

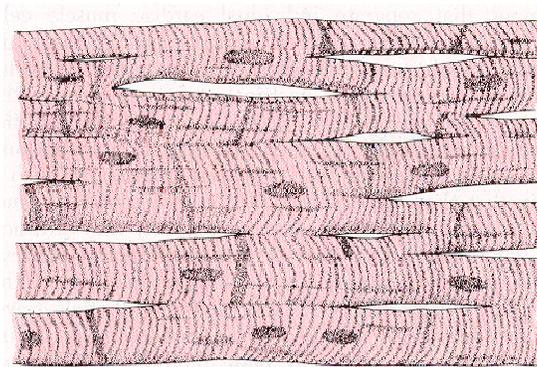
Cardiac Muscle.

Learning Objectives.

At the end of this course, you should be able to :

1. describe the structure of cardiac muscle
2. understand the concept of the functional syncytium
3. give a basic description of the differences between cardiac and skeletal muscle
4. discuss the mechanisms of control of cardiac contraction.

Cardiac or heart muscle resembles skeletal muscle in some ways: it is striated and each cell contains sarcomeres with sliding filaments of actin and myosin. Cardiac muscle cells, also called cardiocytes or cardiac myocytes, are relatively small, averaging 10–20 μm in diameter and 50–100 μm in length. A typical cardiac muscle cell has a single, centrally placed nucleus, although a few may have two or more. As the name implies, cardiac muscle tissue is found only in the heart.



Differences Between Cardiac And Skeletal Muscle Tissues

As do skeletal muscle fibres, each cardiac muscle cell contains organised myofibrils, and the presence of many aligned sarcomeres gives it striations. However, cardiac

muscle cells are much smaller than skeletal muscle fibres, and significant structural and functional differences exist between the two.

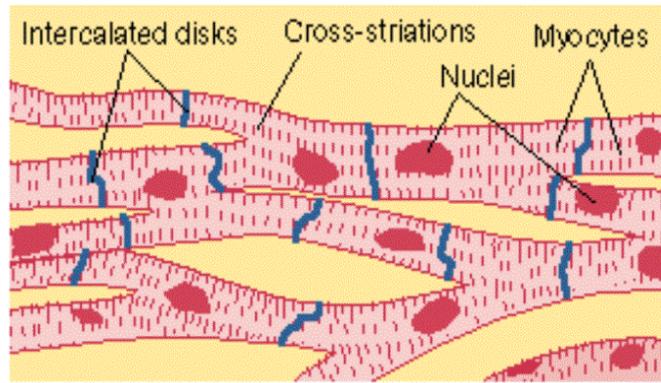
Structural Differences

Important structural differences between skeletal muscle fibres and cardiac muscle cells include the following:

- The T tubules in a cardiac muscle cell are short and broad, and there are no triads. The T tubules encircle the sarcomeres at the Z lines rather than at the zone of overlap.
- The sarcoplasmic reticulum (SR) of a cardiac muscle cell lacks terminal cisternae, and its tubules contact the cell membrane as well as the T tubules. As in skeletal muscle fibres, the appearance of an action potential triggers calcium release from the SR and the contraction of sarcomeres; it also increases the permeability of the sarcolemma to extracellular calcium ions.
- Cardiac muscle cells are almost totally dependent on aerobic metabolism to obtain the energy needed to continue contracting. The sarcoplasm of a cardiac muscle cell thus contains large numbers of mitochondria and abundant reserves of myoglobin (to store oxygen). Energy reserves are maintained in the form of glycogen and lipid inclusions.
- Each cardiac muscle cell contacts several others at specialized sites known as intercalated discs. Intercalated discs play a vital role in the function of cardiac muscle.

Intercalated Discs - at an intercalated disc the cell membranes of two adjacent cardiac muscle cells are extensively intertwined and bound together by gap junctions and desmosomes. These connections help stabilize the relative positions of adjacent cells and maintain the three-dimensional structure of the tissue. The gap junctions allow ions and small molecules to move from one cell to another. This arrangement creates a direct electrical connection between the two muscle cells. An action

potential can travel across an intercalated disc, moving quickly from one cardiac muscle cell to another.



Myofibrils in the two interlocking muscle cells are firmly anchored to the membrane at the intercalated disc. Because their myofibrils are essentially locked together, the two muscle cells can "pull together" with maximum efficiency. Because the cardiac muscle cells are mechanically, chemically, and electrically connected to one another, the entire tissue resembles a single, enormous muscle cell. For this reason, cardiac muscle has been called a *functional syncytium*.

KEY LEARNING POINTS.



- 1. Cardiac muscle cells are known as cardiocytes.**
- 2. Cardiocytes are much smaller than skeletal muscle cells, and rely completely on aerobic respiration.**
- 3. Intercalated discs exist so that the cardiocytes can communicate with a number of other cardiocytes.**
- 4. This direct connection allows the passage of electrical charge directly between the cells, speeding up the transmission of action potentials.**

Functional Differences

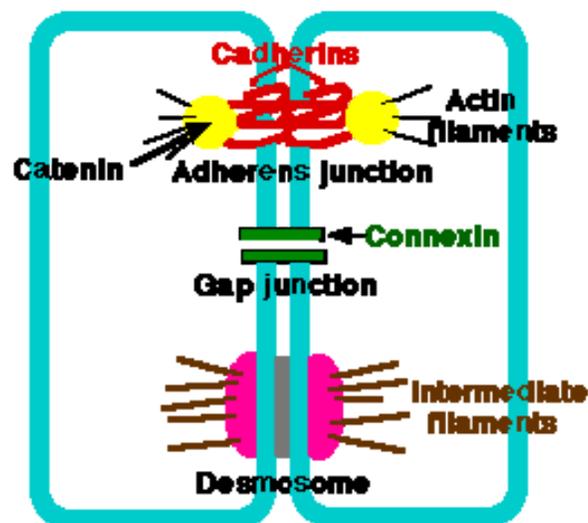
Briefly, the major functional specialties of cardiac muscle are :

1. Cardiac muscle tissue contracts without neural stimulation. This property is called automaticity. The timing of contractions is normally determined by specialized cardiac muscle cells called pacemaker cells (sino-atrial node, atrio-ventricular node).
2. Innervation by the autonomic nervous system can alter the pace established by the pacemaker cells and adjust the amount of tension produced during a contraction, but does not actually stimulate contraction. This comes from within the cardiac cells themselves (automaticity). Even if the autonomic nerve fibres are destroyed (as in a heart transplant) the cardiac muscle will still continue to contract.
3. Cardiac muscle cell contractions last roughly 10 times longer than do those of skeletal muscle fibres. This is because the refractory period in heart muscle is longer than the period it takes for the muscle to contract (systole) and relax (diastole). Thus tetanus is not possible.
4. Cardiac muscle has a much richer supply of mitochondria than skeletal muscle. This reflects its greater dependence on cellular respiration for ATP.
5. Cardiac muscle has little glycogen and gets little benefit from glycolysis when the supply of oxygen is limited. Thus anything that interrupts the flow of oxygenated blood to the heart leads quickly to damage of the affected part.
6. The branches of the muscle fibres interlock with those of adjacent fibres by adherens junctions. These strong junctions enable the heart to contract forcefully without pulling the fibres apart.

Adherens Junctions - adherens junctions provide strong mechanical attachments between adjacent cells. They hold cardiac muscle cells tightly together as the heart expands and contracts.

Adherens junctions are built from:

- cadherins - transmembrane proteins (shown in red in diagram below) whose extracellular segments bind to each other and whose intracellular segments bind to ...
- catenins (yellow) - these are connected to actin filaments.



Gap Junctions - Gap junctions are intercellular channels some 1.5–2 nm in diameter. These permit the free passage between the cells of ions and small molecules (up to a molecular weight of about 1000 daltons). They are cylinders constructed from 6 copies of transmembrane proteins called connexins. Because ions can flow through them, gap junctions permit changes in membrane potential to pass from cell to cell. Because of their action the action potential in heart (cardiac) muscle flows from cell to cell through the heart providing the rhythmic contraction of the heartbeat.

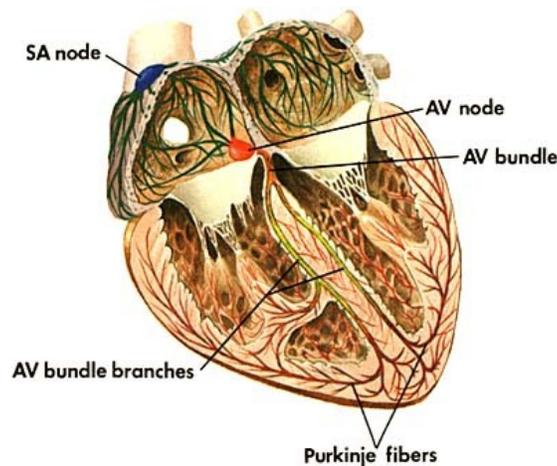
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Cardiac muscle action.

In cardiac muscle (and some types of smooth muscle) the cells are in electrical contact through communicating gap junctions. These are important for the orderly spread of excitation through the heart. This starts with the spontaneous depolarisation of the specialised pacemaker cells in the sino-atrial node, spreads via the atria to the atrio-ventricular node and thence to the conducting fibres in the Bundle of His (in the intraventricular septum) and the Purkinje system. These cells finally activate the bulk of the ventricular muscle in the chamber walls, in each case through direct electrical contacts.



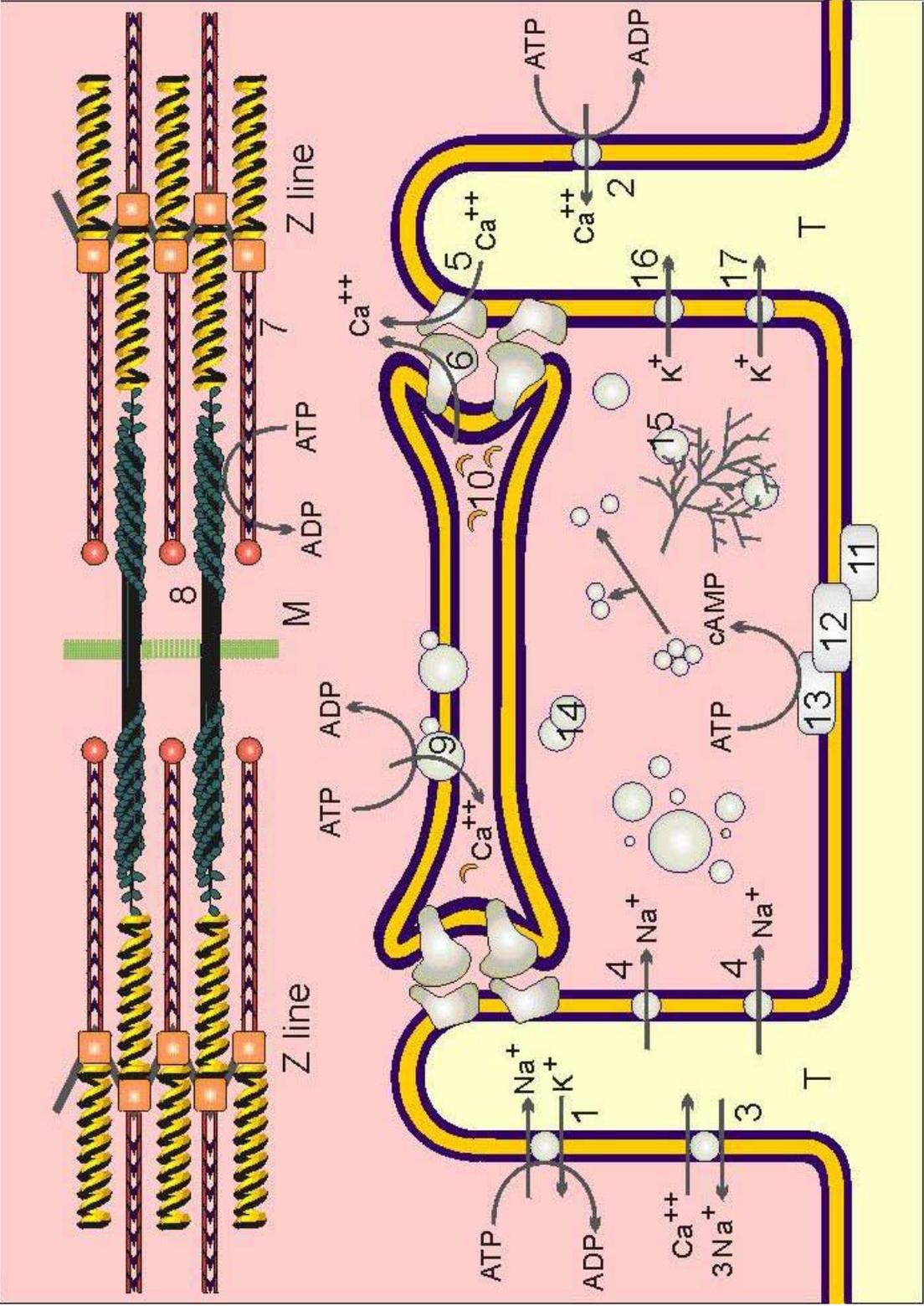
Catecholamine hormones such as adrenalin are released during frightening or stressful situations. They increase the force and frequency of cardiac contractions by binding to β_1 - receptors, which are protein molecules protruding from the outer face of the cardiac sarcolemma (surface of the cardiac cell membrane). These activate G-proteins within the membrane, which in turn activate the enzyme adenylyl cyclase on the inner face of the sarcolemma. Adenylyl cyclase produces cyclic AMP, which is an important second messenger controlling numerous intra-cellular activities. Cyclic AMP activates protein-kinase-A, which phosphorylates many intracellular enzymes, temporarily modifying their properties.

Cardiac muscle contains muscarinic acetylcholine receptors. These are also linked to adenylyl cyclase (via inhibitory G proteins) and to a potassium ion channel in the cardiac sarcolemma. Acetylcholine reduces the levels of cyclic AMP and increases potassium currents, promoting slower, less forceful beats. Many types of smooth muscle also contain gap junctions and muscarinic acetylcholine receptors, but here acetylcholine normally leads to contraction. Depending on the type of smooth muscle, catecholamines may produce either contraction (alpha receptors linked to intracellular calcium stores), or relaxation (beta receptors linked to adenylyl cyclase). This relaxation is apparently mediated by the cyclic AMP-dependent phosphorylation and inactivation of the enzyme myosin-light-chain-kinase, which plays a central role in smooth muscle contraction. Vascular smooth muscle redistributes the blood supply during exercise, and visceral smooth muscle empties the gut in stressful or frightening situations. In contrast to all this, the force of contraction in voluntary muscle is unaffected by circulating hormones.

Control of cardiac contraction

(you may find it easier to print off a copy of the diagram on the next page to refer to during this section).

The diagram shows the control of cardiac muscle contraction in greater detail. The Na/K ATPase or sodium pump (1) works continuously, using the energy from ATP to maintain a high K^+ concentration inside the cells and a high Na^+ concentration in the extracellular fluid (ECF). The cell membrane (sarcolemma) is usually more permeable to potassium ions than to sodium ions, and this gives rise to a membrane potential of about 80mV (negative inside the cell) in relaxed muscle. Calcium ions are also removed from the cytosol into the ECF by an ATP-driven calcium pump (2) in all tissues. Cardiac muscle possesses an additional sodium/calcium exchange protein (3). This export system is driven by the pre-existing sodium ion gradient. The calcium concentration inside resting cells is low, but rises sharply during contractions.



The sarcolemma is very thin (about 6nm) so the 80mV membrane potential equates to a voltage gradient of about 13,000,000 volts per metre. All membrane components are subject to intense electric fields, and protein conformations are greatly influenced by the membrane potential. Voltage-gated ion channels will only conduct over a narrow range of membrane potentials, whereas ligand-gated ion channels (such as the acetylcholine receptor in voluntary muscle) require specific chemical activators.

Contraction in cardiac muscle is triggered by a wave of membrane depolarisation which spreads from neighbouring cells. The change in electric field activates voltage-gated sodium channels (4) in the sarcolemma, each of which allows a few hundred positively charged sodium ions to enter the negatively charged cytosol, further reducing the cardiac membrane potential until the whole sarcolemma is depolarised.

The sodium channel undergoes a second conformational change, as a result of which these channels close spontaneously after a few milliseconds in all excitable tissues. In cardiac muscle, but **not** skeletal muscle, slower voltage-gated calcium channels, probably identical with dihydropyridine receptors (5) take over and maintain a positive inward current for several hundred milliseconds during the plateau phase of the cardiac action potential. As in nerves and skeletal muscle, the membrane potential in cardiac muscle is eventually restored to its resting value by a delayed efflux of positive potassium ions from the cells.

Dihydropyridine drugs (e.g. verapamil, nifedipine) inhibit calcium entry into heart and reduce blood pressure. About 10% of the calcium needed to activate cardiac contraction enters during each beat from the ECF. This is often described as "trigger calcium". The remainder is released from the sarcoplasmic reticulum through a channel known as the ryanodine receptor (6). Ryanodine receptors are widely distributed in the body, and are present in non-muscle tissues such as brain.

Calcium ions from both sources bind to the regulatory protein troponin-C located in the thin filaments (7), leading to a change in filament shape. This allows flexible head groups from the protein myosin in the thick filaments (8) to interact with the

protein actin in the thin filaments. A change in myosin conformation causes the thick and thin filaments to slide against each other and hydrolyse ATP, which provides the energy for contraction. Movement and ATP hydrolysis continue until the calcium ions are removed from the cytosol at the end of each contraction. Most of the calcium ions are returned to the sarcoplasmic reticulum by a calcium pump (9) but about 10% leave the cell via proteins (2) and (3) described above. Calcium ions are stored within the sarcoplasmic reticulum loosely bound to a protein, calsequestrin (10).

In cardiac muscle circulating hormones like catecholamines and glucagon bind to specific receptors (11) on the outer surface of the sarcolemma, changing their shape. This change is communicated via G-proteins (12) within the sarcolemma to adenylyl cyclase (13) bound to the internal face of the sarcolemma. Several G-proteins are known, some activatory, others inhibitory. They all slowly hydrolyse GTP while working, although it is not clear what advantage this confers on the cell. Adenylyl cyclase manufactures cyclic AMP, which is continuously destroyed by a phosphodiesterase enzyme. The steady-state concentration of cyclic AMP depends on the balance between synthesis and degradation. Cyclic AMP in turn controls the activity of cyclic AMP-dependent protein kinase. This enzyme phosphorylates several of the proteins involved in the contraction process, and temporarily alters their properties until a protein phosphatase restores the status quo by removing the phosphate group.

The sodium pump (1) is activated by phosphorylation, which allows it to handle the increased ion traffic across the sarcolemma when cardiac work output rises.

The dihydropyridine receptor (5) is activated by phosphorylation, increasing calcium entry into the cells. The ryanodine receptor (6) is also activated, increasing the rate of calcium release from the sarcoplasmic reticulum. The troponin-I component in the thin filaments (7) is phosphorylated and this reduces calcium binding to the neighbouring troponin-C. (This may be a defence mechanism preventing tetany in cardiac muscle, which would be rapidly fatal.)

A small protein called phospholamban associated with the sarcoplasmic reticulum calcium pump (9) is phosphorylated, and this accelerates calcium uptake by the SR pump (a fast heart rate requires quick relaxation as well as rapid contraction).

The enzymes triglyceride lipase (14) and glycogen phosphorylase (15) are activated by phosphorylation. These enzymes catalyse the first steps in the mobilisation of food reserves. They eventually increase the supply of ATP and provide the energy for the anticipated extra work.

These changes take place in a coordinated sequence over many seconds, so that the initial response to adrenalin may be a pounding heart, but both the rate and the force of contraction tend to return to normal when the stimulation is prolonged.

Skeletal muscle can contract in the absence of extracellular calcium, and skeletal SR shows depolarisation-induced calcium release. In contrast to this, cardiac SR needs external "trigger calcium" to enter the cells via the dihydropyridine receptors during the plateau phase of each action potential to initiate calcium-induced calcium release (CICR). Cardiac and skeletal ryanodine receptors probably differ in their precise intracellular location. Dihydropyridine receptors are also present in some smooth muscles. They are blocked by the important drugs verapamil and nifedipine, which reduce the force of cardiac contraction, while maintaining an adequate cardiac output by relaxing vascular smooth muscle and reducing the peripheral vascular resistance.

The systems which terminate CICR are far from clear. There must be some mechanism, since otherwise rising cytosolic calcium would lock the SR Ca^{++} release channels in the open state. It may be that the ryanodine receptor has a built in relaxation time (like the voltage gated sodium channels in the sarcolemma) or perhaps there is a mechanism to sense the emptying of the SR. The transmembrane protein triadin might provide a link to either measure or modulate calcium binding to the low-affinity binding protein calsequestrin in the lumen of the SR.

The repeated entry of external calcium ions during the plateau phase of each cardiac action potential requires a cardio-specific calcium export system to stabilise the internal calcium concentration. This is achieved by the electrical exchange of one intracellular Ca^{++} ion for three extracellular Na^+ ions in cardiac muscle. The exchange is assisted by the resting membrane potential. Cardiac glycosides such as ouabain and digitalis inhibit the NaK-ATPase, reducing the Na^+ gradient across the plasmalemma in all tissues. This specifically increases the force of cardiac (but not skeletal muscle) contraction by interfering with the cardiac Ca^{++} export system.

KEY LEARNING POINTS.



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