart failure occurs when the heart cannot maintain cardiac output (CO) to meet the demands of the body. Compensation may allow adequate CO at rest but not during exercise (exercise intolerance); decompensation occurs when CO cannot be maintained at rest.
- Systolic failure is due to impaired ventricular contraction, generally as a result of ischaemic heart disease; ejection fraction is  $<45\%$ . Diastolic failure occurs when ventricular filling is impaired; ejection fraction may be normal. Systolic failure is generally accompanied by diastolic failure.
- Left heart failure leads to increased end-diastolic pressure (EDP) and thus an enlarged heart (cardiac dilatation), which reduces cardiac efficiency as shown by the law of Laplace. Consequent high pulmonary vascular pressures lead to pulmonary congestion and dyspnoea and, if severe, pulmonary oedema.
- Right heart failure leads to increased central venous pressure (CVP), with consequent peripheral oedema and hepatomegaly. Most often caused by prior left heart failure (congestive heart failure), but also by chronic respiratory disease (cor pulmonale).
- Compensation: increased filling pressures elevate cardiac force through Starling's law. Neurohumoral mechanisms are activated by the baroreceptor reflex, with increases in heart rate and contractility, veno- and arterial vasoconstriction, and activation of the renin–angiotensin–aldosterone system. The latter increases water and  $\text{Na}^+$  retention so blood volume and CVP increase, cardiac function via Starling's Law but promoting dyspnoea and peripheral oedema. Diversion of blood flow from skeletal muscle can lead to weakness and fatigue, contributing to exercise intolerance.
- Chronic heart failure is associated with structural and functional changes (myocardial remodelling) that further impair performance and are potentiated by noradrenaline, angiotensin II and aldosterone. Increased work can lead to energy deficit,  $\text{Ca}^{2+}$  overload, cell damage and arrhythmias, a leading cause of death.
- Pressure overload leads to cardiac hypertrophy, with increased ventricular muscle thickness (unlike cardiac dilation). Force is increased, but the thicker ventricle impedes filling and contributes to diastolic failure, and capillary density and thus coronary reserve are reduced.

### Chapter 47 Treatment of chronic heart failure

- Therapy of chronic heart failure (CHF) is designed to lengthen survival, slow the progression of cardiac deterioration and improve the quality of life by reducing symptoms.
- In CHF, the sympathetic and renin–angiotensin–aldosterone systems are activated in response to reduced pump function and initially help to maintain cardiac output, but then also drive progressive cardiac deterioration leading to death.
- Drugs that target these systems have become the mainstay of treatment, and include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs),  $\beta$ -blockers and aldosterone antagonists.
- Diuretics are also widely used in CHF to ameliorate the systemic and pulmonary oedema.

- Cardiac glycosides, mainly digoxin, are used as positive inotropes, and also to help control atrial fibrillation which often occurs in CHF.
- Implantable cardiac defibrillators and cardiac resynchronization pacemakers are playing an increasingly important part in treating CHF, and ventricular assist devices may be helpful as a bridge to cardiac transplant.

#### Chapter 48 Mechanisms of arrhythmia

- Arrhythmias (dysrhythmias) are abnormalities of the heart rate or rhythm caused by either disorders of impulse generation or by re-entry, a disorder of impulse conduction.
- Abnormal impulse generation can arise as a result of the unmasking of latent pacemakers.
- Abnormal impulse generation can also be caused by early or late afterdepolarizations, oscillations in the membrane potential during or after the repolarizing phase of the action potential occurring in a region of the heart not normally involved in pacemaking.
- Re-entry occurs when an impulse that is delayed or trapped in one part of the heart emerges one or more times into the rest of the heart, re-exciting it each time this occurs.
- In anatomical re-entry, this trapping occurs when the impulse cycles repeatedly along an anatomically defined circuit, re-entering the rest of the heart at some point during each cycle.
- This circuit typically contains a region of unidirectional block and a region of slowed conduction, such that the impulse is delayed long enough while traversing the circuit so that when it re-enters the adjacent myocardium this is no longer refractory.
- In functional re-entry, the impulse cycles over a circuit which may vary in location, and in which areas of slowed conduction and effective unidirectional block occur as a result of moment-to-moment variations in the electrical properties of the cells within a region of the myocardium.

#### Chapter 49 Supraventricular tachyarrhythmias

- Supraventricular tachyarrhythmias (SVTs) are those originating in one of the atria or in the atrioventricular (AV) node.
- SVTs can cause symptoms such as lightheadedness, palpitations and shortness of breath and are generally not life-threatening, although they can occasionally cause sudden death. Atrial fibrillation is the most common SVT, and arises in ~10% of those over the age of 75.
- Atrial fibrillation is a chaotic atrial rhythm resulting in a lack of effective atrial contraction and a 'irregularly irregular' ventricular rate of <200 beats/min.
- In atrial flutter, the atrial rate is ~300 beats/min, but the ventricular rate is typically half of this as the AV node is able to conduct only every other impulse.
- Paroxysmal supraventricular tachycardias manifest as episodes during which the heart rate increases abruptly to 150–250 beats/min, and are due to the presence of congenital accessory conduction pathways between an atrium and either the AV node or a ventricle.
- Drugs used to treat supraventricular arrhythmias work by reducing abnormal impulse generation by the atrial ectopic focus (rhythm control) and/or by suppressing AV nodal conduction, thereby slowing the ventricular rate by decreasing the proportion of atrial impulses conducted into the ventricles (rate control).

#### Chapter 50 Ventricular tachyarrhythmias and non-pharmacological treatment of arrhythmias

- Tachyarrhythmias arising in the ventricles are common during and soon after acute myocardial infarction (MI) and may also occur weeks to years after MI because the healed infarct scar serves as a substrate for a re-entrant circuit.

- Ventricular tachyarrhythmias can also arise as a result of ischaemic and structural heart disease, and specific varieties can also occur idiopathically in structurally normal hearts.
- Sustained ventricular tachycardia (VT) is defined as a run of successive ventricular ectopic beats at >100 beats/min lasting for >30 s and may cause syncope, heart failure and death if cardiac pumping is sufficiently compromised.
- The ECG in VT demonstrates high-frequency bizarrely shaped QRS complexes which are >120 ms in duration.
- Ventricular fibrillation (VF) is a chaotic ventricular rhythm causing an immediate loss of cardiac output and death unless terminated by defibrillation.
- Direct current cardioversion allows rapid reversion to sinus rhythm of VF and haemodynamically unstable tachycardias.
- In radiofrequency catheter ablation, the pathways or focally automatic sites causing certain tachyarrhythmias are ablated (destroyed) by focal heating delivered via a catheter.
- Implantable defibrillators are used to treat certain lethal ventricular arrhythmias, and act by detecting and identifying VT or VF and delivering burst pacing or a single shock in order to terminate the arrhythmia.
- Electronic pacemakers can be used temporarily or permanently to initiate the heart beat by imposing repeated cardiac depolarizations.

### Chapter 51 Pharmacological treatment of arrhythmias

- In general, drugs used to reduce the severity or occurrence of arrhythmias act by suppressing impulse conduction and/or increasing the refractory period in such a way as to reduce abnormal electrical activity while having tolerably small effects on normal myocardium.
- Anti-arrhythmic drugs are divided into four classes based on their cellular mechanisms, although the classification system excludes various drugs and has a variety of other limitations.
  - Class 1 drugs suppress conduction by blocking Na<sup>+</sup> channels, and are mainly used to suppress supraventricular arrhythmias.
  - Class 2 drugs are β-blockers, and are able to suppress a wide variety of arrhythmias because sympathetic drive to the heart is arrhythmogenic, particularly in the context of ischaemic or structural heart disease.
  - Class 3 drugs increase action potential duration and therefore the effective refractory period by blocking K<sup>+</sup> channels involved in repolarization, and are used to treat both supraventricular and ventricular arrhythmias.
  - Class 4 drugs suppress AV nodal conduction by blocking L-type voltage-gated Ca<sup>2+</sup> channels, and are used to treat supraventricular arrhythmias.
- Digoxin and adenosine do not fall into any class, and are used to suppress supraventricular arrhythmias by suppressing AV nodal conduction.
- Because anti-arrhythmic drugs are often not very effective and some types have use-limiting side effects (including causing certain types of arrhythmias), the trend in arrhythmia management is towards non-pharmacological approaches such as radiofrequency catheter ablation and implantable defibrillators which provide better patient outcomes.

### Chapter 52 Pulmonary hypertension

- Whereas the mean pressure in the pulmonary artery (mPAP) in a normal resting adult is ~16 mmHg, pulmonary hypertension (PH) is defined as a resting mPAP exceeding 25 mmHg.
- PH increases right ventricular afterload, and if sufficient eventually leads to right heart failure.

- PH is classified into five groups, the first of which is termed pulmonary arterial hypertension (PAH).
  - PAH comprises heritable (hPAH) and idiopathic PAH (iPAH), and also PH associated with a number of other conditions (aPAH), and is characterized by a clinical syndrome indicative of severe PH and an increased PVR associated with a unique form of pulmonary vascular remodelling.
  - Groups 2–5 PH are secondary to other conditions, including left heart disease (group 2), diseases causing alveolar hypoxia (group 3), chronic thromboembolism (group 4), and a heterogeneous set of additional conditions which result in an increase in pulmonary vascular resistance (group 5).
- The first clinical manifestation of pulmonary hypertension is gradually increasing breathlessness upon exertion, fatigue, chest pain and peripheral oedema, with symptoms then appearing at rest as PH progresses.
- Unambiguous identification of PH requires measurement of PAP using a transvenous catheter which is advanced into the main pulmonary artery via the right heart.
- PAH prognosis is poor; patients usually die from right heart failure within several years and the only cure is lung transplant.
- Symptoms and possible consequences of PAH can be treated using diuretics, anticoagulants, inhaled O<sub>2</sub> and digoxin.
- Prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase 5 inhibitors are used to delay the progression of the disease although evidence of a meaningful extension of survival by these treatments is not compelling.
- The other forms of PH can generally be managed by treating the cause.

### Chapter 53 Diseases of the aortic valve

- The two principal aortic valve diseases are aortic stenosis (AS) and aortic regurgitation (AR). In AS, there is an obstruction to blood flow out of the left ventricle and across the aortic valve. This creates a pressure load on the left ventricle, to which the myocytes respond by undergoing hypertrophy in a compensatory attempt to lessen ventricular wall stress. However, as the stenosis progresses, the left ventricle dilates and eventually heart failure ensues.
- AS is classically associated with the triad of dyspnoea, angina and syncope. These symptoms are due to the failing left ventricle.
- The only definitive treatment of AS is aortic valve replacement.
- AR is the back flow of blood during diastole from the aorta into the left ventricle. It is due to intrinsic defects in the valve cusps. An important cause is infective endocarditis. The regurgitant flow of blood into the left ventricle creates a volume load, which leads to left ventricular hypertrophy and eventually dilatation and heart failure.
- The only definitive treatment of AR is aortic valve replacement.

### Chapter 54 Diseases of the mitral valve

- The mitral valve separates the left atrium from the left ventricle. In mitral stenosis (MS) structural defects in the mitral valve cause obstruction to the flow of blood from the left atrium to the left ventricle.
- As MS worsens, the pressure gradient across the mitral valve increases and the pressure in the left atrium increases also. The left atrium responds to the increased pressure load by dilating. This can lead to atrial fibrillation and associated thromboembolism.

- The increased pressure in the left atrium forces fluid into the pulmonary interstitium, resulting in shortness of breath.
- Mitral regurgitation (MR) is the abnormal flow of blood from the left ventricle to the left atrium. Acute MR is commonly due to papillary muscle rupture following a myocardial infarction. There is a sudden volume overload on the left atrium, resulting in acute pulmonary oedema.

### Chapter 55 Genetic and congenital heart disease

- Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease, with a prevalence >1 in 500. Often asymptomatic, it is the leading cause of sudden cardiac death in young athletes.
- Long QT (LQT) syndrome is often of no consequence, but strong sympathetic stimulation can trigger ventricular tachyarrhythmias resulting in syncope or more rarely sudden death.
- LQT syndrome is not always genetic; it can also be caused by drugs or be acquired (e.g. heart failure).
- Ventricular septal defect (VSD) is the most common congenital cardiac defect. It is an abnormal connection between the ventricles. Small defects are generally asymptomatic; large defects cause significant left-to-right shunting of blood. Over time this increases the pressure in the pulmonary circulation, and may cause pulmonary hypertension.
- An atrial septal defect (ASD) is an abnormal communication between the atria. It is often asymptomatic but can present with breathlessness on exertion and frequent chest infections. Long-term left-to-right shunting may result in pulmonary hypertension.
- The tetralogy of Fallot is the most common cyanotic congenital heart disease. It is described as 'cyanotic' because a right-to-left shunt exists. Deoxygenated blood (as a result of the pulmonary stenosis) enters the systemic circulation via the ventricular septal defect.