Cellular Myocytes

12

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Abstract

The function of the heart as a pump is ultimately dependent on the coordinated contractions of its chambers to move blood throughout the body. These contractions are produced by cardiac myocytes, the muscle cells of the heart. Understanding of the structure and function of these cells on an individual level provides insights into adaptations of the heart due to normal as well as pathophysiological changes over the course of a lifetime.

Keywords

Actin • Action potential • Adenosine triphosphate • Gap junctions • Intercalated disk • Membrane potential • Myofibril • Myosin • Sarcomere • Sarcoplasmic reticulum • Tropomyosin • Troponin • Transverse tubules

12.1 General Cellular Morphology

All human cells can be thought of as biological machines that are surrounded by a membrane bilayer (plasma membrane). The plasma membrane has a nominal thickness of ~5 nm (50 Å) and encloses the cellular machinery within the intracellular space whose environment is closely regulated for optimal performance. The average diameter of a non-muscle cell is approximately 10–20 μm. The encapsulating membrane is primarily composed of a bilayer of phospholipids, bipolar molecules with hydrophilic head groups, and hydrophobic lipid tails (Fig. 12.1). In addition, the plasma membrane is studded with receptors (Fig. 12.1) for various biochemical signaling molecules (hormones, neurotransmitters, etc.). Also resident in the plasma membrane are a number of ion-specific pumps and channels which function to regulate the ionic composition of the internal environment of the cell (endoplasm). The interior of each cell contains enzymes and organelles that are specialized to support a wide array of biological functions. Key organelles include: the nucleus (which contains the genetic blueprint for cellular function), mitochondria (which converts various energy sources to adenosine triphosphate, or ATP), the endoplasmic reticulum (protein and lipid synthesis as well as calcium storage), and the Golgi apparatus (which supports processing of newly synthesized proteins). The cells of each tissue anchor themselves together and to the surrounding connective tissues via membrane-bound anchoring proteins (Fig. 12.1).

12.2 Cardiac Muscle Cell Morphology

Muscle cells are similar in that they contain these common organelles but distinct in that they also include an elaborate protein scaffold within the cell that is anchored to the cell membrane and the extracellular matrix of connective tissue (Fig. 12.2). Force generation arising from protein–protein interactions within the internal protein lattice leads to the contraction of the cells and pumping of blood by the heart. Mammalian cardiac cells are roughly cylindrical but may also include short branch-like projections. The cells have an asymmetric profile with diameters in the range of 10–20 μm

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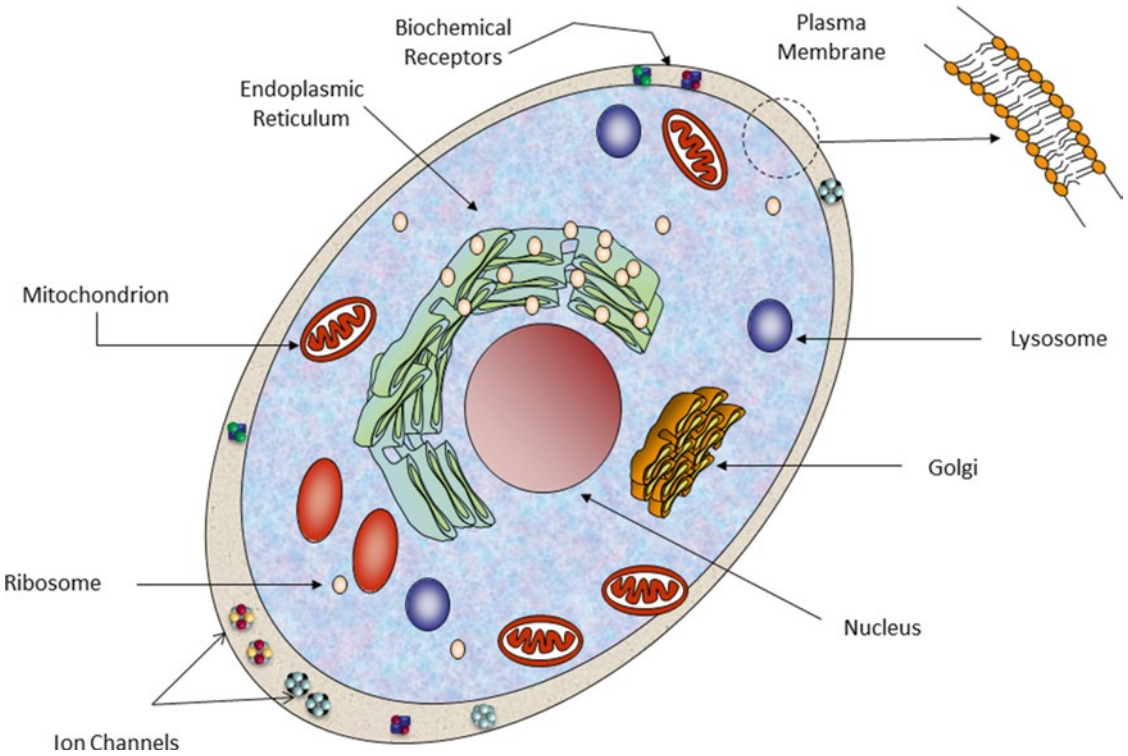

Fig. 12.1 A typical mammalian cell. The intracellular environment is separated from the extracellular environment by a lipid bilayer membrane (see area *encircled* in figure). Each cell contains a nucleus containing chromosomes and a collection of organelles to support biosynthetic and other "housekeeping" tasks. Shown here are the endoplasmic reticulum, ribosomes, mitochondria, Golgi apparatus, lysosomes, various ion channels, and biochemical receptors

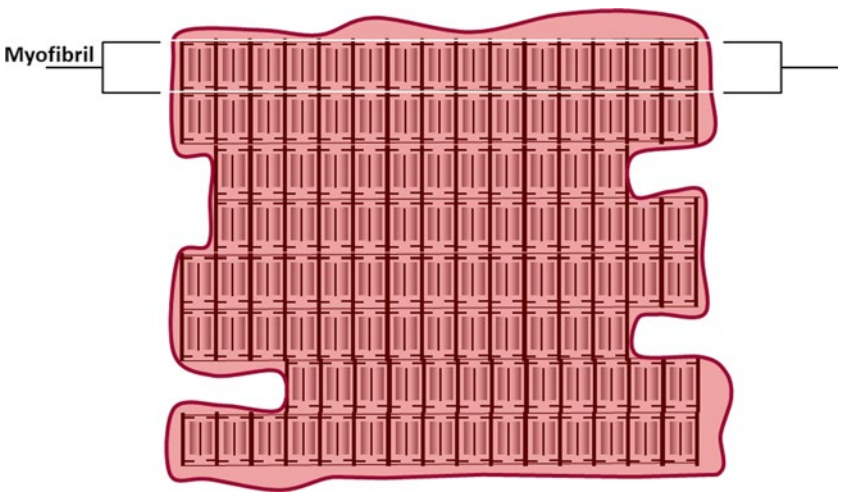

Fig. 12.2 A typical cardiac cell. The intracellular space is largely filled with contractile structures called myofibrils. The nucleus and other organelles that support cellular function are present but are often crowded to the periphery by the contractile apparatus

and lengths on the order of 50–100 μm. Force is produced primarily along the long axis of the cell. Most of the internal volume of myocytes is devoted to a cytoskeletal lattice of contractile proteins whose liquid crystalline order gives rise to a striated appearance under the microscope (Figs. 12.2 and 12.3). As with other cell types, the membrane bilayer contains a collection of ion channels and ion pumps and receptor proteins. In addition, the membranes of cardiac muscle cells contain some proteins which connect cardiac myocytes to one another as mechanical partners and other proteins which facilitate cell-to-cell electrical communications.

12.3 Cardiac Cell Membranes

The surface (or plasma) membranes of cardiac cells are punctuated by openings of membrane-lined channels, the *transverse tubules* (or T-tubules), that pass through the cell and are filled with extracellular fluid (Fig. 12.4). As they traverse the cell, individual T-tubule passages will branch and connect to other transverse tubule channels forming a reticular network that encircles the internal contractile structures known as myofibrils. Abutting the T-tubules, in the sarcoplasm

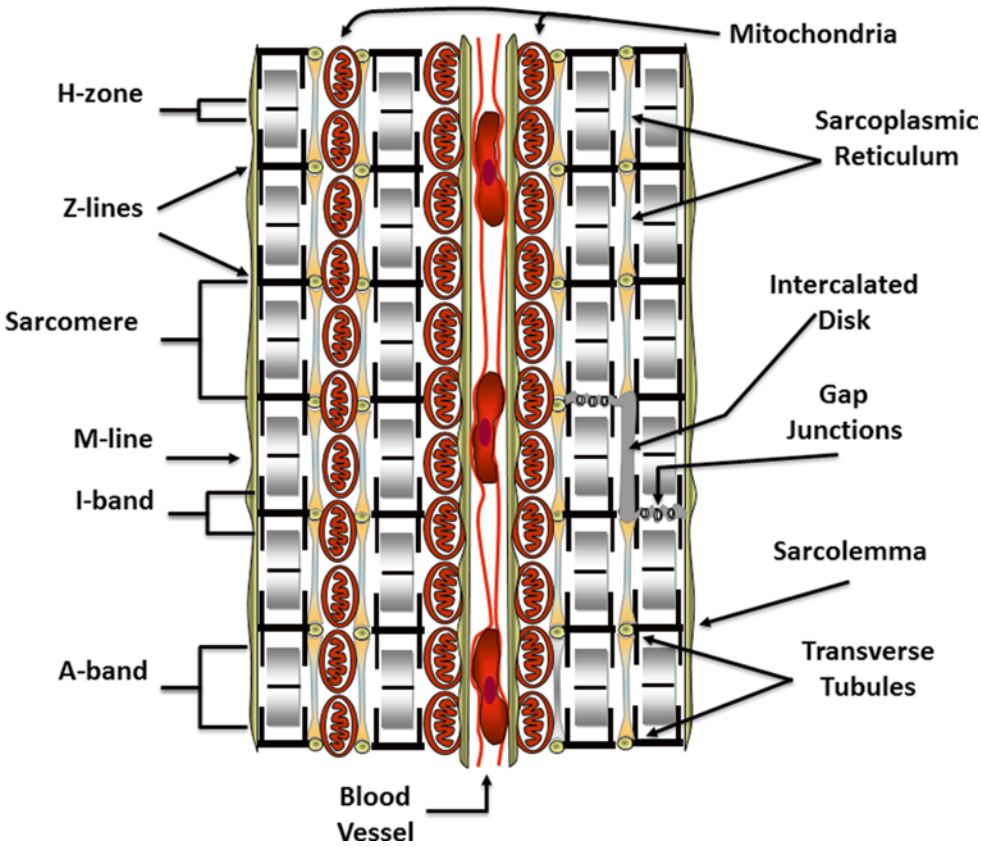

Fig. 12.3 A cross section of cardiac tissue showing two cells separated by a blood vessel containing red blood cells. The repeating sarcomeric structure of the myofibrils and the names of the sarcomeric landmarks are highlighted on the *left* of the figure. On the *right* of the figure, the legend points out the membrane specializations of the cell. These include the intercalated disks, gap junctions, the transverse tubules that punctuate the sarcolemma (plasma membrane), and the sarcoplasmic reticulum. Also shown are mitochondria compacted into a limited space because of the abundance of the myofibrils

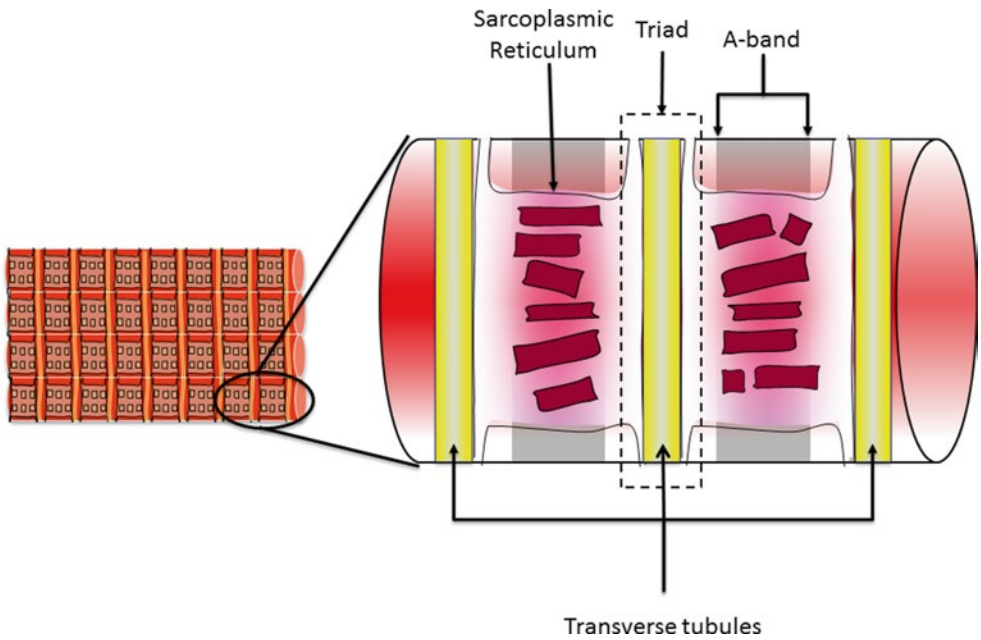

Fig. 12.4 A section of a cardiac cell showing the relationship of the sarcoplasmic reticulum and the transverse tubules (T-tubules). The sarcoplasmic reticulum surrounds each myofibril and lays adjacent to the T-tubules as they pass through a cardiac cell. The junction of the T-tubule with the adjacent sarcoplasmic reticulum is referred to as the *triad*. This close proximity allows the action potentials that pass through the T-tubular system to influence calcium release from the sarcoplasmic reticulum

(cytoplasm) of the myocytes, is the sarcoplasmic (endoplasmic) reticulum, a cytosolic organelle that is specialized to store calcium. The T-tubules provide a pathway for conduction of action potentials through the entire thickness of a cardiac myocyte. Their close association with the sarcoplasmic reticulum helps to couple cardiac action potentials to the release of calcium from internal stores. This arrangement of the T-tubules with the sarcoplasmic reticulum is also found in skeletal muscle, but not within smooth muscles.

12.4 Intercalated Disks

A structure referred to as the *intercalated disk* forms strong mechanical links between myocytes (Fig. 12.5). The intercalated disk structures are formed by the association of membrane-bound proteins projecting from the surfaces of the neighboring cardiomyocytes. The protein components of these membrane plaques include: N-cadherin, desmin,

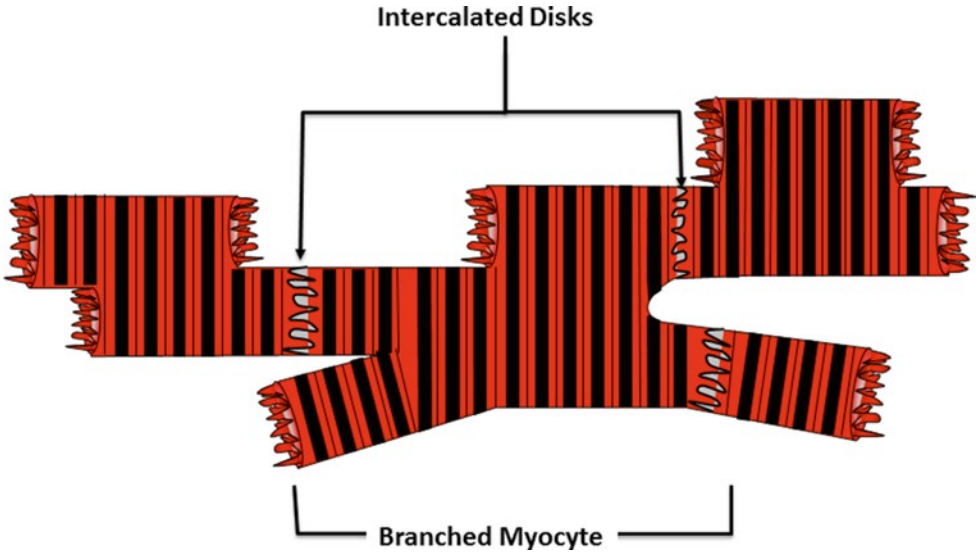

Fig. 12.5 A collection of interconnected cardiac muscle cells showing their characteristic branched structure. At the interface of adjoining cells, there is an interconnection of membrane-bound proteins known as the intercalated disk. This structure mechanically couples the cardiac cells so that the forces generated by each cell are communicated through the vessels of the heart

vinculin, α- and β-catenin, desmoplakin-1, desmocollin-2, and plakoglobin-2 [1, 2]. The tight cell-to-cell coupling of the intercalated disks contributes structural integrity to branches of myocardial cells. This connection of the cardiac myocytes facilitates some lateral shifting and the interdigitation of the cells. However, longitudinal shifting of cardiac myocytes relative to one another is practically impossible (Fig. 12.5). Importantly, it is the structural integrity of the intercalated disks between individual cells that allows force to be transmitted across the myocardium.

12.5 Gap Junctions

Gap junctions form electrical connections between cardiac cells [3]. Membrane proteins known as *connexins* form six-membered rings called *connexons* imbedded in the sarcolemma of cardiac cells (Fig. 12.6a). The connexons on the surface of one cell dock with connexons on the surface of a neighboring cell. A conformational change within the proteins of docked connexons results in openings of aqueous pores or *gap junctions* (Fig. 12.6b). When gap junctions are open, they provide for direct electrical and small molecule communication between the sarcoplasmic spaces of adjoining cells, creating a functional syncytium or network of synchronized cells. This connectivity allows activation signals to be passed from cell to cell in cardiac tissue. Electrical depolarizations can then pass from cell to cell through these gap junctions; this facilitates the seemingly simultaneous, coordinated contractions of cardiac muscle. For more details on movement of electrical signals through heart tissue, the reader is referred to Chap. 13.

12.6 Myofibrillar Structure

The arrangement of contractile proteins in cardiac muscle cells is similar to that found in skeletal muscle. Many contractile protein assemblies, known as *myofibrils*, run parallel to one another along the long axes of the myocardial cells (Fig. 12.2). Myofibrils fill most of the cytoplasmic space of each cardiac myocyte, with the remainder of these cells occupied by the normal intracellular machinery (Fig. 12.3). Each myofibril is composed of a serial array of contractile elements called *sarcomeres*, defined as the smallest functional units within muscle (Figs. 12.3 and 12.7). It is the arrangement of contractile proteins into the sarcomeres that gives cardiac and skeletal muscle the characteristic striated appearance under microscopic examination. At regular intervals along each myofibril, a transverse matrix composed primarily of the proteins α-actinin and actin forms boundaries known as *Z-disks* (or Z-lines; Fig. 12.7). A sarcomere is defined as the arrangement of contractile proteins that resides between two consecutive Z-disks along a myofibril. Actin filaments anchored on each face of a Z-disk extend for 1 μm toward the center of adjacent sarcomeres (thin filaments). Thick filaments of the protein myosin sit in the center of each sarcomere and extend toward the Z-disks at the ends of the sarcomere (thick filament length ~1.6 μm). The thick filaments are connected at their centers by a protein matrix referred to as the *M-line* (or M-disk) and tethered to the Z-disks by filaments of the protein titin. The region of the sarcomere in which the myosin filaments reside is known as the *A-band* (Figs. 12.3 and 12.7). The area between A-bands is known as the *I-band*; each I-band is bisected by a Z-line and is traversed by the actin thin filaments (Figs. 12.3 and 12.7).

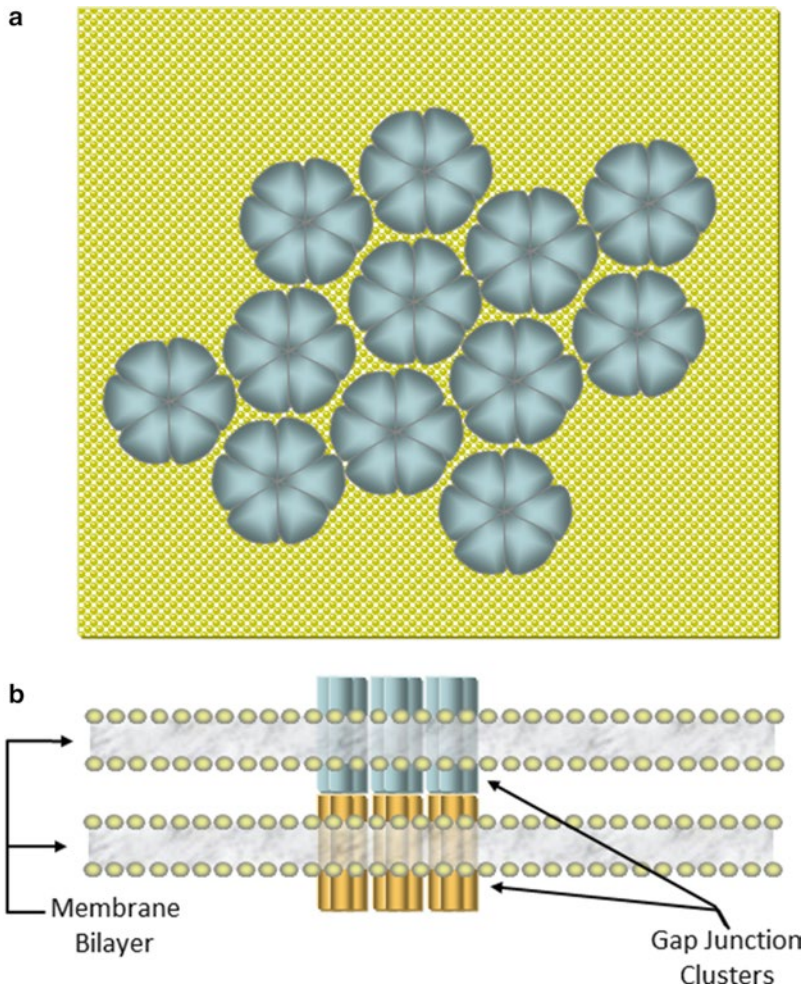

Fig. 12.6 (**a**) Overhead representation of a plaque of connexons on a cardiac membrane. Six connexins form each pore structure (connexons) on the membrane surface which cluster in the intercalated disk regions at cell–cell interfaces. (**b**) Side view of the interface between two cells showing the docking of connexons to form a gap junction between adjacent cells

12.7 Thin Filament

As noted above, the principle structural component of the thin filaments is a double-stranded filament of the globular protein actin (Fig. 12.7). The thin filaments also incorporate the regulatory proteins tropomyosin (Tm) and troponin (Tn). Tropomyosin is a double-stranded α-helical coiled-coil protein that spans seven actin monomers (~35 nm). Troponin is a globular protein complex with three subunits: TnC, a calcium-binding subunit; TnI, a subunit which facilitates inhibition of muscle contraction; and TnT, a subunit that connects the troponin complex to tropomyosin and actin. Tropomyosin molecules are aligned end to end around the helical coil of the thin filament with one Tn complex attached to each Tm molecule. In relaxed muscle, the track traced by tropomyosin as it binds to actin on the thin filament impedes the binding of the myosin crossbridge domains (see below) to actin-binding sites [4]. However, upon myocyte activation and the subsequent increase in myoplasmic calcium concentrations, free calcium binds to TnC inducing a conformational change of the entire troponin complex that is transmitted to tropomyosin. Tm then shifts its position on the actin thin filament, revealing the site on actin required for strong myosin binding. Myosin can then bind to the thin filament in a manner conducive to force production. This association of a tropomyosin-troponin complex over seven actin monomers represents a de facto regulatory subunit along the thin filament. The overlap of Tm molecules creates a mechanism for the communication of the activation signal along the thin filament, making the initiation of force generation via this mechanism highly cooperative [4].

This thin filament-based mechanism for the regulation of contraction is also used for the control of skeletal muscle. In contrast, in smooth muscle (e.g., the muscles of the vascular system, gut, and airways), while the regulation of contraction is also calcium dependent, the regulatory protein troponin is absent. The rise in calcium concentration is sensed by the cytosolic protein calmodulin, and activation occurs via a different thick filament-based mechanism.

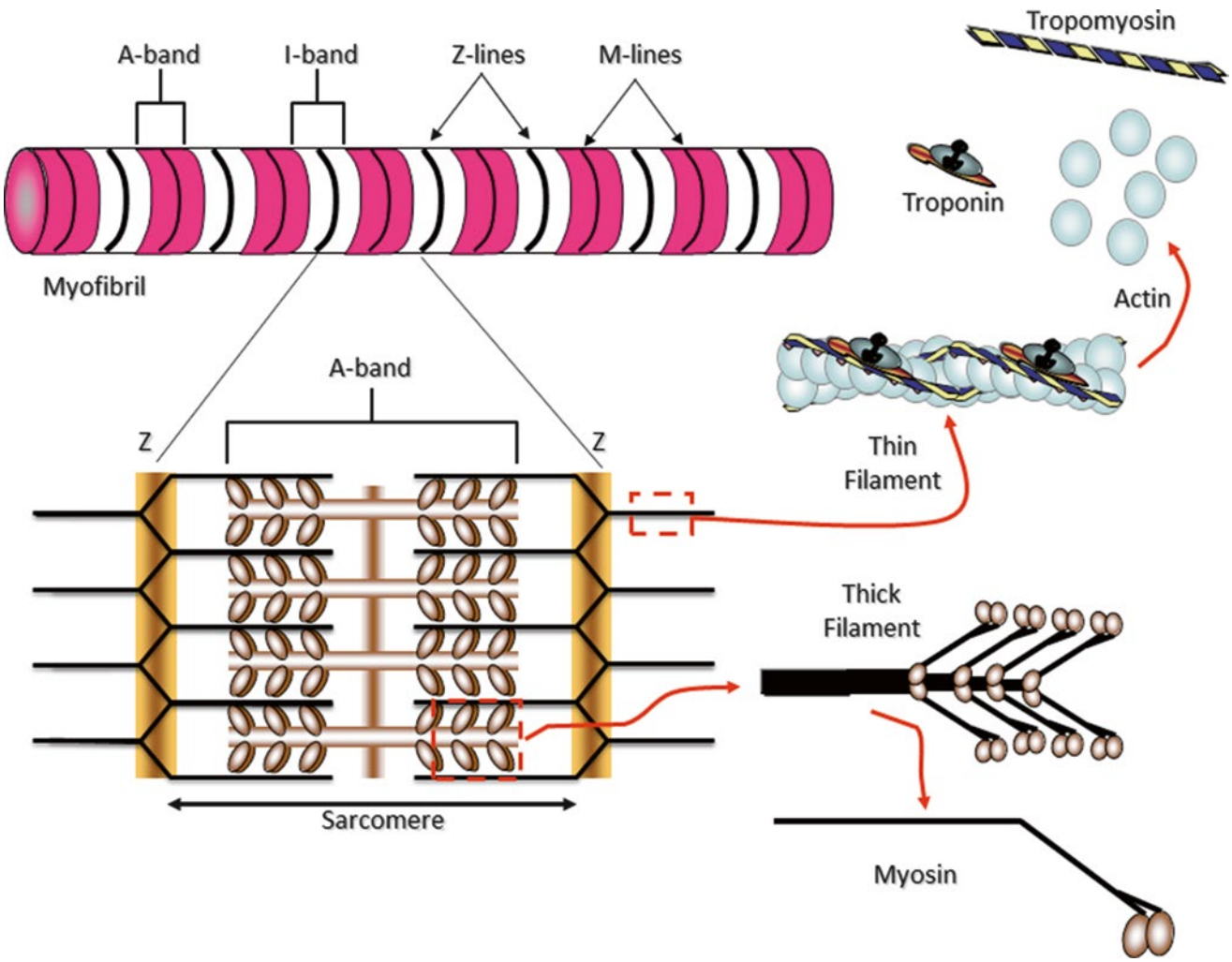

Fig. 12.7 Myofibrils are constructed of repeating sarcomeres within cardiac muscle cells. Each sarcomere is defined as the structures bounded on each end by Z-disks (Z-lines). Thin filaments of the protein actin are attached to the Z-line and reach toward the center of each sarcomere. Two regulatory proteins are found on the double-stranded actin thin filaments—tropomyosin and troponin. Tropomyosin is a double-stranded a-helical protein dimer that binds across seven actin monomers on the thin filament obscuring a binding site for myosin. Troponin is a three subunit globular protein that binds one per tropomyosin. Thick filaments of the protein myosin are found in the center of the sarcomere. The area that contains the thick filaments is also known as the A-band. The myosin molecules are asymmetrically shaped with a coiled-coil "tail" and two globular "head" domains. The head domains bind to actin to form cross-bridges between the filaments and generate contractile force

12.8 Thick Filament

Myosin is the molecular motor protein responsible for force production and movement of muscle cells. The functional protein is a hexamer (six-sub unit) composed of two protein *heavy chains* and four *light chains*. Each heavy chain is asymmetrically shaped with a long alpha-helical "tail" and two globular "head" domains (Fig. 12.7). Associated with each globular head domain are two smaller protein components, the "light chains" of myosin. The heavy chain tails form an alpha-helical coil which completes the assembly of the molecule. The coiled tails of myosin self-associate in an anti-parallel manner to form the backbone of the thick filament (Fig. 12.7). This results in a bipolar structure that has a bare zone in the center and the globular "head" domains of the myosin molecules projecting from each end. These head domains contain an actin-binding site and an ATP hydrolysis site. As will be discussed later, the cyclic interaction of these crossbridge forming head domains to the actin thin filaments forming crossbridges provides the underlying mechanism for myocyte contraction.

12.9 Energy Metabolism

ATP production in cardiac muscle is primarily accomplished via oxidative phosphorylation. Oxidative phosphorylation is a multistep enzymatic process that extracts energy from glucose, fatty acids, and other energy-rich compounds and

converts it to ATP. The energy extraction and ATP production occur in the mitochondria found in the cytoplasmic space of cardiac myocytes. Intracellular concentrations of ATP hover in the 4–5 millimolar (mM) range with additional energy stored in creatine phosphate which acts as a backup to the ATP supply. Creatine phosphate (~20 mM) can be used to regenerate ATP in a one-step enzymatic process catalyzed by the enzyme creatine kinase. There is an absolute requirement for oxygen in the ATP production mechanism, and it is the reason that blood flow to the myocardium is so critical. The amount of ATP and creatine phosphate normally present is insufficient to power the contractile activities and other uses of ATP in heart cells for more than a few beats. Therefore, continuous delivery of nutrients and oxygen and removal of waste products are crucial processes for the normal functioning of the myocardium. For a more detailed description, see Chap. 21.

12.10 Force Production: The Crossbridge Cycle

During diastole, myosin crossbridges bind ATP and hydrolyze it, but cannot use the energy released during hydrolysis to produce force (Fig. 12.8), because of the inhibitory influences of tropomyosin and troponin on the thin filament. The hydrolytic events (Fig. 12.8, step 1) induce conformational changes in myosin that allow it to hold on to the products of ATP hydrolysis (inorganic phosphate (Pi) and adenosine diphosphate (ADP)). The myosin heads then retain most of the energy released during the hydrolysis of the high-energy phosphate bond of ATP. During systole, calcium from the extracellular milieu and the sarcoplasmic reticulum floods the cytoplasm, raising the intracellular calcium concentration from micromolar to millimolar levels. As discussed above, the binding of calcium to TnC initiates conformational changes of the Tm–Tn complex that then moves these protein structures from their blocking position on the thin filament, thus removing inhibition. The energized myosin crossbridges can then bind to the actin-binding sites and thus to the thin filament (Fig. 12.8, step 2). This association with actin catalyzes the release of Pi and ADP and a concomitant force-generating conformational change of the myosin head occurs while it is bound to actin (Fig. 12.8, step 3). The conformational change pulls the thin filament past the thick filament. At the end of the force-generating transition, the vacant enzymatic active site of myosin can rebind ATP (Fig. 12.8, step 4), inducing a structural change which then reduces the affinity of the crossbridge for actin and thus causes crossbridge detachment. The subsequent hydrolysis of myosin-bound ATP, in turn, reenergizes the crossbridge and prepares it for the next force-generating cycle. The cycle continues as long as the intracellular calcium concentration is high enough to keep the Tm–Tn complexes from blocking the myosin-binding sites.

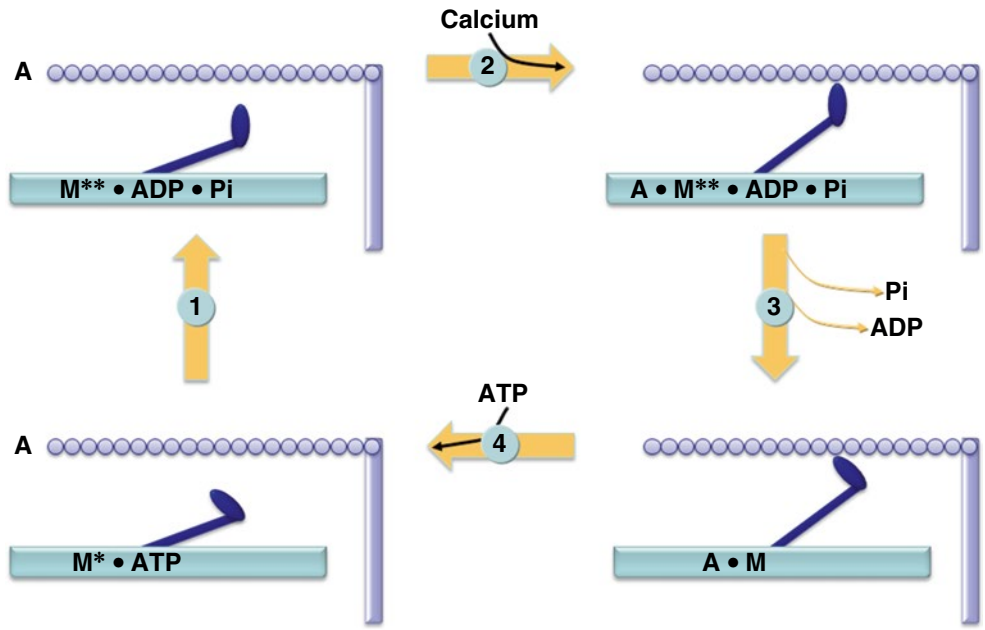

Fig. 12.8 Crossbridge cycle. Step 1: Myosin (M) binds ATP on its globular head domain and hydrolyzes it to ADP and phosphate (Pi); the energized myosin crossbridge (M**ADP-Pi) then waits for activation of the actin (A) thin filament. Step 2: After activation, the energized crossbridge binds to the actin thin filament. Step 3: The association with actin triggers the rapid release of ATP hydrolysis products ADP and Pi from the crossbridge; the release of ADP and Pi is coupled to a conformational change of the crossbridge domain which produces force, pulling the actin thin filament relative to the thick filament. Step 4: ATP binds to the crossbridge as it completes its power stroke causing the dissociation of myosin and actin; this forms the M*ATP state as the conformation of myosin changes again. The crossbridge cycle continues as long as the intracellular calcium concentration is high. At rest the system sits with myosin in an equilibrium between the M*ATP state and the M**ADP-Pi state

12.11 Length–Tension Relationship

The myofibrils of a cardiac myocyte are tethered to the membranes and intercalated disks at each end of the cell via connective protein linkages. Cell length is a dynamic variable with shortening of a cardiac cell occurring with each systolic contraction and stretch of the cell occurring during each diastole as the chambers refill with blood. This means that the myofibrils and sarcomeres also shorten and lengthen during the cardiac cycle. It is important then to realize that there is a direct connection between the overlap of the thick and thin filaments and the resultant force output developed by cardiac muscle cells.

Sarcomere length is defined as the distance from one Z-line to the next Z-line along a myofibril. When the sarcomere length in a cardiac myocyte is approximately 2 μm, this overlap of actin and myosin is optimal, and nearly all of the myosin crossbridge domains are in position to bind to the thin filaments. This configuration of the sarcomere leads to maximal isometric (isovolumic) force production (Fig. 12.9). If the myocyte is stretched, the potential force decreases because of the decrease in the overlap region of crossbridge, binding sites between the thick filaments with the thin filaments. Thus, the decreased force development is directly the result of the reduced potential for possible crossbridge formations as the cell is stretched (Fig. 12.9). If the myocyte is shortened from the full overlap position and then activated, the subsequent force generation also decreases but for a different reason. We have already stated that the arrangement of the thick and thin filaments in the sarcomere is semicrystalline. When the cells become over shortened, several types of filament misalignment are possible such as: (1) the thick filaments can run into the Z-disks and become disordered or (2) the thin filaments can cross the M-line and interact with each other or with myosin crossbridges from the other half-sarcomere. The disorder and/or interference that may occur in an overly shortened sarcomere is the cause for the decrease in myocyte tension. From the graph of the length–tension relationship (Fig. 12.9), you will notice a peak representing the noncompressed full overlap position.

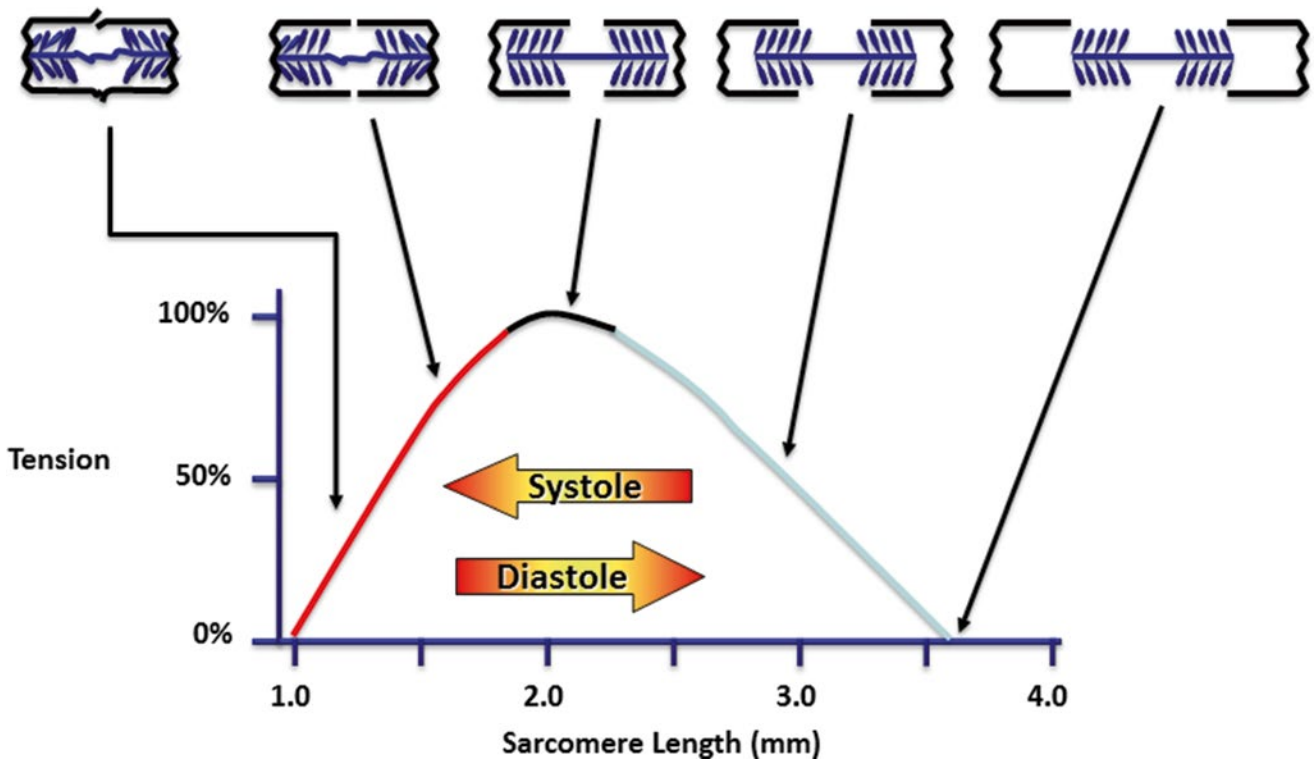

Fig. 12.9 Length–tension relationship. Mechanical coupling between the myofibrils and the membrane is such that a stretch or contraction of the cell alters the overlap of the thin and thick filaments of each sarcomere. At a sarcomere length of near 2.1 μm, there is complete overlap of the thick and thin filaments; if the length is unchanged, the cells have their maximal force production potential. At sarcomere lengths less than ~1.8 μm, the filaments become compressed in the sarcomere and interfere with one another, reducing the force that can be produced. As the sarcomere length is increased from the region that produces maximal force, the overlap of the crossbridge domains of the thick filament and the thin filament decreases with a near linear decline in force-generating potential

Shortening or lengthening the myocyte from this set point will decrease resultant muscle tension. In a normal cardiac cycle, the cell shortens during systole and has its length reset by stretching of the vessel wall during diastole. Since adjustment of the cell length changes the amount of force (or pressure) that can be generated, it is sometimes referred to as the preload of the cell.

12.11.1 Practical Applications of the Length–Tension Relationship

In general, the length of cardiac cells or myocytes is controlled in vivo through their shortening during systole and their being stretched during diastole (Fig. 12.9). That the set point of the length–tension relationship can be tuned in this manner is, in part, the mechanical underpinning for Starling's law of the heart (e.g., stroke volume increases as cardiac filling increases). Furthermore, if cardiac filling adjusts the sarcomere length to a point closer to the plateau of the length–tension relationship (Fig. 12.9), this length change produces an alignment of the contractile proteins that can then result in greater force production during the next systolic period. It then also follows that the increased force, which can occur during the isovolumic (isometric) phase of systole, will result in a greater stroke volume. However, in hypertrophic cardiomyopathies, filling pressures are less likely to stretch the myocytes and reset the length of the cells. In contrast, in dilated myopathies, myocytes may be overstretched during diastole, reducing the pressure building capacity of ventricular muscle.

12.12 Force and Velocity

The velocity of muscle cell shortening depends on the load that it works against. In cardiac muscle the load for the left ventricle is the systemic blood pressure, and it is referred to as the *afterload*. Importantly, as afterload increases the velocity of myocyte, shortening decreases. This relationship can impact ejection fraction as the ventricles are less effective in expelling blood against high systemic pressures.

12.13 Myocyte Hypertrophy

The structure of all muscle cells in the human body respond to the work they are required to do, and cardiac myocytes are no exception. The heart's continuous cycles of filling with blood, contraction, and ejection of blood throughout a person's lifetime maintain the healthy muscular tone of the myocytes. However, physiological and/or pathological conditions (exercise, pregnancy, hypertension, valvular insufficiency, etc.) place stresses on the heart that lead to remodeling. The remodeling of the myocardium, due to increased biomechanical stress, triggers activation of biochemical and neurohormonal signaling pathways that are dependent on the manner in which the stresses are applied to the heart.

Chronic high blood pressure forces the left ventricle to produce a higher internal pressure than normally required for the ejection of blood out of the heart into the aorta. Over time, this *pressure overload* will result in *left ventricular hypertrophy*. As more and more effort is required by the heart to compensate for the hypertension, myocardial protein synthesis is stimulated, and there is an increase in the production of sarcomeric proteins (myosin, actin, etc.). These myocardial proteins are then assembled to build additional myofibrils in myocytes. To accommodate the increase in the number of myofibrils, the cells also add phospholipids to the sarcolemma expanding their diameter and ultimately increasing the thickness of the overall myocardium. This adaptation to hypertension has been termed *concentric hypertrophy* [5, 6].

Alternatively, conditions such as valvular insufficiency, pregnancy, or an arteriovenous shunt can cause the ventricles to experience a *volume overload*; these stresses also result in a structural adaptation of cardiac myocytes. The stimulation of protein synthesis of sarcomeric proteins in these cases results in the addition of additional sarcomeres to existing myofibrils. The elongation of the myofibrils is also accommodated by incorporation of additional phospholipids the plasma membrane resulting in an expansion of cardiac myocytes along their long axes; this is referred to as *eccentric hypertrophy* [5, 6].

An interesting component of these changes in cellular morphology is that the concentric hypertrophy triggers an increase in protein synthesis during early phases of the hypertrophic adaptation, while eccentric hypertrophy first slows protein degradation, reducing myofibril turnover and then increases protein synthesis to extend myofibrillar lengths.

12.14 Cardiac Cell Action Potentials

The electrical activity of cardiac muscle cells is fundamental to normal function and takes advantage of the properties of the cell membrane to selectively pass charged species from inside to outside and vice versa. Most cells build a charge gradient through the action of ion pumps and ion selective channels. The charge difference across a membrane creates an electrical potential known as the resting membrane potential of the cell. In the resting state, the interior of the cell

Table 12.1 Major ionic species contributing to the resting potential of cardiac muscle cells

Ion	Inside (mM)	Outside (mM)	Ratio of inside/outside	$^{*}E_{ion}$ (mV)
Sodium	15	145	9.7	+60
Potassium	150	4	0.027	−94
Chloride	5	120	24	−83
Calcium	10^{-7}	2	2×10^{4}	+129

$^{*}E_{ion}$ is the equilibrium potential calculated from the Nernst equation

carries a negative charge relative to the exterior interstitial environment. The energy available through the discharging of this potential is commonly coupled with cellular functions. In excitable cells, transient changes in the electrical potential (action potentials) are used either to communicate or do work. Importantly, in the myocyte, action potentials are required to initiate the process known as *excitation-contraction coupling*.

The extracellular fluid has an ionic composition similar to that of blood serum. The total intracellular concentration of calcium is higher, but much of it is bound to proteins or sequestered in organelles (mitochondria, sarcoplasmic reticulum). Hence, free intracellular myoplasmic concentrations are very low and are in the micromolar range (Table 12.1).

ATP-dependent ion pumps, ion-specific channel proteins, and ion exchange proteins are all required to maintain the difference in ion concentrations. This separation of charged species across a resistive barrier (in this case, the cell membrane) generates the electrical potential (E_{ion}) mentioned above. For individual ions, the value of this potential can be calculated using the Nernst equation:

$$E_{ion} = -\frac{RT}{zF}\ln\frac{[\text{outside}]}{[\text{inside}]}$$

where R is the gas constant, T is the temperature (K), z is the valence of the ion (charge and magnitude), and F is the Faraday constant.

In Table 12.1, the concentrations of the ions (inside and outside the cell) that play a role in the resting membrane potential of cardiac muscle cells are shown with their respective calculated equilibrium potentials. The measured membrane potential of a cardiac muscle cell is in the range of −90 mV, suggesting that it is primarily determined by either the chloride or potassium distribution. However, measurements of ion movement have shown that chloride is distributed passively across the cell membrane (because of its negative charge, it follows positive ion movement) and can therefore be ignored in such a calculation; this leaves potassium as the dominant ion species in determining the resting potential of the cardiac myocyte.

The membrane potentials of living cells depend not just on their potassium distribution but also on several parameters including the concentrations of the other major ion species on both sides of the given cell membrane as well as their relative permeability. To determine the overall membrane potential (E_m), a modified Goldman–Hodgkin–Katz equation [7] is used to take into account the equilibrium potentials for individual ions and the permeability (conductance) of the membrane for each species such that:

$$E_m = \frac{g_{Na}}{g_{tot}}E_{Na} + \frac{g_K}{g_{tot}}E_K + \frac{g_{Ca}}{g_{tot}}E_{Ca}$$

where g_{Na} is the membrane conductance for sodium (Na), g_K is the membrane conductance for potassium (K), g_{Ca} is the membrane conductance for calcium (Ca), g_T is the total membrane conductance, E_{Na} is the equilibrium potential for sodium, E_K is the equilibrium potential for potassium, and E_{Ca} is the equilibrium potential for calcium. Evaluation of the Goldman-Hodgkin-Katz equation using the values in Table 12.1 and the conductance values for sodium, potassium, and calcium results in a membrane potential of −90 mV for a cardiac myocyte at rest.

As noted above, cells can have a variety of ion selective channels in their membranes. The term *gating* refers to the trigger required for opening a given channel. More specifically, voltage-gated ion channels respond to changes in the local membrane potential of the cell, and ligand-gated ion channels respond to specific circulating biochemical factors. Non-gated channels include: (1) spontaneously active ion channels that have a random frequency of opening and closing and (2) leak channels which seem to be constitutively open though at a low level. In addition to classification based on their control mechanisms, channels are also classified by their ion selectivity and/or the direction of ion passage that such a channel facilitates.

Cardiac action potentials occur because of transient changes in the cellular permeability to Na^+, Ca^{2+}, and K^+. An initial electrical depolarization initiated by current movement through the cell's gap junctions (threshold is ~40 mV above the resting potential) causes the transient opening of voltage-dependent Na^+ channels (Figs. 12.10, 12.11, and 12.12). Opening of these channels causes a transient increase in sodium permeability which further depolarizes the cell and drives the membrane potential toward the (positive) sodium equilibrium potential (Table 12.1; Figs. 12.10 and 12.12). Action potential initiation by the voltage-gated sodium channels in turn

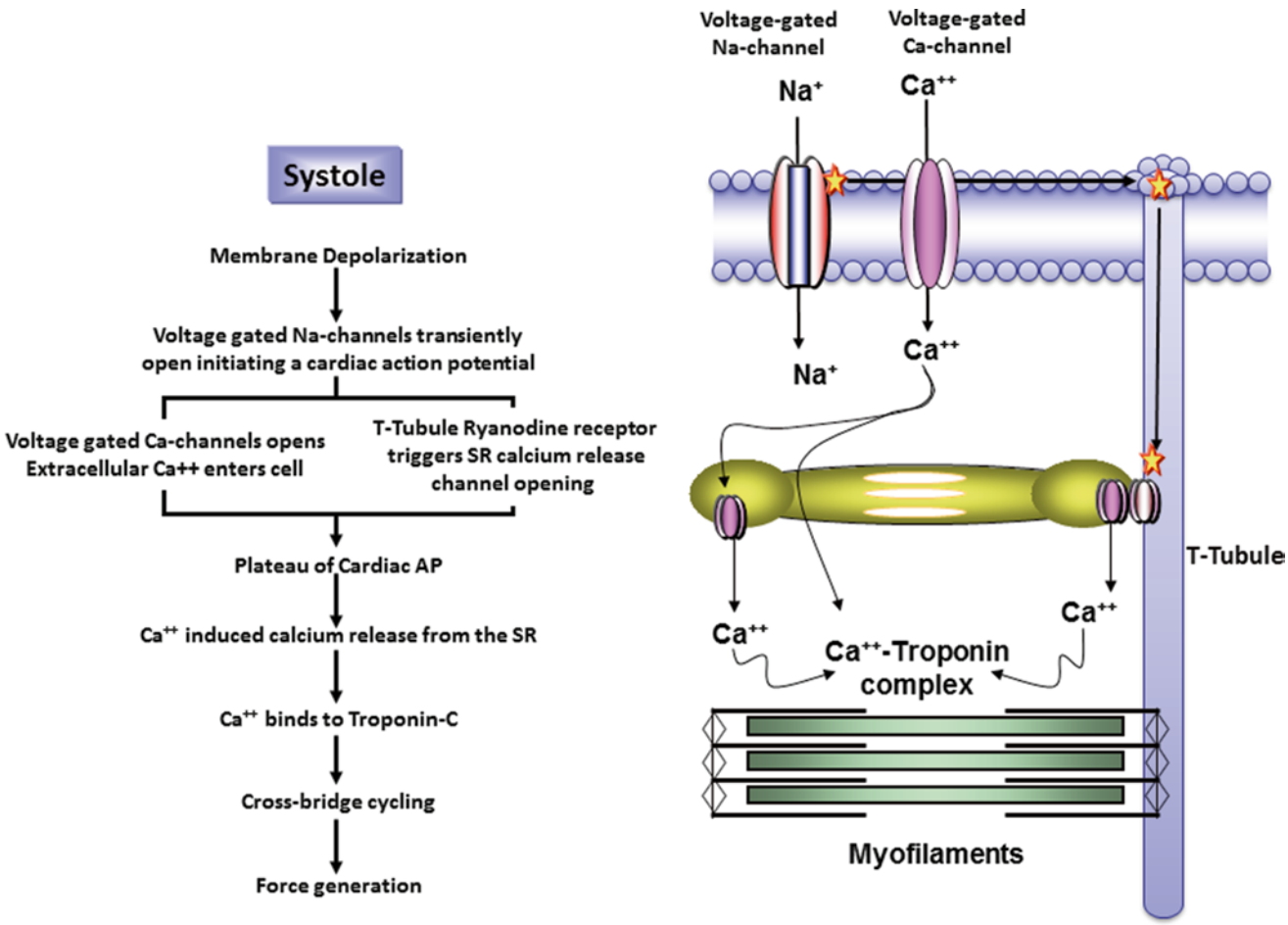

Fig. 12.10 Excitation-contraction coupling. In systole, an electrically depolarizing signal triggers the transient opening of voltage-gated Na channels; the influx of positively charged Na ions further depolarizes the cell. This further depolarization causes the opening of L-type Ca channels (long-duration opening), and calcium enters the cell. This also causes ryanodine receptors in the T-tubules to trigger the release of calcium from Ca channels in the sarcoplasmic reticulum. This initiates the plateau of the cardiac action potential. The rise in intracellular calcium concentration triggers additional calcium release from the sarcoplasmic reticulum via Ca channels. The calcium binds to troponin on the thin filaments, inducing the movement of tropomyosin. Crossbridge cycling begins generating tension in the cardiac myocytes

activates voltage-gated Ca^{2+} and K+ channels. The subsequent opening of the voltage-gated L-type (long opening duration) calcium channels allows calcium to enter the myocyte and sustains the depolarized state, despite the closing of the Na^+ channels. The opening of the voltage-gated K^+ channels is delayed in time and results in potassium efflux from the cell as the ion moves down its concentration gradient. This drives the membrane potential back toward the potassium equilibrium potential (more negative). The timing of these changes depends on the isoforms of the Ca^{2+} and K^+ channel proteins present in each cell with sinoatrial and atrioventricular action potentials lasting ~150 ms, ventricular myocytes ~250 ms, and Purkinje fibers ~300 ms (also see Chap. 13). The primary difference between these cell types is often the duration of the plateau phase (phase 2) which is primarily a response to changes in the isoforms of the Ca^{2+} channels (Figs. 12.12 and 12.13).

The various phases of the cardiac action potential are associated with changes in the flow of ionic currents across the cell membrane. Atrial and ventricular cardiac muscle cells have an extremely rapid initial transition from the resting membrane potential to depolarization (*phase 0*). In phase 0, the Na channels open, and there is a large amplitude, short duration inward Na current (Fig. 12.13). As the sodium channels begin to close, *phase 1* is defined as a small initial repolarization. The opening of the L-type calcium channels causes a calcium influx and is balanced by

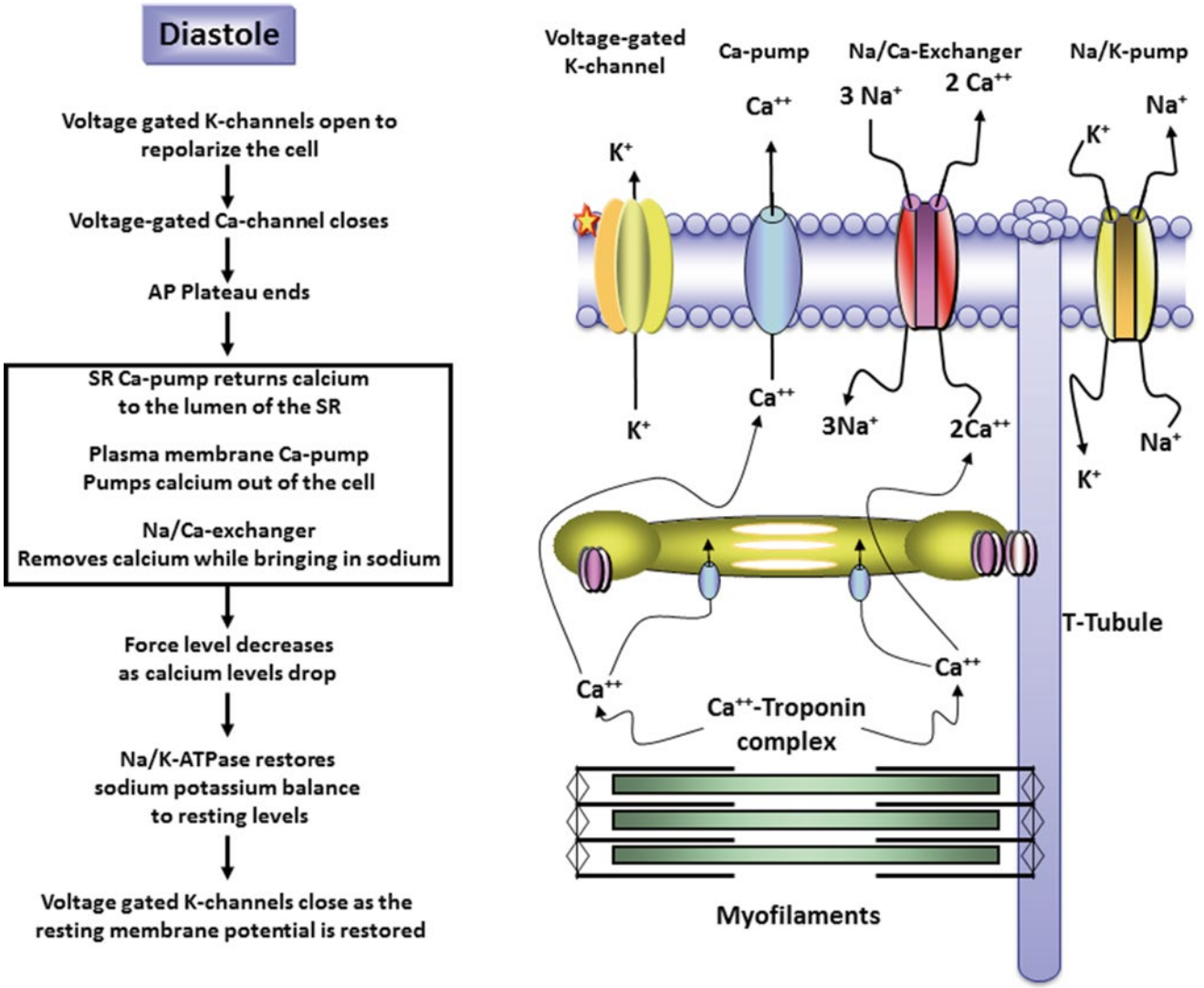

Fig. 12.11 Relaxation of cardiac muscle cells. The depolarization eventually opens voltage-gated K channels. K flows out of the cell, and, as the sarcolemmal Ca channels close, the cell begins to repolarize. Calcium is pumped out of the cytoplasm by ATP-driven pump proteins on the sarcoplasmic reticulum and sarcolemma. Calcium is also expelled from the cell via the Na/Ca exchange protein. To combat the rise in intracellular Na that this causes, the Na/K ATPase pumps K into the cell and Na out, helping to restore the resting potential and the ionic environment that existed before the cell was activated

the potassium efflux via the now open K^+ channels. This balance results in the electrically positive plateau (*phase 2*) of the cardiac action potential profile. As the Ca channels close, the flux of ions through the K^+ channels begins to dominate the membrane potential, and repolarization of the cells begins (*phase 3*). *Phase 4* is the restoration of the resting membrane potential and the closing of the K^+ channels. From the initiation of the action potential through approximately half of the repolarization, the cell is considered *refractory*, meaning that it could not respond to a new depolarization signal.

12.15 Pacemaker Cells

The sinoatrial (right atrium) and atrioventricular (interventricular septum) nodal cells have what are considered to be unstable resting potentials; a gradual rise in resting potential crosses the threshold for opening of T-type (transiently open) calcium channels. The movement of calcium into the cells (phase 0) initiates depolarization. No initial repolarization or plateau occurs, so phases 1 and 2 are said to be relatively absent. Repolarization (phase 3) is accomplished through

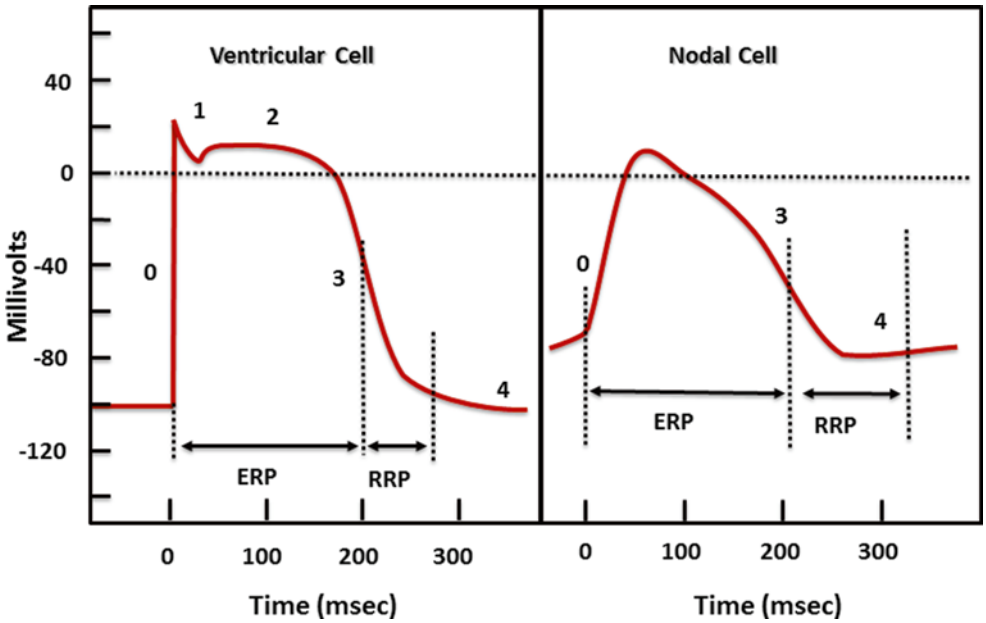

Fig. 12.12 Action potential profiles for ventricular and nodal cardiac cells. **Ventricular cell** (*left*). Before activation, the cell's membrane potential is negative (phase 0—*upstroke*). A small depolarizing event triggers the opening of voltage-gated Na channels (phase 1—*initial repolarization*). As the Na channels close, there is a small recovery in polarization; the voltage-gated Ca and K channels open followed by a *plateau* (phase 2) in the membrane potential. In phase 3, *repolarization*, as the Ca channels close, the K channels remain open, and the membrane potential grows more negative, eventually returning to *resting membrane potential* level (phase 4) where the K channels also close. From phase 0 through the middle of phase 3 is the effectively refractory period (ERP), meaning that another depolarization would not trigger the opening of the Na channels. The remainder of phase 3 is the relatively refractory period (RRP), during which a new depolarizing signal would cause some of the Na channels to reopen. **Nodal cell** (*right*). Pacemaker cells have a different electrical signature to their action potentials. The cells spontaneously rise to the threshold of T-type Ca channels whose opening is the cause of phase 0 upstroke that is not as rapid as that of the ventricular cells. There is no phase 1 or 2 as in ventricular cells. The opening of voltage-gated K channels causes repolarization, phase 3, ultimately reaching an unstable resting potential minimum from which the cells repeat the cycle. The spontaneous rise of the membrane potential has been attributed to leaky Na channels. The refractory periods of nodal cells reflect the potential for opening the T-type Ca channels

the opening of voltage-gated K^+ channels. Once the cell is repolarized (phase 4), leak channels (often attributed to slow Na^+ channels) contribute to instability of the resting potential and a gradual rise to the threshold value of the T-type Ca^{2+} channels (Fig. 12.12).

The sinoatrial node is a specialized collection of cardiac myocytes in the right atrium. These cells have unstable resting potentials that lead to spontaneous depolarizations of this cell cluster with a relatively rapid and regular repeat (i.e., more rapid than all other myocytes). Cardiac activation is governed by the principle of *overdrive suppression*. This principle states that the myocytes with the most rapid frequency of depolarization control the overall rhythm of the heart. Furthermore, the action potential of the sinoatrial node is referred to as a "slow response" because the upstroke of the depolarization is slower than that of the non-nodal cardiac cells that provide the contractile force during atrial or ventricular contraction. However, the rapid repeat of this "slow response" depolarization gives the sinoatrial node overall control of the heart rate. For additional details on this process, see Chap. 13.

12.16 Summary

The heart's function as a pump is dependent on coordinated contractions of its chambers to move blood throughout the body. These contractions are produced by cardiac myocytes, the muscle cells of the heart. This chapter describes the structure and function of these cells and provides insights into adaptations of the heart due to normal and pathophysiological changes over the course of a lifetime.

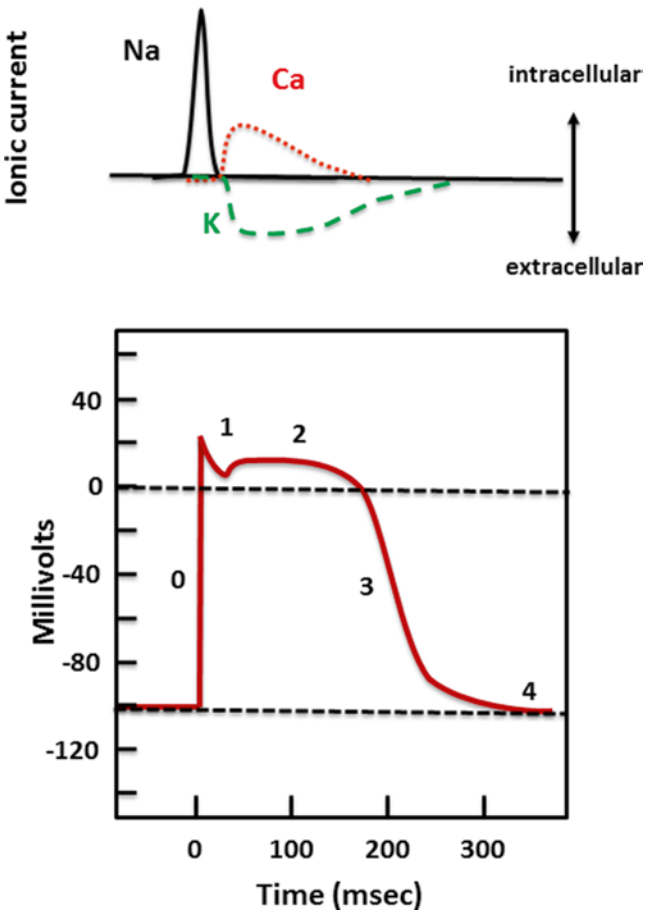

Fig. 12.13 Ionic currents corresponding to the phases of the ventricular action potential. The inward current associated with the opening of the voltage-gated Na channels is responsible for phase 0 of the cardiac action potential. The closing of the Na channels is reflected in the initial repolarization of phase 1. The depolarization of the cell by the Na current triggers the opening of the voltage-gated Ca channels and the voltage-gated K channels whose ionic currents are in balance during phase 2, the plateau. The closing of the Ca channels while the K channels are still passing an outward current causes the repolarization (phase 3) and return to the resting membrane potential (phase 4)

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