16.1.2 Cardiac physiology 3253 Rhys D. Evans, Kenn

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16.1.2 Cardiac physiology 3253 H2S, H2O2, and adipocytokines. Other infiltrating inflammatory cell types including T cells and macrophages have an equally im- portant contribution. Most adipocytokines produced by the cells in PVAT have distinct paracrine effects on the vasculature. These can be proinflammatory/pro-atherogenic (e.g. resistin, IL-6, TNFα, MCP-1) or anti-inflammatory/antiatherogenic (e.g. adiponectin, omentin). The balance between pro-and antiatherogenic adipokines is influenced by conditions such as obesity and diabetes. In human PVAT, PPARγ signalling is a major regulator of adipocytokine pro- duction, and its dysregulation in diabetes, obesity, and insulin resist- ance shifts the balance towards the production of proinflammatory mediators. Until recently, PVAT was considered to have mainly det- rimental effects on vascular homeostasis. However, recent evidence suggests that it ‘senses’ proatherogenic changes in the underlying vascular wall (e.g. changes in ROS production), and can modify its biosynthetic profile by activating PPARγ signalling, leading to in- creased production of ‘antioxidant’ adipokines such as adiponectin and reduced production of ‘pro-oxidant’ adipokines such as IL-6. Therefore, increasing evidence suggests that healthy PVAT may provide local defence mechanisms against vascular injury, and its biosynthetic profile is regulated by complex interactions between PVAT, the underlying vascular wall, and systemic factors. FURTHER READING Allt G, Lawrenson JG (2001). Pericytes: cell biology and pathology. Cells Tissues Organs, 69, 1–11.

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produced by the ATP-dependent movement of the thin and thick filaments relative to one another. Transverse (T-) tubules facilitate extracellular Ca^{2+} entry into the cytoplasm (sarcoplasm) for contraction and signalling. Atrial myocytes differ from ventricular

Section 16 Cardiovascular disorders 3254 myocytes, having few T-tubules but more abundant caveolae. Myocytes of the conduction system are small and possess only a rudimentary myofibrillar structure. Myocytes are attached to adjoining cells and to the extracellular matrix to allow transmission of force. At some regions of contact (the intercalated discs), specialized structures (the gap junctions) contain channels which form contiguous electrical connections between a myocyte and its neighbours and allow passage of ions and small molecules. The sarcoplasmic reticulum surrounds the myofibrils and is a reservoir of the Ca^{2+} which participates in myofibrillar contraction. T-tubules are deep, finger-like indentations of the sarcolemma that abut the sarcoplasmic reticulum at junctional regions in register with the Z-discs of the superficial sarcomeres. Cardiac action potential A potential difference (the membrane potential) is maintained across the plasma membrane (sarcolemma) such that the inside of the cell is negative compared to the outside by about 90 mV. This is caused largely by the efflux of K^+ down its concentration gradient from the cell through K^+ channels and until the electronegative force retaining K^+ in the cell balances the tendency for efflux. When a myocyte is electrically excited, Na^+ channels open and Na^+ enters the cell down its own concentration gradient, producing a rapid inward current and depolarizing the cell towards its equilibrium poten- tial: the initial phase (phase 0) of the action potential. As the myocyte depolarizes, L-type Ca^{2+} channels in the sarcolemma and T-tubules open and Ca^{2+} enters the cell through its concentration gradient. A brief K^+ efflux from the cardiomyocyte is associated with a small, transient repolarization (phase 1). The Na^+ channels close rapidly, but the L-type Ca^{2+} channels remain open for longer, maintaining depolar- ization: phases 1 and 2 of the action potential, where the tendency to depolarize is balanced by repolarizing outward current flow carried by a variety of K^+ channels. The membrane potential in phase 2 is rela- tively stable and hence this phase is also known as the plateau phase. Ca^{2+} entry in close apposition to the junctional sarcoplasmic re- ticulum causes its Ca^{2+}-release channels (ryanodine receptors) to open, discharging about half of the sarcoplasmic reticulum Ca^{2+} res- ervoir into the cytoplasm (Ca^{2+}-induced Ca^{2+}-release). This increase in Ca^{2+} concentration (the Ca^{2+} transient) is sensed by a Ca^{2+}-binding protein (troponin C) that is a component of the thin filament regu- latory complex (the troponin–tropomyosin complex). This initiates myofibrillar contraction, which starts about halfway through phase 2. As the L-type Ca^{2+} channels close, the outward current flow through K^+ channels predominates and the myocyte repolarizes towards the K^+ equilibrium potential (phase 3). Ca^{2+} is removed from the cyto- plasm and returned to the sarcoplasmic reticulum by active transport mediated by the sarcoplasmic/endoplasmic Ca^{2+}-ATPase (SERCA2). Ca^{2+} is also expelled from the cell by the plasma membrane Na^+/ Ca^{2+} exchanger (NCX), which is electrogenic (three Na^+ exchanged for one Ca^{2+}) and tends to prolong the plateau phase. The behaviour of the Na^+/Ca^{2+} exchanger is complex because—depending on the Na^+ and Ca^{2+} concentrations and the membrane potential—it can reverse, thus mediating Ca^{2+} entry and repolarization. This occurs at depolarized potentials, and more so when intracellular Na^+ is in- creased. In phase 4, repolarization is complete and the myocyte is electrically quiescent, with membrane potential maintained by the sodium-potassium pump, until the next depolarization. Cardiac pacemaker and regulation of contractility The sinoatrial node (‘pacemaker’) in the right atrium contains modi- fied myocytes that exhibit a different form of action potential from ventricular myocytes because of differences in the expression of ion

channels. The cell depolarizes spontaneously and gradually during phase 4 until an action potential is produced. This partly results from the presence of hyperpolarization-activated cyclic nucleotide-gated channels which are absent from ventricular myocytes and which open at negative voltages and carry an inward-depolarizing Na+ current (‘funny’ current). Depolarization is then mediated by Ca2+ channel opening. The stimulus is transmitted in a controlled manner via the conduction system (AV node; His–Purkinje system) to all re- gions of the heart. Whole organ physiology The strength of cardiac contraction is both an intrinsic function of the cardiomyocyte, dependent on the initial fibre length (precontraction loading), and on the intrinsic ‘contractility’ of the heart. Cardiac con- tractility is controlled largely by the sympathoadrenal system and the parasympathetic nervous system. β-Adrenergic stimulation increases the tendency of the L-type Ca2+ channel to open (positive inotropism). β-Stimulation also increases relaxation (positive lusitropism) by stimulation of SERCA2 and an increased rate of release of Ca2+ from the troponin complex (relaxation being an energy-dependent pro- cess). The positive chronotropic (rate) effects of β-stimulation result from increased hyperpolarization-activated cyclic nucleotide-gated channel opening, causing an increased frequency of pacemaker de- polarization. These effects are all opposed by the (cholinergic) mus- carinic receptors of the parasympathetic nervous system. The energy requirements of the heart during rest and exertion are influenced by ventricular volume, outflow resistance (hence blood pressure), venous return, and the activity of the autonomic nervous system. An increase in ventricular volume increases wall tension during contraction, and an augmented myocardial oxygen supply is then required to maintain the same systemic blood pressure and stroke volume. The normal integration of the venous return, heart rate, stroke volume, and arterial blood pressure ensures that there is an adequate supply of oxygen and nutrients to the tissues. The activities of the sympathetic and parasympathetic nervous systems contribute to the adjustment of cardiac performance to immediate needs—the former by increasing heart rate and myocardial contractility during exertion and emotion, the latter by maintaining a relatively slow heart rate at rest. Parasympathetic (vagal) fibres in the heart are distributed mainly to the sinoatrial node and the atria; sympathetic innervation is to both the atria and the ventricles. There is a normal diurnal variation in autonomic function, with an increased sympathetic outflow in the mornings, soon after wakening. Coronary blood flow occurs largely in diastole. It is autoregulated to meet myocardial metabolic requirements and may increase five- or sixfold during strenuous exercise. The inner layers of the ven- tricular muscle normally receive a slightly greater blood flow than the outer layers. Haemodynamic and ventilatory responses during exercise take 2–3 min to equilibrate and adjust to an increased work- load and reach a new steady state. Regular exercise to at least 60% of maximal heart rate about three times a week improves effort toler- ance. Measurement of the cardiovascular response to exercise pro- vides an objective assessment of cardiac function.

16.1.2 Cardiac physiology 3255 Introduction The function of the heart is to pump sufficient oxygenated blood containing nutrients, metabolites, and hormones to meet moment- to-moment metabolic needs and preserve a constant internal envir- onment. The heart has two essential characteristics—contractility and rhythmicity. The nervous system and neurohumoral agents modulate relationships between the venous return to the heart, the outflow resistance against which it contracts, the frequency of con- traction, and its inotropic (contractile) state; there are also intrinsic cardiac autoregulatory mechanisms. An understanding of the mo- lecular mechanisms governing cardiac cell behaviour and the mech- anical, electrical, and hormonal control of the heart at a whole organ level is essential for the understanding of cardiac pathophysiology. Cardiac

myocytes Cardiac myocytes (cardiomyocytes) are the contractile cells of the heart, and include ventricular and atrial myocytes, as well as cells specialized to provide the electrical impulse and conduction system. Myocytes constitute the bulk of the cellular volume, but because they are large cells they are fewer in number, being outnumbered by endothelial cells, smooth muscle cells of the vasculature, and fibro- blasts. Replication of ventricular myocytes is believed to decrease rapidly after birth in mammals, and occurs at an extremely low rate in adults, resulting in most cells being terminally differentiated; this is less clear for the atrial myocyte. Terminal differentiation has im- portant consequences for the heart in terms of its limited ability to survive haemodynamic insults or stresses, but also means that the myocardium is essentially resistant to malignant transformation. Morphology of the ventricular myocyte
and its contractile machinery The ventricular myocyte is a large elongated cell (100–150 μm long and 20–35 μm wide) and is packed with striated myofibrils (the contractile elements) that alternate with rows of mitochon- dria (Fig. 16.1.2.1). Each myofibril is roughly cylindrical (2–3 μm in diameter), stretches the length of the cell, and is anchored at each end in a fascia adherens junction. The myofibril comprises sarcomeres arranged in series. Sarcomeres consist of two arrays of filaments: thin filaments, comprised predominantly of the protein actin, interdigitated with thick filaments of myosin. The characteristic striated appearance arises from the organization of these myofilaments within the myofibril (Fig. 16.1.2.1). The thick mito Sarcomere M line I band I band A band H zone Actin (thin filament) Z Z Myosin (thick filament) 1 μm Fig. 16.1.2.1 Upper
panel: electron micrograph of ventricular myocyte showing the structure of the myofibrils. Portions of two myofibrils are shown in the field, with a row of mitochondria (mito) between. Lower
panel: diagrammatic representation of the arrangement of the thick and thin filaments in relation to the striated pattern seen in microscopy.

 filaments are confined to the A-band at the centre of the sarcomere; the thin filaments extend out from either side of the Z-disc (Z- line), crossing the I-band, and penetrate partially into the A-band, where they overlap and interact with the thick filaments. Each Z-to Z-disc repeat constitutes a sarcomere, and the distance between consecutive Z-discs (the sarcomere length) is a measure of the con- tractile state of the myofibril. At the centre of the sarcomere lies the M-line. Each myofibril contains 70–80 sarcomeres. Myocytes have an irregular ‘branched’ morphology; through these branches, each ventricular myocyte typically connects to 10 or more of its neigh- bours to form the three-dimensional branching, syncytium-like structure of the myofibre. Structure of the contractile apparatus Thick filaments The myosin molecule comprises two heavy chains (molecular mass c.200 kDa) and two pairs of light chains (mass 18–28 kDa). The my- osin heavy chains are arranged as dimers, with a tail and two heads (Fig. 16.1.2.2). The tails are packed together to form the shaft of the thick filament, while the heads protrude from the filament and lie close to the thin actin filaments. The myosin heads are the motor units of muscle: they bind and hydrolyse ATP to ADP and convert the free energy of ATP hydrolysis into mechanical work through their interaction with actin in the thin filaments (for details see ‘The mechanism of myofibrillar contraction’). Thin filaments Each thin filament comprises about 300 globular actin subunits (mo- lecular mass 42 kDa). The actin monomers have sites for interaction with the myosin heads and with a regulatory protein complex that confers Ca^{2+} sensitivity. The latter consists of the troponin complex (troponins I, C, and T) and the elongated protein α-tropomyosin (Fig. 16.1.2.2). Troponin complexes are located at intervals along the actin filament. Tropomyosin forms two continuous strands along the thin filament and is responsible for cooperative propaga- tion of regulatory signals. Other structural components of the sarcomere The

thin filaments are attached to the Z-discs in a regular array with filaments on each side in opposite orientation (Fig. 16.1.2.1). The main structural component of the Z-disc is the actin cross-linking protein α-actinin. Z-discs are also associated with the T-tubules and costameres (see next) and contain several additional proteins be- lieved to be associated with cell signalling. The M-line (Fig. 16.1.2.1) contains the protein myomesin that cross-links the thick filaments to maintain their orientation. In addition, the giant protein titin (connectin) extends from the M-line to the Z-disc. Titin contains multiple binding sites for several sarcomeric proteins, including myosin-binding protein-C (MyBP-C; Fig. 16.1.2.2). It contributes to elasticity, passive tension, and thick filament positioning in the sarcomere. Intermediate filaments, costameres, and the plasma membrane skeleton The myofibrils are held in position by scaffold-like webs of inter- mediate filaments made from a (noncontractile) protein, desmin, spanning the sarcolemma, mitochondria, and nucleus. Desmin filaments are anchored to costameres, which circumscribe the lat- eral plasma membrane. Apart from maintaining the spatial organ- ization of the contractile apparatus, the costameres mechanically Troponin T Troponin C Troponin I Myosin-binding protein C Actin Myosin head Myosin rod β-Myosin heavy chain Myosin light chain α-Tropomyosin Fig. 16.1.2.2 Structural arrangement of contractile proteins in the filament overlap zone of the sarcomere. Reproduced from Spirito et al. N Engl J Med 1997; 336: 775–85. Copyright © 1997 Massachusetts Medical Society. All rights reserved.

16.1.2 Cardiac physiology 3257 couple the cells laterally to the extracellular matrix. Associated with the costameres, but closely applied to the entire cytoplasmic aspect of the lateral plasma membrane, is the membrane skeleton, a peri pheral membrane protein network of dystrophin and spectrin. The costameres, membrane skeleton, and intermediate filaments are linked to the glycocalyx and extracellular matrix by sets of integral plasma membrane proteins, notably the integrins and the compo- nents of the dystrophin–glycoprotein complex. Coupling of the plasma membrane to
the sarcoplasmic reticulum The plasma membrane (sarcolemma) contains openings of trans- verse (T)-tubules and the caveolae, which are cholesterol-enriched pits in which signal-transducing and water-channel proteins are concentrated (Fig. 16.1.2.3a). T-tubules are long invaginations of the plasma membrane adjacent to the costameres and myofibril Z-discs, and penetrate deeply into the cell. T-tubules mediate extracellular Ca2+ (Ca2+ o) entry into the cell through the L-type Ca2+ channels. Each myofibril is surrounded by a network of interconnecting membranous tubules and cisternae known as the sarcoplasmic re- ticulum (SR) (Fig. 16.1.2.3a). At multiple sites within this network, the membranes form flattened sacs, the junctional sarcoplasmic re- ticulum (JSR) cisternae, which press tightly against the peripheral plasma membrane and T-tubules (Fig. 16.1.2.3b). The plasma mem- brane and T-tubule domains facing the JSR membrane contain clus- ters of L-type Ca2+ channels, while the nearby domains of the JSR are packed with Ca2+-release channels (Fig. 16.1.2.3), also known as ‘ryanodine receptors’ because of their sensitivity to interference by the plant alkaloid ryanodine. The JSR is the major reservoir of intracellular Ca2+. This close spatial arrangement is important in control of the Ca2+ transient required for myofibrillar contraction. Following contraction, the sarcoplasmic/endoplasmic reticulum Ca2+ATPase-2 (SERCA2) pumps Ca2+ back into the SR lumen, causing myofibrillar relaxation. Connections between cardiac myocytes The myocyte can function as an autonomous contractile unit. To pro- duce a heartbeat, the contractile capabilities of the c.3 billion myocytes that constitute the human heart have to be electromechanically syn- chronized. This requires both an orderly spread of the wave of elec- trical activation and the effective transmission of contractile force from

one cell to the next, throughout the heart. This is achieved by the intercalated discs, formed from specialized regions of the plasma membrane where adjacent cells interact. Intercalated discs are situated at the blunted ends of the main body of the myocyte and its side branches (Fig. 16.1.2.4). Three types of cell membrane junction—the gap junction, the fascia adherens, and the desmosome—connect the adjacent membranes at the disc. The fascia adherens and desmosome are forms of anchoring junc- tion which provide mechanical integrity between adjoining fibres; gap junctions contain clusters of connexons (Fig. 16.1.2.4). These gap junctions are clusters of intercellular channels which span two closely apposed plasma membranes and directly link adjacent cyto- plasmic compartments of neighbouring cells. They form the sites of electrical coupling between individual cardiac myocytes and permit direct cell-to-cell transmission of chemical signals (ions and small molecules of <1 kDa). The combination of connexin isoforms consti- tuting a gap junction channel is a major determinant of its functional properties and varies in different cardiomyocyte subsets. This ar- rangement renders the myocardium into a functional syncytium. Cardiac myocyte subtypes Atrial myocytes are significantly different to the ventricular myocytes just described; they are long and slender, with few or no T-tubules but more abundant caveolae. By producing the peptide hormones atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), they also function as secretory cells. The atria act as blood volume detectors: natriuretic peptides are released in re- sponse to increased central blood volume and participate in the con- trol of sodium and water balance and hence of blood pressure. A third, heterogeneous, group of modified and morphologically distinct myocytes makes up the pacemaker and conduction system. These cells show some resemblance to ventricular and atrial cells, but their primary function is impulse generation and its timed dis- tribution to the contractile myocytes at the appropriate point in the cardiac cycle. Myocytes of the sinoatrial and atrioventricular nodes are typically small (c.5 µm diameter), containing just a few rudimentary myo- fibrils, and small, sparse, gap junctions. These features contribute Ca L-type Ca channel T-tubule local Ca gradient SR lumen a cluster of Ca release channels (RyR) Ca release Ca Ca Na K Na/K ATPase Na/Ca X Ca release from clusters of SR release channels (a) (b) Ca Ca Na Na/Ca X T-tubule L-type Ca channels myofilaments phospholamban P SERCA 2 Ca Ca Ca SR lumen RyR JSR sarcoplasm sarcoplasm Na

Fig. 16.1.2.3 Excitation-Contraction coupling in the heart. (a) L-type Ca2+ channels allow Ca2+ influx across the plasma membrane, creating ICa. This influx increases the local Ca2+ concentration around a cluster of sarcoplasmic reticulum (SR) Ca2+-release channels (ryanodine receptor) in sufficient amounts to open them (Ca2+-induced Ca2+-release). (b) The opening of clusters of SR Ca2+-release channels allows SR Ca2+ reservoir to be discharged into the cytoplasm. Ca2+ fluxes combine to initiate contraction. The contraction process is terminated (1) by SERCA2 (regulated by phospholamban and dependent on phospholamban phosphorylation state), which pumps Ca2+ back into the SR, and (2) by the plasma membrane Na/CaX which expels Ca2+ from the cell. JSR: junctional SR; RyR: ryanodine receptor.

Intercalated disc Desmosome Fascia adherens Gap junction (f) Fascia adherens Desmosome 1 µm Gap junction 20µm 4µm) b ( ) a ((c) (e) (d) 100nm Channel (2 connexons) Connexin Connexon COOH Membrane } Gap
Membrane NH2 Fig. 16.1.2.4 The intercalated disc and cardiac gap junction organization and structure. (a) Clusters of gap junctions at the intercalated discs revealed in a single ventricular cardiac myocyte by immunoconfocal microscopy. (b) One disc-cluster of gap junctions viewed en face (reconstruction from a stack of serial optical sections). One of these immunolabelled spots corresponds to a single gap junction. (c) Electron micrograph illustrating the three types of cell

junction of the intercalated disc. Gap junctions occur where the adjacent plasma membrane profiles run in close contact. The fascia adherens and the desmosome are characterized by a much wider intermembrane space (c.25 nm). (d) Viewing the membrane en face by freeze-fracture reveals the gap junction as a cluster of particles (connexons). (e) The gap junction channel consists of a pair of connexons (hemichannels), one contributed by each of the adjacent plasma membranes. Each connexon is itself formed from six connexin molecules. The specific connexin type or types within the connexon is a major determinant of the functional properties of the gap junction channel. (f) The intercalated disc, permitting intercellular communication; the gap junction is rich in connexins. (a–e) Reprinted from Severs NJ (2000). The cardiac muscle cell. BioEssays, 22, 188–99 (Fig. 5). With permission from Wiley-Blackwell.

16.1.2 Cardiac physiology 3259 to poor coupling, which in the atrioventricular node is essential to slowing of conduction to ensure time for atrial ejection. The cell population is morphologically heterogeneous: cells of the compact atrioventricular node, and those of the surrounding areas (the tran- sitional cells and posterior nodal extension), are distinctive, and myocytes of the His–Purkinje system show a range of morpholo- gies according to their location, progressively increasing in size and myofibril content, and with more developed intercalated discs dis- tally, towards the ventricular myocardium. The cardiac action potential The membrane potential Electrical activity of the heart (membrane potential; action poten- tial) is based on differential distribution of ions across the cellular membranes. This distribution is achieved by the action of ion- transport proteins, including ion pumps and channels. Ion channels Electrical excitation of myocytes involves the movement of ions through specific channels. These are ‘excitable’ proteins embedded in membranes that contain pores capable of opening or closing in response to a stimulus, which could be a change in membrane po- tential, a neurotransmitter or hormone, an intracellular second mes- senger or ion, or mechanical stretch of the membrane. On opening, a channel becomes selectively permeable to a restricted series of ions. There are many different types of channel, often named after the most permeant ion they pass (e.g. Na+, Ca2+, and K+ channels). Ions move down their electrochemical gradients through the channel at high rates (>106 ions/s), distinguishing them from other ion- transport proteins (e.g. the Na+/K+-ATPase or pump, and the Na+/ Ca2+ exchanger (Na/CaX); see ‘The Na+/Ca2+ exchanger (Na/CaX) and the Na+/K+-ATPase’, later on in this chapter) which move ions across plasma membranes several orders of magnitude more slowly. Hence cardiac excitation provides a means of coordinating the con- tractile activities of the four heart chambers and is the basis for the electrocardiograph (ECG; see Chapter 16.3.1). Origin of the membrane potential Cardiac membrane potential is determined by three factors: (1) ionic concentrations across the sarcolemma; (2) the permeability (conductance) of the sarcolemma to specific ions; and (3) the ac- tivity of electrogenic pumps that maintain the ionic concentration gradients. When a ventricular myocyte is at rest (diastole), there is a potential difference of about −90 mV across the plasma mem- brane, the inside of the cell being negative with respect to the out- side. This is principally caused by plasma membrane permeability to K+. The extracellular concentration of K+ (K+ o) is about 4 mmol/ litre, and the intracellular (cytoplasmic) concentration (K+ i) is about 140 mmol/litre, so K+ tends to diffuse out of the cell down its concentration gradient, resulting in the interior becoming nega- tively charged. An equilibrium is thus established where the elec- tronegative force retaining K+ inside the cell (mostly derived from negatively charged intracellular proteins) balances its tendency to diffuse out of the cell down its concentration gradient. This is termed the equilibrium potential (E) and can be calculated from the Nernst equation (see Table 16.1.2.1 for E values of relevant ions). At this potential, there will be no

net flux of K+ ions through K+ channels and, if the membrane is only permeable to K+, then the membrane potential will be equal to EK. The membrane potential at any moment is dependent upon the equilibrium potentials for all permeant species and their rela- tive permeabilities. The actual transmembrane potential difference at rest and the calculated EK are rarely the same owing to a small leakage, mainly of Na+ into the cell down its concentration gradient (Na+ o = 140 mmol/litre, Na+ i = 7–10 mmol/litre). To counteract this leak and to maintain the concentration gradients of Na+ and K+ upon which the generation of the membrane potential depends, the plasma membrane Na+/K+-ATPase uses free energy derived from the hydrolysis of ATP to pump these ions against their concentra- tion gradients. This process is electrogenic (three Na+ extruded for two K+ entering) and generates 3–10 mV of the membrane potential. The action potential The action potential is divided into five phases (Fig. 16.1.2.5). The currents that flow are described in Table 16.1.2.1, Table 16.1.2.2, and Fig. 16.1.2.5. Depolarization from the resting potential is mediated by inward cation current flow. Phase 0 of the action potential When a myocyte is electrically stimulated, Na+ channels (Nav1.5) open and allow Na+ ions to enter the cell. The channels open by sensing potential difference more positive than about −65 mV across the cell membrane (‘voltage gated’; Fig. 16.1.2.5). Excitation depolarizes the cell membrane slightly and this increases the prob- ability of Na+ channel opening. A cardiac myocyte contains many thousands of Na+ channels, hence the current (I) generated by the movement of Na+ ions into the cell (INa) is the sum of the small cur- rents that flow through each individual channel. Positive charge is taken into the cell, the membrane potential increases (becomes less negative) towards the equilibrium potential for Na+ (ENa = +70 mV, Table 16.1.2.1), and the cell depolarizes (Fig. 16.1.2.5). The Na+ cur- rent causes the rapid upstroke (phase 0) of the action potential. The propagation velocity of the action potential across the whole heart is related to the rate of the rapid upstroke. Following activation and opening, the channels close very rapidly, even though the myocyte remains depolarized, a process termed ‘inactivation’. Inactivated channels cannot open again until the cell repolarizes, causing the refractory period during which a further stimulus cannot evoke an- other action potential (Fig. 16.1.2.5). Table 16.1.2.1 Ion concentrations in the quiescent myocyte, and their calculated equilibrium potentials (E). E is calculated from the Nernst equation, E = (RT/zF) ln(ao/ai), where potential E is in volts, T is the absolute temperature, R is the gas constant, F is the Faraday constant, z is the valency, and ao and ai are the extracellular and intracellular activities of the ion in question Ion Intracellular concentration (mmol/litre) Plasma concentration (mmol/litre) Calculated E (mV) Na+ 10 140 +70 K+ 140 4.5 –91 Ca2+ 0.0001 2.3 +131 Cl– 20 110 +45

 The inactivation of each channel decreases the total number of Na+ channels that are conducting such that INa almost entirely in- activates within the first 5 ms of the action potential (the overall ac- tion potential in humans at rest lasts c.350 ms). Some Na+ channels do not inactivate so rapidly, allowing a small inward current to per- sist during the plateau phase of the action potential (phase 2, see next). In late phase 0 some L-type Ca2+ channels (Cav1.2) also start to open, resulting in Ca2+ influx into the cardiomyocyte. Phase 1 of the action potential The characteristic notch observed in phase 1 of the action potential in ventricular myocytes (Fig. 16.1.2.5) is caused by a transient out- ward current (ITO), carried mainly by K+ ions flowing out of the cell (ITO1), but also by some Cl− current (ITO2), that partially repolarizes the membrane. The current inactivates within 30–40 ms but is im- portant in determining action potential duration. A component of ITO appears to be dependent upon intracellular Ca2+ concentra- tion (raised Ca2+ o increases ITO): this is the probable mechanism

underlying action potential shortening during tachycardia. Phase 2 of the action potential Several currents flow during phase 2 (the action potential plateau), including ICa (Fig. 16.1.2.5). L-type (‘long-lasting’) Ca2+ channels, which take longer to activate and inactivate than Na+ channels, open within 3–5 ms of the start of the upstroke and allow Ca2+ to flow into the cell (ICa). L-type Ca2+ channels activate at more positive voltages than Na+ channels (around −35 mV). The influx of Ca2+ maintains depolarization (Fig. 16.1.2.5, Tables 16.1.2.1 and 16.1.2.2), and ini- tiates Ca2+-induced Ca2+-release (CICR) from the SR through the SR Ca2+-release channels (ryanodine receptors), causing the myocyte to contract and hence crucial for excitation–contraction coupling (see next). Hence, Ca2+ has a role in both membrane potential and signal transduction/inotropy. In addition, a slow delayed rectifier K+ cur- rent (IKs) exports K+ in phase 2. The plateau phase (phase 2) of the action potential (Fig. 16.1.2.5) is prolonged in ventricular myocytes because of the properties of several types of K+ channel that give rise to several different K+ cur- rents. The main repolarizing current, IK, is composed of two distinct ‘rectifier’ currents, one activating more rapidly (IKr) than the other (IKs) (see Table 16.1.2.2). Both channels open at positive membrane potentials and close (deactivate) at negative potentials. Hence the plateau of the action potential is the result of a balance of inward (Ca2+) and outward (K+) current flow. Phase 3 of the action potential The final phase of repolarization begins with the termination of ICa and progressively increasing K+ current (IKr and IKs) (Fig. 16.1.2.5). As repolarization proceeds, the sodium-calcium exchanger Na/CaX responds to the increase in cytoplasmic Ca2+ concentration and pro- duces an inward current (INa,Ca) through the exchange of three Na+ entering the cell for one Ca2+ expelled; by producing an inward cur- rent, the Na/CaX slows repolarization and prolongs the plateau. In ventricular myocytes, complete repolarization and a return to a nega- tive resting membrane potential is eventually achieved by (the large) IK1 (the ‘inward rectifier’; Fig. 16.1.2.5; Table 16.1.2.2). The channel through which this current flows possesses peculiar characteristics. Normally, because of the relative concentrations of K+ inside and outside the cell, there is outward movement of K+ ions that becomes ITo IKs ICa INaCa IKr IK1 K currents outward outward inward time Ca and Na/CaX current 1.0 0.1 Ca transient (μM) 1 2 0 +40 −40 −80 0 3 4 Relative refractory period Absolute refractory period Membrane potential (mV) Fig. 16.1.2.5 Ca2+ transient, membrane potential, K+ currents, and Ca2+-related currents during a ventricular myocyte action potential. The inward Na+ current that produces the rapid upstroke of the action potential (depolarization) is not shown. Top panel: phases of the ventricular myocyte action potential. Upper middle panel: changes in cytoplasmic Ca2+ concentration during the action potential (Ca2+ transient). For a period between phase 0 and about midway through phase 3, cardiac muscle cannot be excited with another stimulus: the absolute refractory period. From about halfway through phase 3 until just before the end of phase 3, cardiac muscle is in its relative refractory period, when a stronger stimulus than normal is required to initiate an action potential. The states of refractoriness are related to the ability of ion channels to recover from a stimulus. This recovery is both voltage- and time-dependent. Lower middle panel: K+ currents during one action potential. All K+ currents (ITO, IKs, IKr, and IK1) repolarize the myocyte because of outward K+ movement. Bottom panel: Ca2+-related currents during one action potential. Because of the inward movement of Ca2+, Ca2+ current (ICa) is depolarizing. The Na/CaX produces both outward and inward current (INa,Ca) depending on the phase of the action potential. The inward Na+ current is roughly 8–10 times the size of the Ca2+ current and has largely inactivated by the time of the peak Ca2+ current.

16.1.2 Cardiac physiology 3261 larger the more positive the displacement from EK. However, the IK1 current flows through a channel that first increases its conductance but then decreases it as the cell depolarizes away from EK (anomalous rectification). Thus, there is outward flow of repolarizing current only over a narrow voltage range (around −30 to −80 mV)—another reason for the prolonged cardiac action potential because a large, rapid, outward K+ current does not flow despite the membrane po- tential approaching 0 mV during the plateau phase. IK1 is responsible for the main (background) flow of K+ giving rise to the membrane potential. The channels through which IK1 flows are numerous in ventricular cells, fewer in atrial cells, and absent in pacemaker cells. The current is therefore large in ventricular cells and this is the reason that the resting membrane potential of ven- tricular myocytes lies near EK, whereas atrial cells have a more posi- tive (less negative) resting membrane potential, and SA nodal cells do not have a stable resting potential. Table 16.1.2.2 Plasma membrane currents in the cardiac myocyte Current Name/Ion Activated by Blocked by Gene Protein Function Inward currents INa (Fast) Na+ current; Na+ Depolarization Tetrodotoxin, local anaesthetics SCN5A Nav1.5 Rapid upstroke of action potential (phase 0) ICa,L L-type Ca2+ current (‘long-lasting’); Ca2+ Depolarization Verapamil, Cd2+, dihydropyridines CACNA1C Cav1.2 Ca2+ influx that activates CICR, provides some Ca2+ for contraction (phase 0–2) ICa,T T-type Ca2+ current (‘transient’); Ca2+ Activates on depolarization but at more negative potentials than
L-type current Ni2+, mibefradil CACNA1G CACNA1H Cav3.1 Cav3.2 Channel density high in pacemaker and conducting tissue so may contribute to pacemaker activity (phase 4). Role in ventricular cells unclear (phase 2) If Hyperpolarization- activated, cyclic nucleotide-gated cation channel; Na+, K+ Hyperpolarization, noradrenaline, cAMP, autonomic nervous system Cs+, ZD7288, ivabradine, zatebradine, cilobradine HCN2 HCN4 HCN2 HCN4 Exists in sinoatrial node and Purkinje fibres bringing membrane potential slowly to threshold (phase 4); also known as ‘funny’ current Inward and outward (reversible) current INa/Ca Na/CaX current;
Na+, Ca2+ Ca2+ i (Na+) Ni2+, KB-R7943 NCX1 SLC8A1 NCX 3Na+-1Ca2+ exchange. Expels Ca2+ from the cell, maintains inward current flow near end of action potential, at positive potentials may reverse and mediate Ca2+ influx (phase 3, 4) Outward currents ITO Transient outward current; K+ (ITO1); Cl- (ITO2) Depolarization 4-Aminopyridine KCNA4 KCND2 KCND3 Kv1.4 Kv4.2 Kv4.3 Early repolarization (phase 1; notch) ICl Chloride current; Cl- cAMP CFTR Early repolarization ICl,Ca Ca2+-activated chloride current Ca2+ CLCA1 Early repolarization IKur Ultra-rapid delayed rectifier; K+ Depolarization Tetraethylammonium, Cs+, Ba2+, 4- aminopyridine, flecainide, nifedipine, diltiazem, bupivacaine, propafenone, quinidine KCNA5 Kv1.5 Repolarization of cell (phase 1, 3) IKr Rapid delayed
rectifier; K+ Depolarization Tetraethylammonium, Cs+, Ba2+, E-4031, dofetilide, D-sotolol, cisapride, BRL32872 KCNH2 hERG hERG, Kv11.1 Repolarization of cell (phase 2, 3) IKs Slow delayed rectifier; K+ Depolarization Chromanol 293B KCNQ1 KvLQT1 Kv7.1 Repolarization of cell (phase 2, 3) IK1 Inward (anomalous) rectifier; K+ Depolarization from EK Conductance of channel increases then decreases to zero at 0 mV Cs+, Rb+, Ba2+, intracellular Mg2+, spermidine, spermine KCNJ2 KCNJ12 Kir2.1 Kir2.2 Prolongs action potential duration, background K+ conductance. (phase 3, 4) Ip Na+/K+ pump current (INaK); Na+, K+ Na+ i, K+ o Cardiac glycosides ATP1A1 3Na+-2K+ ATPase exchanger. Maintains low [Na+]i IK,ACh Acetylcholine- activated K+ current (inward rectifier); K+ ACh, parasympathetic nerves Ba2+ KCNJ3 KCNJ5 Kir3.1 Kir3.4 Muscarinic receptor-coupled. Activates additional K+ channels so slowing pacemaker potential (phase 3, 4) IKATP ATP-activated K+ current; K+ ATP, nicorandil KCNJ11 Kir6.2 (SUR2A) Cardiac ATP homeostasis and metabolic matching (phase 1, 2); SUR subunits are sulphonylurea receptors

 Phase 4 of the action potential This phase relates to the membrane potential during the electric- ally silent period between excitatory events in ventricular myocytes (Fig. 16.1.2.5); phase 4 is stable in these cells. Besides the underlying IK1 activity, it is accompanied by an electrogenic active sodium- potassium exchange giving rise to a Na+/K+ pump current (IP). Differences in ion channel distribution alters the stability of phase 4 due to differing ionic currents and leading to spontaneous depolar- ization associated with pacemaker activity (‘pacemaker potential’). Regional variations in action potential The configuration of the cardiac action potential differs regionally within the heart (Fig. 16.1.2.6) because ion channel expression varies between cells. In the sinoatrial node, INa is very small and the main current responsible for the depolarizing upstroke is ICa, car- ried mainly by L-type Ca2+ channels (ICa,L). The only repolarizing current is IK. IK1 is absent and, as mentioned earlier, this partially explains why sinoatrial node cells have a more depolarized ‘diastolic’ potential than ventricular myocytes. Sinoatrial node cells depolarize spontaneously during phase 4 (Fig. 16.1.2.6), owing to the absence of IK1 and the presence of a current activated on hyperpolarization called the ‘funny’ current (If), carried mainly by Na+ through hyperpolarization-activated cyclic nucleotide-gated (HCN) chan- nels, but also current (ICa,T) resulting from an influx of Ca2+ through voltage-dependent T-type (‘transient’) Ca2+ channels (abundant in these cells; see Table 16.1.2.2). Phase 4 is often termed the ‘pre- or pacemaker potential’ in nodal cells and is caused by the gradual de- crease in IK and increase in If and ICa,T (Fig. 16.1.2.6). Once the cell has depolarized to a voltage at which L-type Ca2+ channels open (the threshold), a more rapid depolarization (caused by ICa,L) oc- curs, forming the upstroke (phase 0) of the sinoatrial node action potential. Acetylcholine (ACh) activates IK,ACh, which helps drive the membrane potential towards EK and slows the rate of depolarization, while β-adrenergic stimulation increases the slope of the pacemaker potential and heart rate through an effect on If, affecting heart rate (Fig. 16.1.2.7). Atrial and ventricular myocytes do not have pacemaker poten- tials and spontaneously discharge only when injured or when there is abnormal ionic balance. The longest action potential is in Purkinje fibres (Fig. 16.1.2.6) and this acts as a ‘gate’ preventing retrograde activation by depolarization of adjacent ventricular myocytes. The mechanism of myocyte contraction Excitation–contraction coupling The electrical events throughout the heart initiate and regulate con- traction (Fig. 16.1.2.5). Coupling of the electrical excitation of the heart to contraction (termed excitation–contraction coupling or EC coupling) by Ca2+ ions involves the interaction of several proteins involved in Ca2+ homeostasis (Fig. 16.1.2.3). The T-tubules carry depolarization deeply into the cell. During diastole (phase 4), when cytoplasmic Ca2+ concentrations are low (c.0.1 μmol/litre), Ca2+ is sequestered by the Ca2+-buffering protein calsequestrin within the JSR. Depolarization (phase 0) then opens the L-type Ca2+ chan- nels in the T-tubule and plasma membrane allowing influx of Ca2+ (Figs. 16.1.2.3 and 16.1.2.5) and producing ICa (Fig. 16.1.2.5). Ca2+ influx increases the local cytoplasmic Ca2+ concentration around clusters of SR Ca2+-release channels in the JSR sufficiently to open them (i.e. CICR), the number of channels activated in this way being mainly, though not exclusively, determined by the size of the Ca2+ Sinoatrial node Threshold potential 0 mV –50 mV –80 mV Atrial muscle Atrioventricular node Purkinje fibre Ventricular muscle 0 mV Fig. 16.1.2.6 Regional configurations of the action potential. In the sinoatrial (SA) and atrioventricular (AV) nodes, the cells spontaneously depolarize during diastole (phase 4 depolarization). When the membrane potential reaches a threshold, the complete action potential is initiated. Because the SA nodal cells have the fastest phase 4 depolarization, they act as the cardiac pacemaker. Adrenergic stimulation Threshold 0 – 50 Membrane potential (mV) Pacemaker potential Threshold 0 – 50 Membrane potential (mV) Cholinergic stimulation Normal rate Normal rate Fig. 16.1.2.7 Change in heart rate

produced by altering the phase 4 slope of the pacemaker potential in the sinoatrial (SA) node. β-Adrenergic stimulation increases (increased If), and cholinergic stimulation decreases (increased IK, ACh), the slope of the pacemaker potential, affecting the time taken to reach threshold.

16.1.2 Cardiac physiology 3263 current. CICR provides amplification, as the small ‘trigger’ Ca2+ in- flux through the L-type Ca2+ channels evokes a much larger release of Ca2+ from the SR into the cytoplasm; also, the release of Ca2+ from the SR is under precise control as it is closely matched to the amount of Ca2+ influx. Cytoplasmic Ca2+ concentration rises to between 1 and 3 μmol/litre (Fig. 16.1.2.5). The release of Ca2+ eventually ceases because the L-type Ca channels inactivate, so the trigger influx de- clines, leading to closure of SR Ca2+ release channels. The mechanism of myofibrillar contraction Ca2+ release from the SR activates the contractile apparatus of the sarcomere (Figs. 16.1.2.2 and 16.1.2.8). The temporal relationship between the action potential, the Ca2+ transient, and the subse- quent development of tension is shown in Fig. 16.1.2.9. Sarcomere shortening is caused by the interaction of motor protein myosin in the thick filaments with actin in the thin filaments (Fig. 16.1.2.8). Myosin heads bind and hydrolyse ATP, retaining bound ADP and phosphate, and trapping the free energy of hydrolysis within the myosin molecule. The myosin–ADP–phosphate complex then binds to actin, leading to the release of the stored energy by a con- formational change that moves the actin filament by about 10 nm relative to the thick filament. This is known as the cross-bridge cycle (Fig. 16.1.2.8) and results in the sliding of the thin filament past the thick filaments, and sarcomere shortening. If the muscle is under load, the cross-bridge cycle generates force and work is done (the maximum efficiency is more than 60% in intact muscle). The mech- anical characteristics of contracting muscle can be described in terms of the relationship between shortening speed and force, and between sarcomere length and force (Fig. 16.1.2.10a). Maximum force is produced under isometric conditions, while maximum shortening speed is observed in unloaded muscle. Power output is the product of force and velocity and is optimal at about 30% of max- imum shortening speed (Fig. 16.1.2.10a). The isometric force produced by a muscle depends on the sarco- mere length, being optimal at 2.00–2.25 μm where the overlap of thick and thin filaments is optimal and such that all the myosin cross-bridges can interact with actin (Fig. 16.1.2.10b). In the heart, the sarcomere length is generally less than optimal, with ‘preload’ stretching the sarcomere to 2.1 μm at the end of diastole and the sarcomere shortening to 1.6 μm during systole. In this length range, stretching the cardiac muscle when it is relaxed leads to increased force in the subsequent contraction. This characteristic is respon- sible in part for the Frank–Starling mechanism of the heart. Control of contraction by Ca2+ Muscle contraction is initiated by an increase in cytoplasmic Ca2+, which binds to the troponin complex of the thin filament. Troponin comprises three subunits. Troponin C is a Ca2+-binding protein; in cardiac myocytes, the thin filament is activated when a single Ca2+ ion binds to troponin C. Troponin I is the inhibi- tory subunit. In relaxed muscle, the Ca2+ concentration is low and troponin I binds to a site on actin which blocks the binding of myosin cross-bridges, thus preventing cross-bridge cycling. In the presence of activating Ca2+ concentrations, Ca2+ binds to troponin C which then binds troponin I, preventing its interaction with actin, permitting actin–myosin interaction. The third compo- nent, troponin T, binds to troponin C and troponin I and also to tropomyosin, independently of the Ca2+ concentration, thereby anchoring the regulatory complex on the thin filament (Fig. 16.1.2.2). There are cardiac-specific isoforms of troponin I and troponin T, while troponin C is present in heart as the isoform found in skeletal muscle. The tropomyosin lies in a groove be- tween actin filaments, inhibiting interaction between actin and Action potential Force Ca transient Fig. 16.1.2.9 The relationship between the ventricular action

potential, the Ca2+-transient and the generation of force. The peak of force production is not achieved until near the end of the plateau phase of the action potential and lags behind the peak of the Ca2+-transient, reflecting the time required for Ca2+-induced Ca2+-release and cross-bridge cycling. (a) (e) (d) (b) (c) ADP ADP Pi Pi ATP actin filament myosin head myosin filament ATP
Fig. 16.1.2.8 The cross-bridge cycle. Exchange of ATP with ADP (a) on either a load-bearing (b) or a resting-length myosin head (c) results in a conformational change in the myosin head, causing a rapid dissociation of the myosin head from actin ((b) to (d) and (c) to (d), respectively). Following detachment from actin, the ATP is hydrolysed to ADP and Pi, both of which remain tightly bound to the myosin head (e). Hydrolysis is accompanied by a major conformational change which represents the reversal or a repriming of the power stroke. If an actin site is within reach of the myosin head, it will bind rapidly and reversibly to the actin site (a). When the myosin head binds actin, the interaction can promote a major change in conformation (the power stroke) which is accompanied by the dissociation of Pi ((a) to (b)). This step approximates to isometric contraction (no relative movement of actin and myosin), whereas the (a) to (c) steps approximate to an isotonic contraction (relative movement, with a release of the myosin 'spring'). This power stroke consists of a reorientation of part of the myosin head that results in the displacement of the tip by up to 10 nm. Reproduced with permission from S. Weiss and M. A. Geeves.

 myosin heads. Ca2+ binding to troponin C induces a conform- ational change, resulting in a shift of the tropomyosin in the actin groove and exposing the myosin head-binding sites. The Ca2+-sensitivity of cardiac myocytes is increased by stretch, promoting relaxation at the start of diastole (short sarcomere lengths) and activating contraction at the start of systole (long sarco- mere lengths). Moreover, this 'stretch activation' is delayed so that the enhanced contractility is synchronized with systole, thus con- tributing to the Starling effect.
Termination of contraction Sarcoplasmic/endoplasmic reticulum ATPase type 2 (SERCA 2) Contraction is terminated predominantly by Ca2+ reuptake into the SR by activation of SERCA2, an ATP-requiring Ca2+ pump expressed in the network of nonjunctional SR surrounding the myofibrils (Fig. 16.1.2.3a). SERCA2 activity is regulated by the extent of phosphor- ylation of the SERCA2-associated protein phospholamban associ- ated with the activities of protein phosphatase-1, inhibitor-1 and PKCα, together with covalent modification by SUMOylation and acetylation. The Na+/Ca2+ exchanger (Na/CaX) and the Na+/K+-ATPase The sarcolemmal Na/CaX antiporter contributes to lowering cyto- plasmic Ca2+ during the latter part of the action potential (phases 3 and 4) and during diastole (Fig. 16.1.2.5 and Table 16.1.2.2). Its activity is regulated by Ca2+ i through a large intracellular loop con- taining two Ca2+-binding domains. The Na/CaX utilizes the energy associated with the concentration and electrical gradients for Na+ to expel Ca2+ from the cell. It is electrogenic, promoting depolar- ization under these conditions. The exchange is sensitive to Na+ i concentration: when membrane potential is near its diastolic level and Na+ i is at normal physiological concentration, the Na/CaX will eject Ca2+ from the cell; if Na+ i increases by a few mmol/litre and the membrane potential becomes depolarized, the exchanger can re- verse and mediate Ca2+ entry. The sarcolemmal Na+/K+-ATPase is responsible for Na+ i extru- sion. Cardiac glycosides (e.g. digoxin) inhibit the Na+/K+-ATPase, preventing Na+ extrusion, which indirectly reverses the Na/CaX into Ca2+ o uptake mode. Under these conditions, Ca2+ uptake by the SR may be increased, thereby augmenting the cardiac Ca2+ pool and facilitating CICR. The net effect of the cardiac glycosides is to increase the cytoplasmic concentration and availability of Ca2+ re- sulting in an increased force of contraction (positive inotropy). Ventricular myocytes possess other minor systems to decrease cytoplasmic Ca2+ concentrations, including

the plasma membrane Ca2+ ATPase and mitochondrial Ca2+ uptake. SERCA2 and Na/CaX contribute about 70% and 25%, respectively, towards relaxation, though these figures vary greatly between species. Whole organ physiology The cardiac cycle Electrical events initiate the cardiac cycle with depolarization of the sinoatrial (SA) node in the upper right atrium (Fig. 16.1.2.11). Cardiac muscle acts as a functional syncytium. Communication between neighbouring cells is mediated by gap junctions which form arrays of cell-to-cell channels. The generated action potential spreads from the sinoatrial node across the functional syncytium at a speed of 1.0–1.2 m/s. The first mechanical response is atrial systole. The atria comprise a single functional syncytium, and the vent- ricles also comprise a single, separate, syncytium. These two syncytia are not contiguous with each other and not capable of activating each other directly. The conduction of the electrical impulse from atrium to ventricle normally occurs only through the atrioven- tricular (AV) node (Fig. 16.1.2.11), a region of slow conductance at 0.02–0.1 m/s. This delays activation of the cells of the bundle of His (a) 1.0 0.5 0 0 0.5 1.0 Velocity Force Power 100% 0% 1.0 1.5 2.0 1 1 2 3 4 2 3 4 2.5 3.0 3.5μm Tension (b) Fig. 16.1.2.10 Force–velocity–power relationship in cardiac muscle. (a) Force–velocity relationship (red symbols, black line). Maximum force is produced under isometric conditions (velocity V = 0), while maximum shortening speed is observed in unloaded muscle (force P = 0). The power-velocity relationship (blue symbols, green line) is a parabola with maximum power being produced at an intermediate force and velocity. (b) Length–tension relationship in cardiac muscle. At sarcomere length greater than 2.0 μm (examples 2, 3), isometric tension depends on the amount of overlap between myosin cross-bridges and actin filaments. At shorter sarcomere lengths (down to 1.6 μm; example 1), tension is reduced because of interference of thin filaments from opposite ends of the sarcomere. Below 1.6 μm sarcomere length, myosin filaments interfere with the Z-line and tension falls rapidly. The range of sarcomere lengths during a normal cardiac cycle is shown in blue. Actin filaments: grey; myosin filaments: red.

16.1.2 Cardiac physiology 3265 arising from the AV node and allows time for completion of ven- tricular filling. The conduction velocity in the bundle of His is from 1.2 to 2.0 m/s. The impulse passes via the right bundle branch and the two branches (anterior and posterior) of the left bundle, and spreads rapidly (2.0–4.0 m/s) through the Purkinje fibres and each muscle cell to produce an orderly sequence of ventricular contrac- tion (Fig. 16.1.2.11). Atrial and ventricular depolarization (P wave and QRS complex, respectively) and repolarization (T wave) can be recorded on the ECG (Fig. 16.1.2.12). While the recorded ECG is a summation of all the individual ac- tion potentials of the myocytes, the ECG voltage is much less than direct action potential recordings (about 1 mV compared to about 100 mV) because of the resistance of body tissues between the heart and the ECG electrodes. The specialized cells of pacemaker tissue have an inherent rhythmicity (unstable phase 4 membrane poten- tial) that is shared by the sinoatrial node, the atrioventricular node, and Purkinje tissue. Unlike other myocardial cells, these cells do not maintain a diastolic intracellular potential of about −90 mV but tend to depolarize spontaneously. Because the sinoatrial node has the fastest inherent discharge (depolarization) rate, and because there is a brief period after depolarization of the whole heart during which a further stimulus is ineffective—the absolute refractory period—the sinoatrial node is normally the pacesetter for the heart. However, if this does not occur, pacemaker tissue in the atrioventricular node, the bundle of His, or the Purkinje system will assume this role, in which case the heart rate is then considerably slower. Mechanical events The mechanical events following depolarization of the atrial and ventricular muscle and their timing in relation to the ECG, to pres- sure and flow changes, and to heart sounds are shown in five phases in Fig. 16.1.2.13. After the P wave, and coinciding with atrial sys- tole, ‘a’ waves appear in

left atrial and right atrial pressure tracings due to atrial contraction, and an ‘a’ wave can be seen in the jugular venous pulse. Atrial contraction increases ventricular filling by about 10% (phase 1). The onset of ventricular contraction coincides with the peak of the R wave of the ECG; a rapid rise in intraventricular pressure closes the mitral and tricuspid valves, causing the first heart sound; mitral valve closure slightly precedes tricuspid valve closure and two components of the first heart sound may be heard (M1-T1). During this short isovolumetric period (phase 2 of Fig. 16.1.2.13), the pressure rises rapidly in the ventricles. When ventricular pres- sures exceed those in the pulmonary artery and aorta, the outflow valves open and ventricular ejection follows. The highest flow rate is in early systole, and pressures in the aorta and pulmonary artery rise. Normally, between 50 and 70% of the ventricular volume is ejected during systole (the ejection fraction), and this can be seen in the volume curve included in Fig. 16.1.2.13 (phase 3). The jugular venous pulse, during ventricular contraction, has a positive deflection in early systole, the ‘c’ wave, due to right ven- tricular contraction and bulging of the tricuspid valve into the right atrium. Descent of the tricuspid ring caused by ventricular contrac- tion then produces a negative ‘x’ descent, but as atrial inflow con- tinues the pressure rises in the atria and great veins, producing the ‘v’ wave. This reaches its peak just before the opening of the tricuspid valve, declining during early ventricular filling as the negative ‘y’ des- cent. The changes in the pulmonary veins and left atrium are similar. As the strength of ventricular contraction declines in late systole, coinciding with the end of the T wave, the aortic and pulmonary valves close, producing the dicrotic notch seen on both aortic and pulmonary artery pressure tracings in Fig. 16.1.2.13. Aortic closure slightly precedes pulmonary closure, and together these are respon- sible for the two components of the second heart sound (A2-P2). A short period of further rapid decline in ventricular pressure ensues without change in the ventricular volume (the period of isovolumetric ventricular relaxation, phase 4), and at the end of this the mitral and tricuspid valves open. Valve opening is not normally audible. There is a pressure gradient from atrium to ventricle so that a period of Aorta Right bundle branch Anterior fasicle Purkinje system Posterior fasicle Left bundle branch Sinoatrial node Atrioventricular node Bundle of His Superior vena cava Fig. 16.1.2.11 Diagram of the heart showing the impulse-generating and impulse-conducting systems. From Junqueira LC, Carneiro J, (2005). Basic histology, 11th edn. McGraw-Hill, New York. 10 mm 1 mm Voltage (in mV) Seconds S P R T U P VAT Isoelectric line 1.0 0.5 0 PR segment ST segment Q–T interval 0.04 0 0.2 0.4 0.6 0.8 1.0 QRS interval Q P–R interval Fig. 16.1.2.12 Diagram of electrocardiographic complexes, intervals, and segments. VAT, ventricular activation time. From Goldschlager N, Goldman MJ (1989). Principles of clinical electrocardiography, 13th edn. Appleton and Lange, East Norwalk, CT.

 rapid ventricular filling follows, which coincides with the timing of the third heart sound. The rapid ventricular filling is reflected in the shape of the ventricular volume curve and is followed by a period of slower filling (phase 5), with a final sudden small increment from the next atrial contraction as ventricular diastole ends (phase 1). Third heart sounds are normally audible in children and young adults, but over the age of about 40 years this usually indicates ele- vation of ventricular end-diastolic pressure (most frequently in the left ventricle). The myocardium and valvular structures become stiffer with ageing, and large increases in ventricular end-diastolic pressure are then required to tense valvular structures and generate audible vibrations. A fourth heart sound usually indicates abnormal ventricular function, with increased end-diastolic pressure. A fourth heart sound precedes the Q wave of the ECG, which must be distin- guished from a normal splitting of the two components of the first heart sound. The latter occurs after the Q wave (Figs. 16.1.2.12 and 16.1.2.13). Normal volumes, pressures,

and flows The blood volume in normal adults is about 5 litres (haematocrit 45%), and, of this, about 1.5 litres are in the heart and lungs—the central blood volume. The pulmonary arteries, capillaries, and veins contain about 0.9 litres, with only about 75 ml being in the pulmonary capillaries at any one instant. The volume of blood in the heart is about 0.6 litres. Left ventricular end-diastolic volume is about 140 ml, stroke volume about 90 ml, and end-systolic volume around 50 ml, reflecting an ejection fraction (stroke volume/end- diastolic volume) of between 50 and 70%. The right ventricular ejec- tion fraction is similar. Of the 3.5 litres in the systemic circulation, most—at least 60% of the total blood volume—is in the veins. The systemic veins con- taining most of the blood volume are thin-walled and easily disten- sible, and input of blood into the contracting heart is associated with only small changes in venous pressure: they act as a blood volume reservoir or 'buffer'. By contrast, ejection of blood into the much less distensible arterial tree produces large pressure changes. The normal values for pressures generated in the heart and great vessels during the cardiac cycle are shown in Table 16.1.2.3. Pressures are measured with reference to a zero pressure empir- ically set at 5 cm below the sternal angle with the patient recum- bent. 'Normal' arterial blood pressure is considered later (see next, 'Regulation of systemic arterial blood pressure'). Cardiac output is the product of stroke volume and heart rate (stroke volume = end-diastolic volume – end-systolic volume). It is related to body size and is best expressed as litre/min per m2 of body surface area: the 'cardiac index'. The mean cardiac index under resting and relaxed conditions is 3.5 litre/min per m2, and values below 2 and above 5 are abnormal. The cardiac index de- clines with age. In persons of average size, resting whole body oxygen consumption is about 240 ml/min, and the difference in oxygen content between arterial and mixed venous blood is about 40 ml/litre (arteriovenous oxygen difference), giving a basal car- diac output of 6 litre/min. In normal subjects, the arteriovenous difference in oxygen content at rest is maintained within narrow limits, from 35 to 45 ml/litre; values of 55 ml/litre and above are always abnormal. Pulmonary or systemic vascular resistance is estimated by dividing the difference between mean inflow pressure (pulmonary artery or aortic) and mean outflow pressure (left atrial or right atrial, usually in mm Hg) by the flow (usually in litre/min) through the respective circulations. In normal subjects and patients without intracardiac shunts, this flow is the cardiac output. Normal pulmonary vascular resistance is less than 2 mm Hg/litre per min (hybrid resistance units, Wood units; equivalent to 16 MPa.S.m−3, 160 dyn.S.cm–5). Arterial blood pressure is the product of cardiac output and total peripheral (systemic) resistance. Stroke work is the integral of instantaneous ventricular pressure with respect to stroke volume, but is usually estimated as the product of stroke volume and mean ejection pressure. The orderly sequence of contraction in the normal cardiac cycle coordinates changes in Ventricular and aortic pressure (mm Hg) Ventricular volume (ml) Aortic blood flow (l/min) Pressure (mm Hg) Phases of cardiac cycle Carotid pressure (n = dicrotic notch) Radial pressure Left ventricular volume (at c′ , the mitral valve closes; at o′ , it opens) Right atrial pressure (left is similar) Jugular venous pressure, showing a, c, and v waves Pulmonary arterial pressure Right ventricular pressure 0 130 65 0 5 3 0 30 15 0 1 2 3 4 5 P R T U 1 2 3 4 o c a v n n c Diastole Atrial systole Ventricular systole Time (s) Electrocardiogram Heart sounds (phonocardiogram) Aortic pressure (at o, the aortic valve opens; at c, it closes) Left ventricular pressure 0 0.2 0.4 0.6 0.8 120 80 40 o′ c′ Fig. 16.1.2.13 Events of the cardiac cycle at a heart rate of 75 beats/ min. The phases of the cardiac cycle, identified by the numbers at the bottom, are: (1) atrial systole; (2) isovolumetric ventricular contraction; (3) ventricular ejection; (4) isovolumetric ventricular relaxation; and (5) ventricular filling. Note that aortic pressure actually exceeds left ventricular pressure in late systole, but the momentum of the blood keeps it flowing out of the ventricle for a short time before the aortic valve is eventually forced shut, causing the

second heart sound. The pressure relationships in the right ventricle and pulmonary artery are similar. The jugular venous pulse is similar in form to that seen in the right atrial pressure tracing. The ‘c’ wave interrupts the ‘x’ descent of the ‘a’ wave. The decline in pressure from the peak of the ‘v’ is the ‘y’ descent; the rate of decline reflects speed of ventricular filling. Modified with permission from Ganong WF (2005). Review of medical physiology, 22nd edn. McGraw-Hill, New York.

16.1.2 Cardiac physiology 3267 instantaneous pressure and flow, so maximizing the transfer of energy to the circulation. Normal left ventricular work output at rest is about 6 kg/m2 per min. Myocardial mechanics When a muscle is activated to contract, it develops a potential for doing work. In isolated skeletal and heart muscle preparations, the stretching force applied to the muscle—and therefore the length of the muscle—can be varied before contraction; this is the preload. The activated muscle will begin to shorten when it has generated a force sufficient to overcome that exerted by the attached weight or load against which it contracts. When the force exerted by the load is so arranged that it is not applied to the relaxed muscle and is ap- plied only after the muscle has begun to develop tension, it is termed the afterload. If this load is so large that the activated muscle is un- able to overcome it, and so cannot shorten, the contraction produces tension only, and the contraction is isometric. When shortening does occur, external work is done. If the load is constant during the shortening, the contraction is said to be isotonic; if it changes, it is auxotonic. The tension produced by both skeletal and cardiac muscle during contraction depends on initial fibre length; during afterloaded iso- tonic contractions from a particular length, the amount and the speed of fibre shortening, and the tension developed, all depend upon the afterload. Over a range of loads the initial velocity of muscle shortening is most rapid and the most extensive shortening occurs when the load is smallest. The inverse relationship between initial velocity of fibre short- ening and load in an isotonic contraction is a fundamental one for both skeletal and cardiac muscle. There is, however, a major differ- ence between the two types of muscle in that the relationship at any one given length is constant in a skeletal muscle, whereas in cardiac muscle there are variations in inotropic state that are accompanied by considerable changes in the relationship between force and velocity. A positive inotropic effect produces a more extensive contraction from the same initial length and afterload, and a faster maximum velocity of shortening (Vmax). An increase in initial fibre length with no increase in inotropic state increases the force of contrac- tion but does not, however, change the maximum velocity of short- ening. This means that the force of contraction of cardiac muscle varies with fibre length ((pre-)loading)—for example, heterometric regulation, an aspect of the Frank–Starling relationship—but con- tractile force also independently varies with the ‘intrinsic’ contract- ility of the cardiac muscle fibre (inotropy)—homeometric regulation. This is illustrated in Fig. 16.1.2.14. The contraction of the intact heart can be visualized as being similar mechanically to the afterloaded contraction of an isolated muscle strip. For the left ventricle, the preload is the distending force which stretches the muscle fibres in end-diastole (i.e. a func- tion of ventricular filling), and the initial afterload is the force the ventricle must generate in order to open the aortic valve and eject blood against the systemic vascular (total peripheral) resistance. At the end of ejection, the ventricular muscle is isolated from the peripheral circulation, with the afterload then supported by the competent aortic valve, and the muscle relaxes against a compara- tively small force. Relaxation of the heart is an active process due to ATP-dependent withdrawal of calcium ions from the cytoplasm surrounding the myofibrils. ‘Active’ relaxation is still proceeding in the ventricular wall when the atrioventricular valves open, and, if it is delayed—as in the hypoxic

heart—the slower relaxation in- creases the stiffness of the ventricular wall and impedes filling. Wall thickness is also a determinant of compliance and relaxation rate. For this reason, filling pressures are higher for the thicker and stiffer left ventricle than for the thinner and more distensible right ventricle (Table 16.1.2.3). When the left ventricle is hypertrophied Table 16.1.2.3 Normal resting values for pressures in the heart and great vessels Site Systolic pressure (mm Hg) Diastolic pressure (mm Hg) Mean pressure (mm Hg) Right atrium ‘a’ up to 7, ‘v’ up to 5 ‘y’ up to 3, ‘x’ up to 3 Less than 5 Right ventricle Up to 25 End pressure before ‘a’ up to 3;
end pressure on ‘a’ up to 7 Not applicable Pulmonary artery Up to 25 Up to 15 Up to 18 Left atrium (direct or indirect
pulmonary artery/capillary wedge) ‘a’ up to 12, ‘v’ up to 10 ‘x’ up to 7, ‘y’ up to 7 Up to 10 Left ventricle 120 End pressure before ‘a’ up to 7;
end pressure on ‘a’ up to 12 Not applicable Vmax Poa Pob Poc Force (afterload) Velocity of shortening a b c Fig. 16.1.2.14 Idealized relationships between velocity of fibre shortening and afterload or force developed during contraction of a strip of cardiac muscle under three different conditions. Curves a and b were obtained with the muscle in the same inotropic state but with a longer initial fibre length (greater preload) for curve b. Curves b and c were obtained with initial fibre length the same but with contractility increased in c by the addition of a drug producing a positive inotropic effect. The terms Vmax and P0 describe, respectively, a hypothetical maximum shortening velocity in the absence of any load (hence the broken lines), and the force developed in an isometric contraction. An increase in initial fibre length increases P0 but not Vmax; a positive inotropic change increases both P0 and Vmax.

 due to chronic pressure overload, as in systemic hypertension or aortic stenosis, it becomes stiffer and filling pressures may then be abnormally high. Myocardial metabolism The heart depends on oxidative metabolism to synthesize sufficient ATP to supply its energetic needs, including the generation of ionic gradients and cross-bridge cycling. In the normal myocardium about 70% of energy is derived from lipid oxidation and about 30% from glucose oxidation, with glycolysis contributing relatively minor amounts of ATP anaerobically. Of plasma lipids utilized for oxida- tion by the heart, nonesterified (‘free’) fatty acids (NEFA) are an im- portant energy source, especially in starvation and exercise when their plasma concentration is increased, but substantial fatty acid supply is also derived from circulating triacylglycerols (triglycer- ides; TAG) in plasma, including those contained in very low density lipoprotein and, in the post-prandial state, chylomicrons. Lipolysis of TAG in the lipoprotein particles is achieved by ac- tivity of the enzyme lipoprotein lipase (LPL), expressed in high copy number in the myocardium. LPL monomers are synthesized in the cardiomyocytes but are translocated in their active (dimer- ized, glycosylated) forms to their physiological site of action on the luminal surface of coronary endothelium, to which they are at- tached by a GPIHBP1 (glycosylphosphatidyl inositol-HDL binding protein 1)-heparan sulphate proteoglycan anchor (and from which they can be detached by heparin). Fatty acids liberated from TAG by LPL are assimilated into the underlying cardiomyocyte via fatty acid transporters (including fatty acid translocase; FAT/CD36), possibly by the same route as NEFA, where they undergo mito- chondrial β-oxidation for ATP production. Besides fatty acids and glucose, the heart can also readily oxidize lactate (in the presence of adequate oxygen provision) and ketone bodies (acetoacetate, 3-hydroxybutyrate) as well as amino acids. The cardiomyocyte is rich in mitochondria (Fig. 16.1.2.1). Cardiac substrate selection is partly a function of plasma sub- strate concentration and plasma metabolic hormonal milieu, but it changes characteristically in cardiac and metabolic disease. In

ventricular hypertrophy, myocardial metabolism reverts to a more fetal pattern of increased glucose utilization and diminished lipid oxidation. A similar pattern may also be seen in cardiac failure of diverse aetiologies. An explanation for this phenomenon is that since fatty acid molecules are more reduced and glucose mol- ecules more oxidized (and some ATP can be derived from glucose by anaerobic substrate-level phosphorylation in glycolysis), greater amounts of oxygen are required to oxidize lipids than carbohydrates (glucose: 3.7 mol ATP/mol O2; palmitate: 2.8 mol ATP/mol O2), hence switching from fatty acid to glucose utilization may increase myocardial oxidative efficiency. By contrast, in diabetes mellitus lack of insulin or its signalling results in decreased glucose up- take (myocardium expresses insulin-sensitive GLUT-4 as well as GLUT-1 glucose transporters) and oxidation by cardiomyocytes, with increased reliance on fatty acid utilization in keeping with the increased circulating lipids. This may lead to decreased efficiency of the diabetic myocardium and has been suggested as the mechanistic basis of diabetic (nonischaemic) cardiomyopathy. By contrast to cardiomyocytes, the conducting system of SA and AV nodes and the His–Purkinje cells relies more on anaerobic gly- colysis for its energy provision. Regulation of cardiac function Four essential factors determine the performance of the heart: (1) venous return, (2) outflow resistance (afterload), (3) inotropic state or contractility, and (4) heart rate. Changes in cardiac per- formance are accomplished by mechanisms that alter these four determinants. Venous return, preload, and the Frank–Starling relationship The relationship described independently by Frank and Starling between end-diastolic fibre length and force of contraction is shown in Fig. 16.1.2.15 and is the mechanism underlying the in- trinsic ability of the heart to eject whatever blood volume (within limits) it is presented with, and hence to match RV output precisely with LV output. When the ventricle ejects against a constant pres- sure, variations in venous return alter the degree of stretch of the muscle fibres in diastole, and this determines contraction strength and work output. The number of active force-generating sites in each fibre increases as it lengthens so that, within limits, the force of contraction and stroke work are positively related to end-diastolic fibre length (heterometric regulation). The relationship is curvi- linear when stroke work is plotted against end-diastolic pressure as an index of preload, reflecting the exponential relationship between end-diastolic pressure and end-diastolic volume. When stroke work is plotted against end-diastolic volume, the relationship between stroke work and preload is linear. The response of the heart at any particular time depends upon: (1) the intrinsic contractile state of the muscle (i.e. the biochemistry and contractile machinery); (2) the prevailing neurohumoral state (e.g. increased sympathetic outflow produces a more forceful con- traction (positive inotropic effect) at any given end-diastolic fibre length); (3) extrinsic inotropic influences—drugs which have either positive or negative inotropic effects. End-diastolic fibre length Stroke work (force of contraction) Positive inotropic effect Negative inotropic effect Fig. 16.1.2.15 The Frank–Starling relationship: the relation between left ventricular end-diastolic fibre length and left ventricular stroke work. Also shown, the displacement upward and to the left with an increase in contractility and downward and to the right with a reduction in contractility. Similar but not identical curves are obtained by plotting left ventricular stroke work as one measure of the force of contraction against ventricular end-diastolic pressure or volume (see text). Similar function curves may be obtained from both ventricles and both atria.

16.1.2 Cardiac physiology 3269 End-diastolic fibre length is determined by the force distending the ventricle at end-diastole, and end-diastolic pressure provides a reasonable indication of this force when the ventricle has normal distensibility or compliance; this is the preload. The systemic venous return and the elastic properties of the myocardium produce the end-diastolic distending pressure

for the right ventricle, and the pul- monary venous return and myocardial elasticity that for the left ven- tricle. For clinical purposes, it is convenient to equate venous return with preload because, as it changes from beat to beat, it adjusts the strength of the subsequent ventricular (and atrial) contraction by varying the force stretching the relaxed cardiac muscle and changing end-diastolic fibre length. Outflow resistance or afterload Pulmonary and aortic valve opening pressures are determined largely by the pulmonary and systemic vascular resistances, as shown for the latter in Fig. 16.1.2.16. These resistances, together with an inertial component dependent upon the mass of blood within the vessels, the compliance (stiffness) of the vessels, and the physical characteristics of each vascular tree combined with the pul- satile nature of the flow, constitute the impedance to ventricular out- flow. This is the load against which the ventricle must contract and shorten. As this load is not applied in diastole to the relaxed muscle, it then being supported by competent aortic and pulmonary valves, it is described clinically as the afterload: it becomes applied to the muscle only after the ventricle has begun to develop tension. Regulation of systemic arterial blood pressure The regulation of the systemic circulation is well adapted to the vital function of maintaining constant, adequate tissue perfusion. There is a need to maintain a relatively constant arterial blood pressure when there are changes in posture and circulating blood volume. Systemic blood pressure is necessarily relatively high because selective tissue arteriolar tone is used to direct the available systemic blood flow to organs requiring augmented supply of substrate and oxygen as a re- sult of increased work and metabolism; this demands a high tonic arteriolar tone and hence high systemic vascular resistance. Systemic BP = CO × SVR, hence BP is regulated by those factors affecting CO (stroke volume, heart rate), as well as SVR (principally resistance vessel radius). The baroreceptors mediate rapid responses to alter- ations in aortic pressure, while a variety of hormonal and physical factors regulate the circulating blood volume. Baroreceptors The baroreceptor regulatory system comprises two groups of mechano- (stretch) receptors, which are widespread in the thoracic cardiovascular system, with high pressure cardiopulmonary baro- receptors located in the systemic arterial system, and low-pressure volume receptors found in the large systemic veins of the thorax. Of the former, one group is clustered in the carotid sinuses near the bifurcations of the common carotid arteries in the neck, and a second group is located in the arch of the aorta. These respond to an increase in central arterial pressure by the firing of impulses, which pass by the glossopharyngeal (IX) and vagus (X) cranial nerves to the solitary tract nucleus in the medulla and inhibit sympathetic efferent outflow. Efferent impulses from these central connections pass via the right vagus nerve mainly to the sinoatrial node, and via the left vagus mainly to the atrioventricular node. The effect is to decrease the heart rate and the force of atrial contraction. There is also attenu- ation of sympathetic discharge to arteriolar smooth muscle in the limbs and visceral circulation, resulting in a release of peripheral ar- teriolar constriction and, therefore, peripheral vasodilatation. Thus, the immediate response to a rise in arterial pressure is slowing of the heart rate, reduced force of atrial contraction, and reduced vascular resistance. The net effect of this negative feedback system is to offset the elevation in blood pressure. Conversely, lowering blood pressure diminishes stimulation of the stretch receptors and reduces afferent traffic to the solitary tract nucleus, resulting in reduced inhibition of sympathetic outflow. There is, then, a quickening of the heart rate together with peripheral vasoconstriction so that the blood pressure increases. The changes in heart rate take place within 1 to 2 s and changes in vasomotor control within 5 to 6 s. Baroreceptor mechanisms effectively modulate the responses of blood pressure to postural change. Additionally, they adapt to main- tain the normal circadian variation in blood pressure (see ‘Diurnal variation in autonomic function’, later on in this chapter). They also maintain elevated arterial blood pressure in systemic hyperten- sion: the baroreflex acts around a ‘set point’

of blood pressure, and this is altered in systemic hypertension. Sensory input to the reflex is reduced in disorders of the autonomic nervous system (e.g. auto- nomic neuropathy), and in the prolonged weightlessness of space flight. Blood volume The circulating blood volume is relatively small, and a large propor- tion is contained in the veins (capacitance vessels; Fig. 16.1.2.16) so that any change in blood volume will affect venous return and, therefore, cardiac output and blood pressure. When blood volume is large and the veins full, there is little reduction in venous return on standing and cardiac output is maintained. However, when ef- fective blood volume is reduced and the veins are relatively empty, Pressure (mm Hg) 120 80 40 0 Systolic Diastolic TA Aorta Arteries Arterioles Capillaries Venules Veins Vena cava Fig. 16.1.2.16 Diagram of the changes in pressure as blood flows through the systemic circulation. The total cross-sectional area of the vessels (TA) increases from 4.5 cm2 to 4500 cm2 in the capillaries. The major resistance to flow is at the arteriolar level, associated with the greatest decrease in blood pressure. Modified and reproduced with permission from Ganong WF (2005). Review of medical physiology, 22nd edn. McGraw-Hill, New York.

 on standing there is pooling of blood in the veins of the legs and a reduction in venous return and cardiac output, so that arterial blood pressure falls. Baroreceptor responses become evident within a few beats, the heart rate increases, and cardiac output and blood pressure are restored. Circulating blood volume is kept relatively constant by a combination of mechanisms which include systemic venous stretch (volume) receptors in the great veins and atria, together with the actions of natriuretic peptides, the renin–angiotensin–aldosterone system, vasopressin (ADH; AVP), and osmolality. Natriuretic peptides The discovery of secretory granules in the atria of the heart, and the demonstration in 1981 that they produce a natriuretic factor that in- hibits the reabsorption of sodium in the distal tubule of the kidney, enhanced understanding of the regulation of blood volume and car- diac performance. Three natriuretic peptides, all containing a similar 17 amino acid ring structure, have subsequently been identified. • Atrial natriuretic peptide (ANP) is a 28 amino acid peptide pre- sent in the circulation, and concentrations increase during volume expansion. ANP release is also stimulated by vasoconstrictors, atrial tachycardia, endothelin, and sympathetic stimulation of β-receptors. The right atrium contains about 2–4 times as much activity as the left, and release of the hormone is mediated largely by atrial wall distension. The effect is to produce a diuresis and to reduce cardiac and circulating blood volume and hence central venous pressure (i.e. the opposite effect to aldosterone). ANP also has a vasodilator action and opposes the vasoconstricting effects of noradrenaline and angiotensin II (inhibits renin and aldos- terone release). • The second natriuretic peptide was identified in brain tissue and is now referred to as B-type natriuretic peptide (BNP). It is a 32 amino acid peptide, large amounts of which are found in the vent- ricles of the human heart, and circulating levels are increased in ventricular hypertrophy and cardiac failure. B-type and ANP have similar actions. The half-life of B-type is about twice that of ANP, making it easier and more reliable to measure in blood, whence it may be used to diagnose and monitor heart failure. • The third natriuretic peptide to be identified was C-type natriuretic peptide. This is distributed widely in tissues, but circulating con- centrations are low, hence while ANP and BNP have an essentially endocrine role, CNP is considered to be a paracrine effector. It is released by cardiac endothelium and exerts a local vasodilator ef- fect in complement with the NO and PGI2 systems, thereby consti- tuting at least part of the endothelium-derived hyperpolarization relaxant activity. It also acts as a paracrine growth/trophic factor and has anti-inflammatory activity. In brief summary, natriuretic peptides contribute to the regula- tion of cardiac and circulating blood volume and of

blood pressure. Both B-type natriuretic peptide and N-terminal pro-brain natri- uretic peptide (NT-proBNP: an inactive 76 amino acid product of the BNP prohormone, released on BNP cleavage and release) are useful adjuncts to the clinical evaluation of dyspnoeic patients in that levels are elevated when breathlessness is due to cardiac failure. Renin–angiotensin system The renin–angiotensin–aldosterone (RAA) system, which is both local and systemic, is of major importance in the regulation of circulating blood volume and the maintenance of normal blood pressure. Enhanced activity of systemic renin and angiotensin in- creases the production of aldosterone, which promotes reabsorp- tion of sodium by the kidney and expansion of circulating blood volume. All components of the renin–angiotensin system are dis- tributed widely throughout tissues—including the brain and the heart—and increased activation of the system increases the risk of cardiovascular events. Angiotensin II is a potent vasoconstrictor that has a number of additional important actions on the vascu- lature (Fig. 16.1.2.17). The angiotensin-converting enzyme (ACE) inhibitors in clinical use diminish angiotensin II production lo- cally and in the circulating blood, resulting in vasodilatation and decreased blood pressure. They may be used to offload the failing heart (decrease afterload). Both local and general effects appear important in mediating the benefits that accrue from the use of these drugs in the management of hypertension and congestive cardiac failure, and in the reduc- tion in rates of recurrence of coronary events in ischaemic heart disease by retarding the rate of atherosclerosis. The mechanisms mediating the latter include antioxidant effects, decreasing oxida- tive stress by a reduction in the production of potentially damaging free radicals (effects which are independent of blood pressure), anti-inflammatory effects, and augmentation of the profibrinolytic effects of bradykinin. Angiotensin II receptor-blocking drugs have also been shown to produce similar outcomes. Regulation of nitric oxide production A recently recognized contribution to endothelial function, which affects the afterload, is related to nitric oxide production, and its inhibition by asymmetric dimethylarginine (ADMA). Asymmetric dimethylarginine is produced by the physiological degradation of methylated proteins. ADMA inhibits the production of nitric oxide, which is derived directly from l-arginine, present in all cells. ADMA levels are regulated by the balance between its production and its metabolism. The balance may be disrupted in clinical situ- ations, for example, in renal impairment. Reduced renal function increases the level of ADMA and this reduces endothelial dilatation. ADMA concentrations are also increased by low density lipopro- tein (both native and oxidized), hence ADMA-induced blunting of NO-mediated vasodilatation potentially aggravates dyslipidaemic coronary artery disease. Ventricular volume and afterload Ventricular volume also has a major effect on afterload, as pres- sure is equal to force per unit area. The force acting radially on the inner surface of the whole ventricle at any time during systole is the product of the intraventricular pressure and ventricular surface area at that time. If the left ventricle is assumed to be a sphere (surface area = πd2), the force opposing ejection at any time during con- traction is the product of the intracavity pressure and πd2 at that time. Thus, a doubling in left ventricular diameter from a normal value of 5–10 cm would result in a fourfold increase in the force opposing ejection for the same intracavity systolic pressure; the ven- tricle would need to develop greatly increased wall tension to over- come that force. Because wall tension developed during systole is the major determinant of myocardial oxygen consumption, the contrac- tion will clearly be much less efficient in the larger heart for the same stroke volume and ejection pressure (stroke work).

 During a normal heartbeat, the afterload is greatest at the be- ginning of ejection (rapid rise in pressure and maximum volume; Fig. 16.1.2.13), but decreases thereafter as the pressure reaches a plateau and then declines as the ventricle becomes smaller

(i.e. its diameter increases). There is, therefore, a matching of the afterload to the declining intensity of the contraction as it proceeds to com- pletion (end-systole), and fibres shorten at a relatively constant rate. This is less obvious in a large heart with low ejection fraction, where the volume change during ejection is a smaller proportion of the total ventricular volume. The end-diastolic volume is influenced by preload, afterload, cir- culating blood volume, the inotropic state of the ventricle, heart rate, and neurohumoral influences. It is smaller in the erect than in the horizontal position because of reduced venous return, and it decreases with a moderate increase in heart rate because of an as- sociated positive inotropic effect. The proportion of end-diastolic volume ejected during systole, the ejection fraction (normal 50–70%), is a useful index of overall left ventricular function and is easily meas- ured noninvasively by nuclear gated blood-pool scanning, two- dimensional echocardiography, and magnetic resonance imaging techniques. The ejection fraction is found to increase with exercise and with positive inotropic interventions. Values for normal right ventricular ejection fraction are of the same order as those for the left side of the heart. Role of the sympathoadrenal system in normal and failing hearts Catecholamines have positive inotropic, lusitropic, chronotropic, and dromotropic effects on the normal heart. The inotropic effect of catecholamines on the force of contraction is achieved by a pro- tein kinase-A (PKA)-mediated phosphorylation of the L-type Ca2+ channel, which increases the probability of channels opening when the cell is depolarized, thus increasing ICa. Positive lusitropism (myocardial relaxation) occurs by a PKA catalytic subunit- mediated phosphorylation of phospholamban which inhibits SERCA2 in its hypophosphorylated state (Fig. 16.1.2.3a): phos- phorylated phospholamban does not inhibit SERCA2. The effect of phospholamban phosphorylation is thus to activate SERCA2 and stimulate Ca2+ reuptake into the SR, and augment myofibril relax- ation. In addition, PKA phosphorylates cardiac troponin I, and this increases the rate of dissociation of Ca2+ from troponin C, increasing the rate of dissociation of myosin cross-bridges from actin (i.e. stimulating relaxation). Positive chronotropism is achieved by increasing the frequency of depolarization in the sinoatrial node. Upon stimulation of the sympathoadrenal system, If (generated by HCN channels; Table 16.1.2.2) is activated to depolarize the mem- brane to the threshold level more rapidly and increase the rate of production of action potentials. The positive chronotropism of the sympathoadrenal system is in part mediated by the binding of PKA- derived cAMP to these HCN channels. This shifts their voltage de- pendence of activation to more depolarized potentials and increases both the rate of channel opening and the maximal current level. The net result is an increased frequency of depolarization and the heart rate increases. Sympathomimetic agents speed conduction in the AV node (positively dromotropic). In heart failure, the myocyte becomes relatively unresponsive to β-adrenergic agonists, and consequently phosphorylation of the proteins responsible for the control of contractility is diminished. The β1-adrenergic receptor abundance is downregulated and the ex- pression of proteins which antagonize β1-receptor signalling is in- creased, thus the efficacy of β-agonism is diminished. Many drugs that mitigate heart failure are targeted at the proteins that regulate the inotropic state. There is evidence also that SERCA2 expression is decreased, and this may contribute to the elevated cytoplasmic Ca2+ Renin Angiotensin I Angiotensin II Angiotensin III Aldosterone Vasoconstriction, increased blood pressure Vascular smooth muscle cell proliferation Endothelial dysfunction Inhibition of PAI-1 and PAI-2 Myocyte hypertrophy, ventricular remodelling Vasopressin secretion Extracellular matrix formation Renal tubular sodium reuptake Renal salt and water retention Reduced collagen turnover Increased blood volume Angiotensinogen Angiotensin converting enzyme Angiotensinases Chymase Hypotension Decreased sodium delivery Sympathetic stimulation Fig. 16.1.2.17 The renin–angiotensin system.

 concentrations sometimes seen in diastole during heart failure, with slowed cross-bridge dissociation kinetics. This forms the mechan- istic basis for the poor relaxation and diastolic dysfunction character- istic of diastolic heart failure, associated with hypophosphorylation of PKA and PKG sites on cardiac titin (connectin, the giant c30,000 amino acid protein responsible for the passive elasticity of the muscle fibre), and the worsened mechanical function of the heart in this condition. Myocardial function is greatly altered by changes in inotropic state or contractility. Positive inotropic effects are thought to be medi- ated by activation of excitation–contraction coupling mechanisms and are associated with an increased influx of calcium ions into cardiomyocytes and a more powerful contraction. Changes in the in- tensity of excitation–contraction coupling (homeometric) are inde- pendent of the Frank–Starling (heterometric) mechanism. Increases in the intensity shift the curve upwards and to the left, and decreases shift it downwards and to the right (Fig. 16.1.2.15). With a positive inotropic effect, the force of contraction, however measured, is in- creased for a given end-diastolic fibre length and, if the afterload is the same, the initial velocity of fibre shortening is also increased (Fig. 16.1.2.14). In the intact heart there is more complete emptying during systole and hence a lower end-systolic volume and higher stroke volume. Positive inotropy is achieved by increased PKA/ cAMP activity, associated with phosphorylation of phospholamban (though with altered lusitropy), sensitization of troponin C to Ca^{2+}, and phosphorylation of L-type Ca^{2+} channels. Increased sympathetic stimulation, some drugs, calcium, and an increase in heart rate it- self (the staircase or Bowditch phenomenon; post-ectopic potenti- ation, see ‘Heart rate’, next section) have positive inotropic effects. An increase in afterload can also cause a small increase in inotropy. Myocardial depressants, such as hypoxia and most anaesthetic drugs, have negative inotropic effects. Increased parasympathetic stimula- tion produces acetylcholine-mediated negative inotropic effects that are confined almost entirely to the atria because of the anatomical distribution of vagal cholinergic endings in the myocardium. It is difficult to measure inotropic changes accurately in the human heart because changes in the intensity of excitation–contraction coupling and changes in the Frank–Starling relationship, though separate, are nevertheless closely interlinked. The peak rate of change of intraventricular pressure (peak dP/dt) is a useful index of change in contractility (with changes in the maximum rate of pressure rise (+dP/dtmax) relating to inotropy and changes in the maximum rate of pressure fall (–dP/dtmax) relating to lusitropy), provided that preload, afterload, and heart rate remain constant. Heart rate Frequency of contraction is the fourth essential determinant of cardiac performance. Normal heart rate is 60–100 beats/min, but varies with age. Tachycardia may be defined as HR more than 100 beats/min and bradycardia as HR less than 60 beats/min. Heart rate is regulated by intrinsic and extrinsic mechanisms. The former includes the increased heart rate observed with increased venous return and right atrial stretch (Bainbridge reflex). The latter may be considered as either neural (i.e. based on the autonomic supply to the heart through the two cardiac plexi at the base of the heart, with sympathetic stimulation being positively chronotropic and parasympathetic stimulation being negatively chronotropic) or humoral (e.g. catecholamines, thyroid hormones, and calcium acting as positive chronotropes and muscarinic alkaloids and po- tassium acting as negative chronotropes). Heart rate during rest and exertion may vary from 45 to 200 beats/min in the healthy young adult. As changes can occur within seconds, an increase in heart rate is the usual and most effective way of producing a rapid increase in cardiac output. It plays the major role in the response to exercise, during which stroke volume does increase (more so in athletes and when in the erect, rather than the supine, position) but the changes are less marked than those of rate. In addition, an in- crease in contraction frequency itself produces a positive inotropic effect, whereby the force of contraction

increases and reaches a new steady state within a few beats. This is termed the ‘positive staircase’, Treppe, or Bowditch effect. It may be a consequence of an augmented movement of calcium ions into myocardial cells with increased frequency of action potentials, combined with diminished time for outward movement of calcium between beats. More forceful contractions also follow premature beats—the phe- nomenon of post-extrasystolic potentiation—and the mechanism is probably the same. The extrasystole occurring prematurely is a weak contraction because of decreased filling time and an uncoor- dinated activation of the ventricle when the ectopic focus is within the ventricle. The next beat is delayed because of the refractory period of the extrasystolic beat, but is a more powerful contraction because of increased filling time and ventricular volume, and in- creased contractility. Calcium-dependent changes similar to those of the Bowditch effect are probably responsible for the latter, and the increased contractility is independent of volume loading ef- fects. Recently it has become clear that intrinsic circadian clocks are involved in the control of heart rate, with time-of-day de- pendent oscillations in clock gene expression. The cardiomyocyte circadian clock influences many myocardial processes, including ion channels. Coronary blood flow Coronary blood flow accounts for about 4% of the cardiac output. The heart extracts most (70%) of the oxygen carried in the coronary circulation under resting conditions, the arteriovenous difference for oxygen across the heart being about 110 ml/litre, while that for the whole body is only about 40 ml/litre under resting conditions. Therefore, large increases in myocardial oxygen requirements must be met largely by increases in coronary blood flow, and this may in- crease five-or sixfold during strenuous exercise. The greater part of this flow is to the left ventricle, of which at least two-thirds occurs during diastole because of the throttling effect systole has on myo- cardial perfusion. The main coronary arteries are on the superficial (epicardial) surface of the heart, and because of this, and the hin- drance to coronary flow during systole, the subendocardial region of the left ventricle is more vulnerable to perfusion deficits in rela- tion to oxygen need than the outer two-thirds of the muscle wall. Despite these mechanical problems, flow is normally evenly distrib- uted throughout the myocardium so that when regional coronary blood flow is measured experimentally using injected radioactive microspheres (in dogs), the ratio of endocardial to epicardial flow is approximately unity. In fact, the inner layers of the heart probably receive slightly more blood (up to 10%) than the outer layers. This is consistent with the subendocardium developing more tension than

 the subepicardium, and is evidence for a greater rate of myocardial oxygen consumption in the inner layers. Myocardial oxygen requirements and coronary blood flow are finely adjusted and matched, with coronary vascular resistance subject to autoregulation. The nervous system and the heart The heart is richly supplied with sympathetic adrenergic nerves, whose terminals reach atrial and ventricular muscle fibres and im- pinge upon all pacemaker tissue, including the sinoatrial and atrio- ventricular nodes and Purkinje fibres. Sympathetic stimulation leads to an increase in myocardial contractility and heart rate, and in the rate of spread of the activation wave through the atrioven- tricular node and the Purkinje system. This is mediated by local noradrenaline release, which interacts with β-adrenergic receptors. The key elements in these regulatory mechanisms are calcium ions and cAMP. The activated β-receptor increases adenyl cyclase activity and the conversion of ATP to cAMP. Nonadrenergic noncholinergic cotransmitters have recently been isolated and recognized as im- portant adjuncts to autonomic efferent transmission. These include nonpeptides such as ATP, dopamine, and (at least in the enteric system) GABA and 5-hydroxytryptamine (5-HT), but also peptides. Peptide cotransmitters released with noradrenaline and acetylcho- line have now been isolated and shown to influence

autonomic function, and include neuropeptide Y (NPY), GnRH, and substance P. Neuropeptide Y is a peptide of 36 amino acids that is colocated with noradrenaline in most sympathetic nerves and is released with sympathetic stimulation. It is a powerful pressor agent with direct arteriolar vasoconstrictor action and also potentiates the pressor ac- tion of noradrenaline. The distribution of parasympathetic fibres is much more limited in the heart, being confined to the sinoatrial and atrioventricular nodes and the atria, with few, if any, fibres reaching the ventricles in humans, except perhaps in anatomical relation to coronary ar- teries and Purkinje tissue. The effects of parasympathetic nerve stimulation are mediated by local acetylcholine release, which slows the heart rate and speed of conduction through the atrioventricular node and Purkinje tissue, and depresses atrial contractility. The negative inotropic effects are associated with a lowering of the con- centration of intracellular cAMP. The effect of the nervous system on the heart at any one time is the sum of the activities of these two opposing control systems. They usually vary reciprocally. Under resting conditions, vagal inhibitory effects predominate, maintaining a slow heart rate, there being vir- tually no sympathetic outflow. With exercise, there is withdrawal of vagal activity and an increase in sympathetic outflow. Afferents from stretch receptors in the carotid sinus and aortic arch—the baroreceptors—also have a considerable effect on cardiac perform- ance, this effect being mediated via the adrenergic nervous system and vagal withdrawal. A fall in blood pressure reduces stretching in the carotid sinus and inhibitory afferent traffic so that the sympa- thetic outflow increases. As a consequence of this combined vagal and sympathetic effect, there is a quickening of the heart rate within one or two beats, a positive inotropic effect, and also a constriction of systemic veins and arterioles that increases preload and afterload. Elevation of pressure in the carotid sinus has the reverse effect. In cardiac failure, there is reduced variability in heart rate due to these autonomic mechanisms as there is then a predominance of adren- ergic activity. There are also mechanoreceptors in all four chambers of the heart (identified in dogs) and in the coronary vessels, which give rise to depressor reflexes. Their clinical relevance is uncertain, but they may contribute to the bradycardia and hypotension occurring in some patients with acute myocardial infarction—in particular to the syn- cope that patients with critical aortic stenosis may experience with the onset of exercise when there is sudden left ventricular distension. Vagal afferents from reflexogenic areas in the infarcting left ventricle may be responsible for the bradycardia, gastric distension, nausea, and vomiting which frequently occur with the onset of inferior or posterior myocardial infarction, but not usually of anterior infarc- tion, which is generally associated with a marked increase in sym- pathetic activity. The cardiac receptors connected to afferent fibres running in cardiac sympathetic nerves, however, are very important because they are responsible for the perception of cardiac pain. Receptors have also been identified (in animals) at the junction of pulmonary veins with the atrial wall. These respond to mechanical distension with increased sympathetic outflow to the sinus node and inhibition of secretion of antidiuretic hormone from the posterior lobe of the pituitary gland. The result is a quickening of the heart rate and diuresis. Autonomic efferent activity The autonomic outflow to the heart is controlled by multiple inte- grative sites within the central nervous system, with complex inter- actions between afferent and central inputs. Autonomic responses are mediated through the suprapontine and bulbospinal pathways— both those arising ‘reflexively’ and those arising from various types of volitional or central ‘command’. Nevertheless, intrinsic mechan- isms are sufficient for adequate cardiac function in the absence of autonomic control, as prolonged survival after cardiac transplant- ation has shown. But in the denervated heart, dependent on intrinsic and humoral mechanisms, there is blunting of the normally rapid physiological adjustments mediated by the autonomic nervous system. Diurnal variation in autonomic function Variations in vascular tone and control of blood

pressure and of hormone secretion and platelet function occur in a predictable way throughout the 24-h cycle. In normal subjects, there is a cir- cadian rhythm of blood pressure changes that is not seen in pa- tients after cardiac transplantation, who have denervated hearts. There is a decline in both blood pressure and heart rate at night, and increases in both soon after wakening. This is due to a normal adrenergic surge in the early morning, which results in increased vascular tone and blood pressure. Increased forearm vascular re- sistance in the morning, with a reduction in the afternoon and evening, can be clearly identified in humans by assessing responses to α-adrenergic blockade. It is likely that this occurs in coronary vessels as well. Measurable early morning increases in circulating catecholamines and in the propensity for platelets to aggregate can also be documented. The circadian rhythm of autonomic function is correlated with a significant tendency for myocardial infarction and sudden cardiac death to occur more frequently in the morning, soon after wakening.

 There is also an increase in the occurrence of angina pectoris in the early morning, independent of the level of physical activity. Exercise and the heart: Cardiac reserve The heart responds to exercise with an increase in cardiac output, and values of 30 litres/min may be achieved in a trained athlete. Exercising muscles extract more oxygen from the blood, but the re- sponse of the cardiac output is the principal determinant of delivery of oxygen to tissues and is the limiting factor for aerobic exercise. The cardiac response to exercise involves all the mechanisms al- ready discussed. Interaction within the central nervous system between higher and autonomic centres augments sympathetic dis- charge, and there is a withdrawal of vagal parasympathetic out- flow. The heart rate increases immediately, and redistribution of peripheral flow increases venous return and preload (increased end-diastolic volume). There is venoconstriction, particularly in the large-volume splanchnic circulation, and vasoconstriction and increased oxygen extraction in inactive parts. In active parts, there is vasodilation. This is most evident in the vascular beds of the ex- ercising skeletal muscles and of the heart itself. The overall effect is a marked lowering of total peripheral vascular resistance, which re- duces afterload and encourages greater systolic emptying of the left ventricle (decreased end-systolic volume). Stroke volume increases during exercise in the upright position. During light to moderate exercise (running or cycling), for up to about 80% of maximum ex- ercise capacity there is an almost linear relationship between work intensity and heart rate response, cardiac output, and oxygen up- take. With further exercise, the heart rate and cardiac output re- sponses level off while additional increases in oxygen consumption occur by increased oxygen extraction and a greater widening of the arteriovenous difference for oxygen. The venous return increases in relation to the elevated cardiac output. Vasodilation in the working muscles that receive the bulk of the redirected blood permits high flow rates into the systemic venous capacitance vessels. Because of adrenergically mediated venoconstriction, the capacity of this system is reduced, so that blood moves rapidly into the right atrium. Venous return is also enhanced by the pumping action of the rhythmically contracting working muscles, by a decrease in intrathoracic pressure with forced inspiration, and by an increase in intra-abdominal pressure. The augmented pulmonary blood flow results in only slight increases in pulmonary artery pressure because of the distensibility of the large pulmonary arteries, an increased area of the pulmonary ca- pillary bed due to the recruitment of more capillaries, and the low resistance offered by the normal pulmonary circulation (see Table 16.1.2.3), that is, the response of the pulmonary vasculature to in- creased RV output (CO) and increased PA pressure is to dilate pul- monary blood vessels and decrease pulmonary vascular resistance. Since the pulmonary circulation is in series with the right and left sides of the heart, this

is a vital mechanism to permit the increased CO to traverse the lungs and explains why the RV does not need to maintain such high pressures as the LV, and hence is much thinner. The elevated cardiac output and larger stroke volume result in in- creased systolic blood pressure and pulse pressure, even though the afterload itself is reduced. Enhanced neurohumoral activity from ad- renergic stimulation of the heart and the adrenal glands (increased circulating adrenaline and noradrenaline) effect positive inotropic changes, to which tachycardia also contributes because of the Bowditch effect. There is a shift in the Frank–Starling relationship to the left, increased speed and force of cardiac contraction, and ele- vated ejection fraction and stroke volume. Peak +dP/dt is increased, and there is a rapid rise in coronary blood flow to meet myocar- dial oxygen requirements that increase linearly with the product of systolic blood pressure and heart rate. However, the increased heart rate is achieved by a shortened diastolic interval, leaving less time for coronary flow to occur. This may become limiting at very high heart rates. During moderate exercise, these changes together re- sult in a decreased or unaltered end-diastolic volume and decreased end-systolic volume. With severe exercise, end-diastolic dimensions and end-diastolic fibre length are slightly increased and the Frank– Starling mechanism then operates and further augments the force of contraction. The haemodynamic and ventilatory responses evoked by an in- crease to a new steady workload take about 2–3 min to equilibrate and adjust oxygen supply to the greater demand. Protocols for ex- ercise testing are therefore usually based on work increments at 3- min intervals to allow time for a new ‘steady state’ to occur (e.g. in the standard Bruce exercise protocol). A steady state becomes pro- gressively more difficult to maintain as maximal exercise capacity is approached. Glycogen is used by the working skeletal muscles as a source of stored energy, and the anaerobic metabolism which ensues produces lactic acidosis and thereby further increases ven- tilation. As all cardiopulmonary transport mechanisms reach max- imum levels, shortness of breath, fatigue, and muscle pain become limiting symptoms; motivation then becomes a determinant of the duration of exercise. Ageing reduces the efficacy of cardiopul- monary transport mechanisms and, hence, exercise capacity. The heart rate response at peak exercise reflects this. In healthy individ- uals aged 20 years it is about 200 beats/min, and at 65 years about 170 beats/min. When exercise stops, the cardiopulmonary and metabolic changes return rapidly to resting levels, the rate following an exponential pat- tern in the first few minutes; the excretion and metabolism of lac- tate and other substances, and the dissipation of heat generated take longer (time constant of about 15 min or more). Reduced circulatory function slows the recovery rate. Training effects Regular exercise to about 60% of maximal heart rate for 20–30 min three times a week is the minimum requirement for improved effort tolerance due to a training effect. The resting heart rate be- comes slower, while the cardiac output is maintained by an in- creased end-diastolic volume and ejection fraction, and therefore stroke volume. In a ‘trained’ exercising individual, there is a reduced heart rate response to a standard submaximal workload, and sys- temic blood flow is more effectively distributed away from visceral and skin circulations to working muscles. Changes in muscle mito- chondria permit increased oxygen consumption. There is suggestive animal evidence that prolonged endurance training increases the calibre of coronary arteries and enlarges capillary surface area rela- tive to cardiac muscle mass. Myocardial protein synthesis increases. Adrenergic mechanisms appear to be involved in mediating this trophic response. Rhythmic exercise (e.g. running) and isometric exercise (e.g. weightlifting) have different physiological effects. The blood pressure rises disproportionately during the latter. The mech- anisms are partly reflex and partly mechanical from the contracting

 muscles. Isometric exercise training is not recommended for cardiac patients because of the increased afterload it imposes. Regular exercise has other

effects: it increases feelings of well- being and lowers blood pressure in normotensive and mildly hyper- tensive subjects. There are also diverse exercise-related hormonal changes, including increased insulin sensitivity and the reduction of glucose-stimulated insulin secretion—of particular relevance to patients with type 2 diabetes. Regular exercise also improves the availability of nitric oxide, with its important vascular effects. These are considered elsewhere. To summarize, changes in the four essential determinants of cardiac function—preload, afterload, heart rate, and contractility— combine to augment cardiac output and oxygen delivery during exercise. Measurement of the cardiovascular response to exercise is essential for the objective assessment of cardiac function. FURTHER READING Abdel-Aleem S, Lowe JE (2012). Cardiac metabolism in health and di- sease. Kluwer Academic Publishers, New York, NY. Bers DM (2001). Excitation-contraction coupling and cardiac contrac- tile force, 2nd edition. Kluwer, Dordrecht. Durgan DJ, Young ME (2010). The cardiomyocyte circadian clock: emerging roles in health and disease. Circ Res, 106, 647–58. Ganong WF (2005). Review of medical physiology, 22nd edition. McGraw-Hill, New York. Herring N, Paterson DJ (2018). Levick's introduction to cardiovascular physiology, 6th edition. CRC Press, Boca Raton, FL. Houser SR, Margulies KB (2003). Is depressed myocyte contractility centrally involved in heart failure? Circ Res, 92, 350–8. Ieda M, Zimmerman W-H (2017). Cardiac regeneration (cardiac and vascular biology). Springer, New York, NY. Kaestner L (2012). Calcium signalling: approaches and findings in the heart and blood. Springer Science Media, Berlin. Kardami E, et al. (2010). Cardiac cell biology. Springer Science Media, Berlin. Katz AM (2006). Physiology of the heart, 4th edition. Lippincott Williams and Wilkins, Philadelphia, PA. Ko Y-S, et al. (2004). Three-dimensional reconstruction of the rabbit atrioventricular conduction axis by combining histological, desmin, and connexin mapping data. Circulation, 109, 1172–9. Libby P, et al. (ed.) (2008). Braunwald's heart disease: a textbook of cardi- ovascular medicine, 8th edition. Saunders Elsevier, Philadelphia, PA. Opie LH (2013). Stunning, hibernation and calcium in myocardial is- chemia and reperfusion. Kluwer Academic Publishers, Boston, MA. O'Rourke B (2010). Be still, my beating heart: never! Circ Res, 106, 238–9. Pappano AJ, Wier WG (2019). Cardiovascular physiology, 11th edition. Mosby Physiology Series, Elsevier, Philadelphia, PA. Severs NJ (2000). The cardiac muscle cell. BioEssays, 22, 188–99. Severs NJ, et al. (2004). Gap junction alterations in human cardiac dis- ease. Cardiovasc Res, 62, 368–77. Solaro RJ, Tardiff JC (2013). Biophysics of the failing heart: physics and biology of heart muscle. Springer Science Media, Berlin. Willis MS, Homeister JW, Stone J (2014). Cellular and molecular pathobiology of cardiovascular disease. Academic Press–Elsevier, Amsterdam. Young ME (2006). The circadian clock within the heart: potential in- fluence on myocardial gene expression, metabolism, and function. Am J Physiol Heart Circ Physiol, 290, 1–16. Zipes DP, Jalife J (2013). Cardiac electrophysiology, 6th edition. Saunders Elsevier, Philadelphia, PA.

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