

Cardiac Muscle Contraction

The general principles of skeletal muscle contraction also apply to cardiac and smooth muscle contraction but there are a number of interesting and important differences.

Structure of the Heart

The human heart has four chambers:

Atria. The top two chambers that receive blood from the body or lungs.
Ventricles. The bottom two chambers. The right ventricle pumps blood to the lungs to pick up oxygen, The left ventricle pumps blood to the rest of the body and is the strongest chamber.

The insect heart is a simple tube. Heart contractions push the blood towards the head but because insects have an open circulatory system, there is no return circuit. The blood moves through the body cavity until it reaches the heart again. For most insects, heart contraction is initiated and regulated predominantly by external nerves; thus insect hearts are neurogenic. In contrast, vertebrates, tunicates, and some molluscs have myogenic hearts. The heart beat is initiated and regulated by specialized groups of muscle cells.

Cardiac muscle

Cardiac muscle (another type of striated muscle in vertebrates) has many similar properties to skeletal muscles but there are some important differences. Hearts of course vary greatly in size, shape and complexity from animal to animal - ranging from insects with a simple tube that pumps blood or hemolymph around an open circulatory system to our closed circulatory system and a four chambered heart. The basic principles that underlie cardiac muscle cell function though remain pretty much the same.

1) The heart contains pace-maker cells that produce the depolarization and action potentials to drive cardiac cell contraction. In other words heart contraction is not neuronally driven but self-driven or myogenically driven. (Of course there is an exception to every rule and some invertebrates the pacemaker cells are modified neurons that are attached to the heart). Some vertebrates hearts are innervated by neurons from the sympathetic and parasympathetic nervous systems but these neurons act in a modulatory function only.

2) Each muscle cell is a single cell not multinucleate like skeletal muscle. Like skeletal muscle cells each cell contains multiple myofibrils and in the cases of higher vertebrates an extensive sarcoplasmic reticulum and T-tubules. The SR and T-tubule system is not as extensive in animals with small cardiac muscle cells (myocytes) such as frogs and in many invertebrates. Therefore depending on the size of the cardiac muscle cells contraction can depend on Ca^{+2} release from the SR and/or Ca^{+2} influx from external sources outside the cell. This can

be tested as removal of external Ca^{+2} strongly affects frog cardiac cell contraction but rat cardiac cells still can contract as they rely more on release from the SR.

3) Cardiac muscle cells are linked to each other with gap junctions. This allows an action potentials to rapidly travel from cell to cell and makes the heart work as a unit. This allows the pacemaker cells, the sinoatrial node cells, to generate the action potential which is in turn relayed via the gap junctions throughout the heart to generate contraction through out the heart.

3) There are different types of cardiac muscle cells ranging from the pacemaker cells in the sinoatrial node to the ventricular cells that produce the contraction of the heart chambers. All use the same mechanisms of excitation-contraction coupling but as we'll see there are distinct features to the sinoatrial cells that allow them to be pacemakers.

4) The action potential in cardiac cells is quite different from skeletal muscle and neuronal action potentials in that voltage-gated Ca^{+2} channels play a much larger role. See section on cardiac channels and action potentials

5) The mechanism of triggering the Ca^{+2} release channel in the sarcoplasmic reticulum is not the same as in vertebrate skeletal muscle cells. See section on Ca^{+2} release channels in the skeletal muscle lectures to review the differences between the two.

Cardiac muscle channels

Pumps and transporters - Cardiac cells also have the same types of pumps and transporters as skeletal muscle cells. In particular they have:

1) $\text{Na}^{+}/\text{K}^{+}$ ATPase pump - to establish the electrochemical gradients of Na^{+} and K^{+}

2) Ca^{+2} ATPase pump - uses energy from ATP to remove 2 Ca^{+2} from the inside to the outside of the cell or into the sarcoplasmic reticulum to ensure that internal Ca^{+2} concentrations remain low (10^{-7} mM internal). Some cardiac cells (i.e. lower vertebrates, invertebrates) do not have an extensive sarcoplasmic reticulum and thus most of the Ca^{+2} that is used to trigger contraction is from extracellular sources.

3) $\text{Na}^{+}/\text{Ca}^{+2}$ cotransporter - to also remove Ca^{+2} from the inside of the cell and uses the energy from the cotransport of 3 Na^{+} molecules to export 1 Ca^{+2} .

Channels - cardiac muscle cells share many of the same ion channels as neurons and skeletal muscle cells.

1) leak channels - leak K^{+} channel

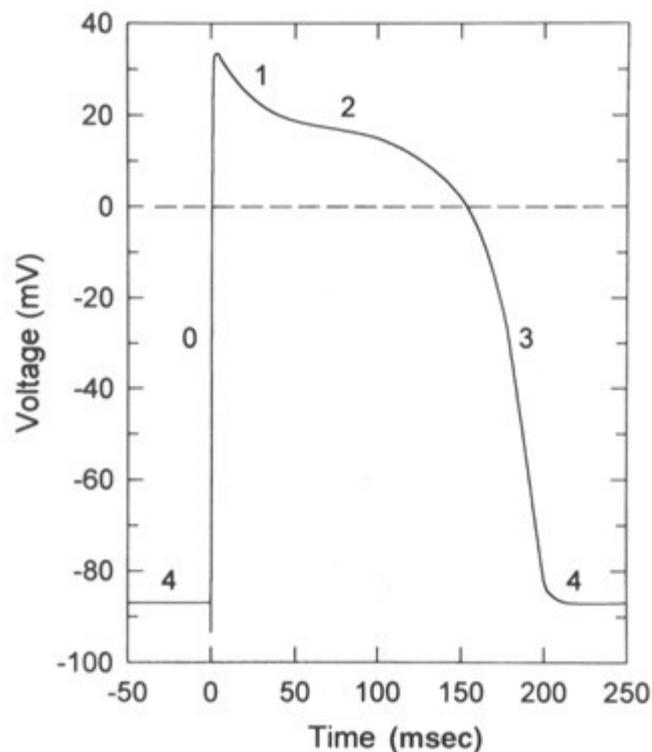
2) voltage-gated Na^{+} channels - there is a skeletal muscle voltage-gated Na^{+}

channel which properties very much like the neuronal voltage-gated Na^+ channel we have already discussed at length. TTX - sensitive as we saw above. This channel is of course responsible for the production of the action potential. Once opened the influx of Na^+ through the channel further depolarizes the membrane thus opening more Na^+ channels and this regenerative cycle continues until the Na^+ channels start to inactivate and the delayed K^+ channel begins to open.

3) voltage-gated K^+ channel - the delayed rectifier K^+ channel which we have already seen in neurons with exactly the same properties. In other words has a high threshold and needs a strong depolarization to open and works to bring the membrane back to resting potentials.

4) voltage gated Ca^{+2} channels - in cardiac cells the Ca^{+2} channel plays a much greater role during the action potential. These channels are the high threshold Ca^{+2} channels, called L channel or DHP (dihydropyridine) channel). The cardiac DHP channel is very similar to the skeletal muscle DHP Ca^{+2} channel and are found concentrated in the T-tubules in those cardiac cells with extensive T-tubules and SR.

Action potential in ventricular cardiac cells



(Figure from "Cell Physiology Source Book")

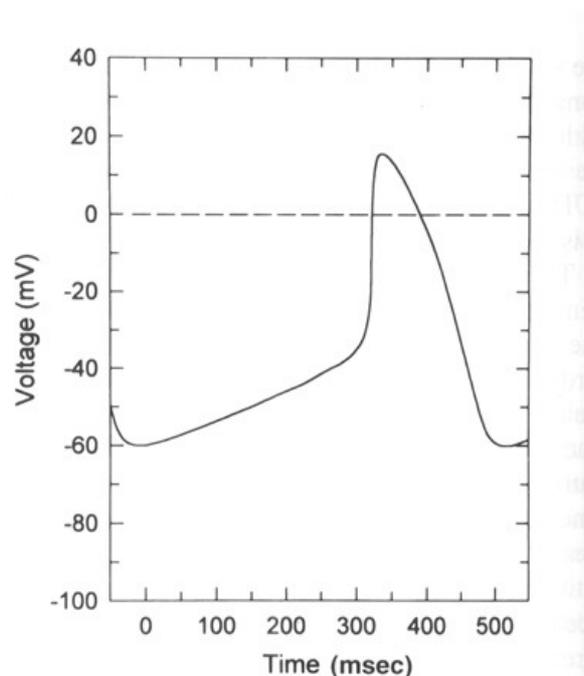
The above diagram is an action potential recorded in the ventricular cardiac cell of the heart. 4) Resting potentials in these cells is set by a large K^+ permeability due to a combination of the leak K^+ channel and a voltage-gated

K⁺ channel (called the inward rectifier K⁺ channel) that is open at rest. This means that rest is very close to E_{K⁺}.

- 0) The rising phase of the action potential is set by the cardiac voltage-gated Na⁺ channel which has properties very similar to the neuronal and skeletal muscle voltage-gated Na⁺ channels.
- 1) 1-2) As the voltage-gated Na⁺ channels produce the rising phase and then start to inactivate two channels will now be opening, the delayed rectifier K⁺ channel and the voltage-gated Ca²⁺ channel (L or DHP channel). There are many Ca²⁺ channels in these cells and thus this channel dominates the membrane potential producing a long plateau of depolarization. This plateau is a balance between the open Ca²⁺ channels and the open K⁺ channels. Remember the Ca²⁺ channel only slowly inactivates and thus this plateau can persist for 100-200 msec.
- 3) Finally the voltage-gated Ca²⁺ channel inactivates and the voltage-gated K⁺ channels will now dominate and the membrane potential will repolarize to rest (E_{K⁺} in these cells). Then the voltage-gated K⁺ channels will close, the voltage-gated Na⁺ channels will switch from the inactive to the closed state and the membrane is set back at 4) ready to fire again.

The long Ca²⁺ plateau allows Ca²⁺ inside the cell to elevate enough to generate contraction in the case of those cardiac cells that rely on external Ca²⁺ sources.

Action potential in sinoatrial cardiac cells



(Figure from "Cell Physiology Source Book")

Sinoatrial cells have the ability to spontaneously fire action potentials in a repeated fashion without any external influence. These cells are the pacemaker cells of the heart and once an action potential fires in these cells it is propagated via gap junctions to other regions of the heart first to the atrial cells and then eventually making it to the ventricular cells.

The generation of the action potential in these cells is very similar to the ventricular cardiac cells with a few major exceptions.

1) These cells do not have a stable rest. There is a spontaneous slow depolarization that brings the membrane from -60 mV to threshold for the action potential (about -40 mV).

2) The action potential is driven by the voltage-gated Ca^{+2} channel or the voltage-gated Na^{+} channel (some pacemaker cells use only the voltage Ca^{+2} channel). The rising phase is due the opening of the voltage-gated Ca^{+2} channel (L or DHP channel again) and thus is slower than in other excitable cells.

3) As the Ca^{+2} channel inactivates the membrane is repolarized by the delayed rectifier K^{+} channel as in other excitable cells.

4) What makes these cells then spontaneously depolarize once the delayed K^{+} channel has closed is the presence of an ion channel that is activated by hyperpolarization. In other words a channel that opens when the membrane reaches $E_{\text{K}^{+}}$ and allows Na^{+} to flow into the cell. (Called the funny channel in some literature). Therefore the Na^{+} influx will depolarize the membrane to open the voltage-gated Ca^{+2} channels and at the same time close the funny channel.

Modification of cardiac muscle function

The Ca^{+2} channels in cardiac myocytes act as important control points for controlling the heart. Release of neurotransmitters from the autonomic nervous systems can increase or decrease heart contraction.

Epinephrine: released from the sympathetic nervous system. Binds to the β -adrenergic receptor which is a G protein associated membrane receptor. This triggers a signal transduction cascade outlined below that activates the G protein (G_s - stimulates) that activates adenylate cyclase to produce cAMP.

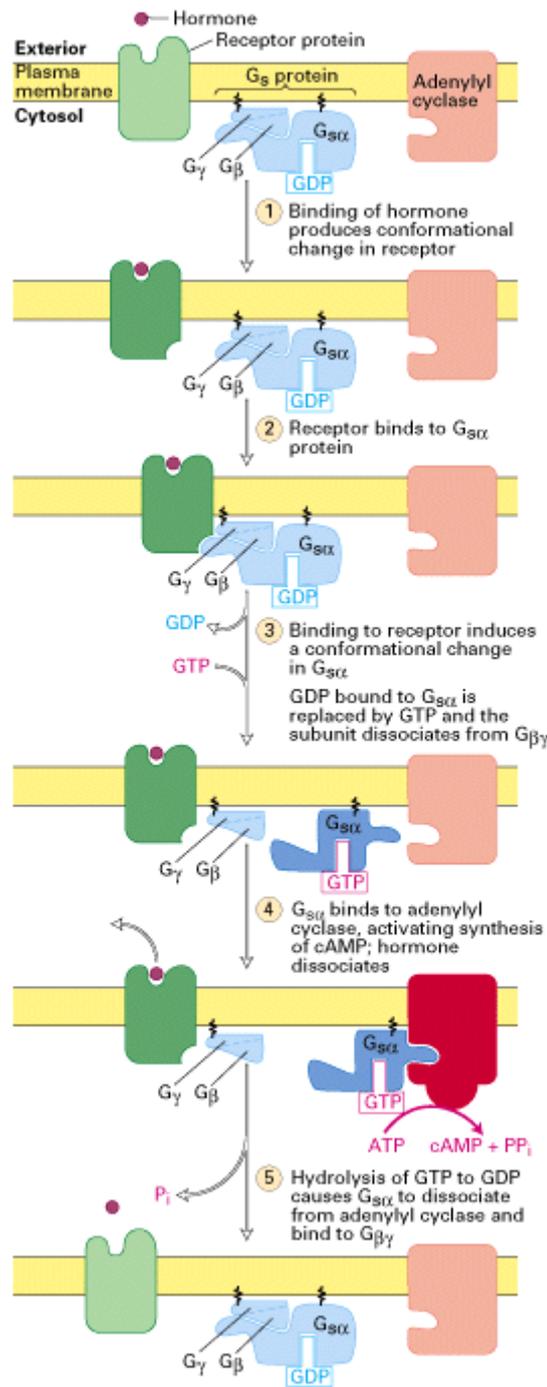


Figure 20-16. Activation of adenylyl cyclase after binding of epinephrine. (From "Molecular Cell Biology")

The increase in cAMP stimulates PKA (protein kinase A) which in turn phosphorylates the voltage-gated Ca^{2+} channel (L channel). This phosphorylation results in a protein conformational change that enhances the channels activity. This new conformation of Ca^{2+} channel opens more readily (i.e. less time between action potentials) and opens for longer (i.e. more Ca^{2+} flow into the cell = greater $[Ca^{2+}]$ intracellular = greater contraction).

Note: Epinephrine stimulates glycogen breakdown in skeletal muscles.

Epinephrine through binding to its G protein associated receptor results in the G protein stimulation of an enzyme glycogen phosphorylase kinase. As its name implies glycogen phosphorylase kinase phosphorylates glycogen phosphorylase to activate this enzyme. As you all remember glycogen phosphorylase takes glycogen and breaks it down into glucose1-phosphate to initiate glycolysis. Glycogen phosphorylase kinase can be stimulated by two mechanisms G protein and increase in Ca^{+2} internally and in this way during periods of concentrated activity the glycogen energy stores of muscles can be mobilized.

Acetylcholine: released from parasympathetic nervous system.

Binds to the muscarinic receptor a G protein associated receptor. The G protein activated in this case is a G_i α subunit that inhibits adenylate cyclase. Therefore in this case acetylcholine works to block any rise in cAMP and thus blocks activation of PKA so that it can not phosphorylate the Ca^{+2} channel.

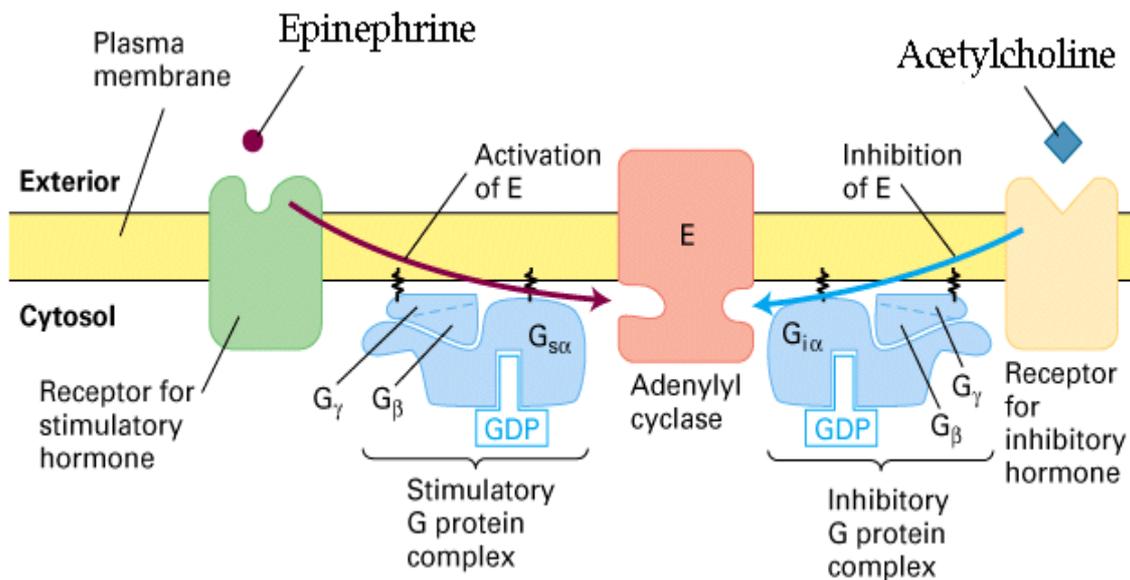


Figure 20-18. Epinephrine activates adenyl cyclase while acetylcholine inhibits. (From "Molecular Cell Biology")

Acetylcholine also works through the muscarinic receptor to stimulate the opening of a K^{+} channel. The muscarinic receptor stimulates a G protein α subunit that directly activates a K^{+} channel. The opening of the channel suppresses the excitability of the membrane and less suppresses muscle and heart contraction.

Some major points on the properties of Cardiac Muscle.

This document will consider how the heart works as a pump, concentrating on the electrical properties of cardiac muscle.

Cardiac muscle fibres encircle the chambers of the heart: when the fibres contract, the chambers become smaller and blood will be expelled from them; when the muscles relax, blood enters the chambers again. The atrio-ventricular valves prevent blood from going into the atria when the ventricular fibres contract, instead blood must leave via the pulmonary artery or the aorta. The aortic and pulmonary valves stop blood entering the ventricles from arteries; the ventricles must fill from the atria. Therefore, the heart works as a pump simply by the fibres surrounding the chambers alternately contracting and relaxing, combined with the presence of valves that allow the ventricles to fill from only the atria and to expel their contents solely into the arteries.

The contraction of the heart is called systole and the relaxation, diastole; the final e is a separate syllable in both terms. The left and right sides of the heart beat in unison. Atrial systole occurs just before ventricular systole and the atria are in diastole when ventricular systole is occurring. After ventricular systole, all of the heart is in diastole.

The heart continues to beat regularly when its nerve supply is cut, which skeletal muscle would not do, and even continues to beat when it is completely removed from the body; this is called inherent rhythmicity. The first experiments into the nature of inherent rhythmicity were carried out by **Stannius** on frogs' hearts, which differ from human hearts. In frogs there is only one ventricle and it has no coronary circulation; the wall of the ventricle is sufficiently thin to obtain all its needs from the blood within the ventricle. The chambers corresponding to the atria are called auricles and there are left and right auricles; the venae cavae do not open directly into the auricles but into another chamber, the sinus venosus, which drains into the right auricle. Humans in embryo, like frogs, have a sinus venosus and an auricle but the two chambers combine during development to form the right atrium.

After **Stannius** tied a ligature between the sinus venosus and the right auricle, the sinus venosus carried on beating at the same rate as before but the rest of the heart, though it continued beating, did so more slowly. When **Stannius** tied a second ligature around the heart between the auricles and the ventricle, the auricles were not affected but the ventricles beat more slowly than before. Therefore all the chambers of the heart have inherent rhythmicity but the part that normally drives the heart, which is called the pacemaker, is in the sinus venosus and it has a higher frequency than the other parts of the heart. Warming the sinus venosus accelerates the heart, cooling down the sinus venosus slows it; changing the temperature of the ventricle has no effect on the heart rate as the pacemaker is not affected.

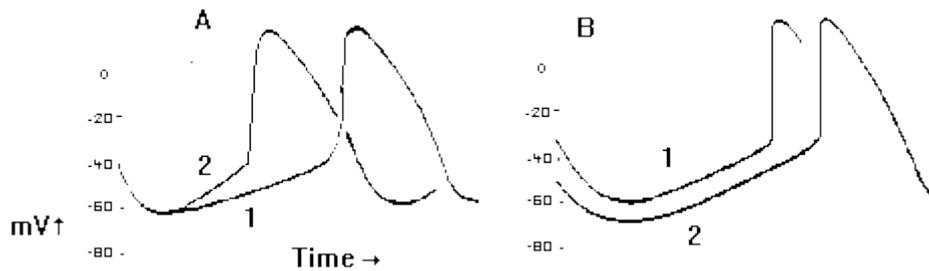
Mammalian hearts do not have a sinus venosus, so where is their pacemaker? When warm rods were used to apply heat to localised parts of the heart, there was an acceleration of the heart when the rod was applied to the sino-atrial node, but not when the rod was applied to other parts of the heart; therefore the sino-atrial node is the pacemaker of the mammalian heart. The sino-atrial node is a region of the right atrium, near the opening of the superior vena cava, where the cardiac muscle cells are smaller than normal; the node is in the part of the atrium that was originally the sinus venosus.

The membrane potentials of cardiac muscle cells have been studied since the 1950's to find out how inherent rhythmicity arises. The membrane potentials of cells in the sino-atrial node differ from those of nerve and skeletal muscle in several respects: the action potential in cardiac muscle is long, lasting 200ms or more. The resting membrane potential is around -50 to -60mV; it is less polarised than in other excitable tissues because the sodium permeability is higher and, therefore, the membrane potential is further from the potassium equilibrium potential in the sino-atrial node. The inherent rhythmicity is due to the membrane potential depolarising spontaneously so that it reaches the threshold of its own accord. The depolarisation during diastole, sometimes called the pacemaker potential, is due to more cations entering the cell than leaving it; at least some of the cations going into the cell are calcium but changes in permeability to sodium and potassium may also have a role.

In humans the inherent rhythmicity has a rate of 100-120 beats/min. The resting heart rate is around 70 beats/min and it is lower in fit than in normal people; in exercise the rate may rise as high as 200 beats/min. Therefore, the heart rate can be both accelerated (tachycardia) or slowed (bradycardia) and it is the autonomic nervous system that does this; the autonomic nerves do not initiate the heart beat, they just control its rate, which is called a chronotropic effect. Sympathetic fibres produce a tachycardia and parasympathetic fibres, which reach the heart in the vagus, produce a bradycardia. Usually both branches of the autonomic nervous system are active throughout the entire range of heart rates: at slow rates there is a lot of parasympathetic activity but still a little sympathetic activity; at high heart rates, there is a large amount of sympathetic activity but still some parasympathetic activity.

Sympathetic activity accelerates the heart by making the depolarisation during diastole be more rapid so that the threshold is reached earlier. In the diagram below, Section A shows the effect of sympathetic stimulation on the sino-atrial node; trace 1 is a control record and trace 2 the response to sympathetic stimulation. Parasympathetic activity produces a bradycardia by increasing the permeability of the cells to potassium so that the membrane potential gets closer to the potassium equilibrium potential and is hyperpolarised; therefore the membrane potential at the beginning of diastole is further from the threshold and takes longer to get there. This is illustrated in Section B of the diagram below where trace 1 is a control record and trace 2 the response to activity in the vagus. Note that the change in heart rate is produced by altering

the length of diastole and systole is little affected; this has implications for the filling of the heart that will be considered in the course.



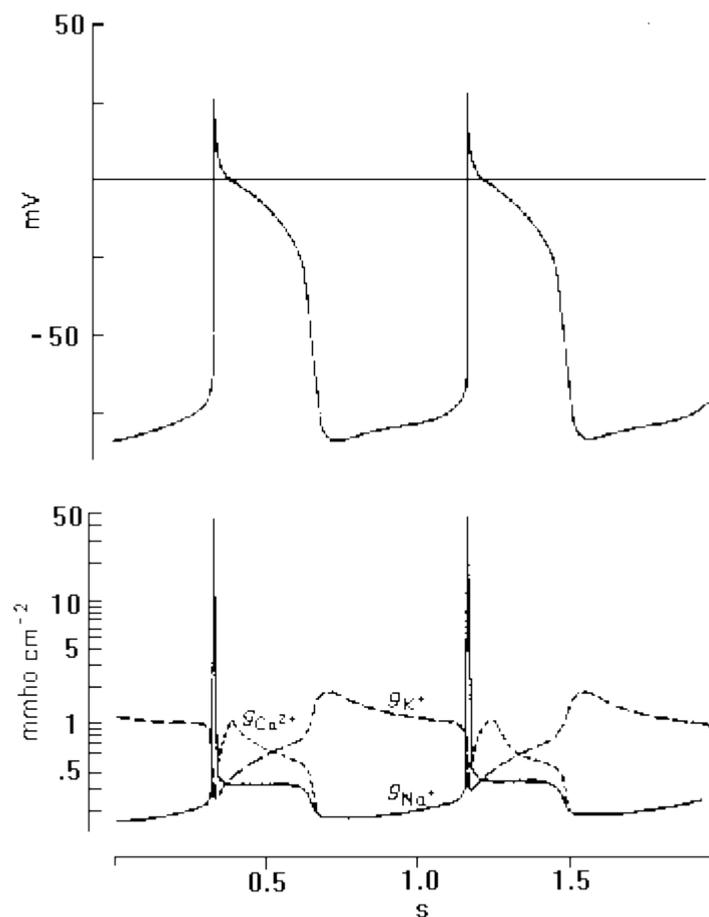
How does the action potential spread from the pacemaker to the rest of the heart? If the heart were made of skeletal muscle, this would be impossible because the action potential could not jump from one muscle fibre to another, but in cardiac muscle the fibres branch and join so that all the fibres are continuous with each other. The fibres consist of individual cells, separated by cell membranes called intercalated discs, but the discs do not stop action potentials travelling along the fibre, as ordinary cell membranes would, because there are low electrical resistance pathways which are, presumably, water filled pores, through the intercalated discs. Cardiac muscle behaves electrically as if the cells had fused together so it is called a functional syncytium. Once an action potential has been generated in one part of the heart, it will spread over the whole heart so the pacemaker of the heart will be the first part of the heart to reach its threshold, which is usually the sino-atrial node. If part of the heart is damaged, that part may depolarise more rapidly and become the pacemaker; these abnormal pacemakers are called ectopic foci. The heart rate is controlled by the autonomic fibres going to the sino-atrial node so when an ectopic focus is present, the heart rate cannot be controlled.

The action potential travels through the heart along a particular route. The atrial and ventricular cardiac muscle fibres are separated from each other by fibrous tissue, which does not conduct action potentials, except for a single strand of cardiac muscle at the top of the interventricular septum, the bundle of His, which is the only way that the action potential can get from the atria to the ventricles. At the atrial end of the bundle of His, there is a region where the cardiac muscle cells are small and the region is called the atrio-ventricular node. The action potential travels from the sino-atrial node to the atrio-ventricular node through the atrial fibres; if you look hard enough, you may find some differences between the cells on the direct route from one node to the other and the cells in other parts of the atria but the differences are slight and unimportant. The cells of the atrio-ventricular node are small so that their conduction velocity is low and the action potential takes a long time to get through the node; this allows atrial systole to be completed before ventricular systole begins.

The action potential travels from the atrio-ventricular node to the ventricles along the bundle of His; if the bundle is damaged the ventricles will still beat

because of their own inherent rhythmicity but the heart rate will be slow and ventricular systole will not always immediately follow atrial systole. The bundle of His is made up of fibres with a large diameter, called Purkinje tissue, which radiates throughout the ventricles, so that all cardiac muscle cells are close to some Purkinje tissue. The conduction velocity of Purkinje tissue is high, and its function is to conduct action potentials rapidly to all parts of the ventricles. Note that Purkinje tissue is modified cardiac muscle, not nervous tissue, and that its high conduction velocity is due to the large diameter of its fibres; it is not myelinated. The rapid conduction of the action potential to all parts of the ventricle ensures that ventricular systole begins almost simultaneously throughout the ventricles, allowing the ventricle to pump efficiently; if the fibres at one end of the ventricle were beginning to contract when fibres at the other end were relaxing, blood would be moved from one end of the ventricles to the other and little blood would be pumped into the arteries.

The action potential and the ionic permeabilities of ventricular muscle are different from the sino-atrial node and are illustrated in the diagram below. Note that ions carry charge so permeabilities to them can be expressed electrically as conductances (g), which are the reciprocal of resistance.



Some of the features have important implications: the action potential starts to repolarise, then has a plateau before fully repolarising; the plateau is due to calcium ions entering the fibre. The calcium ions are important in connecting

the action potential to the contraction (excitation-contraction coupling) using a troponin and tropomyosin system that has some similarities with and differences from the system in skeletal muscle. Cardiac muscle fibres have a smaller diameter and a longer action potential than skeletal muscle fibres, so larger amounts of calcium ions will enter the fibre during an action potential and will diffuse further to the centre of the fibre in cardiac than in skeletal muscle. Also, in cardiac muscle the increase in intracellular calcium concentration, produced by the influx of calcium, makes calcium be released from the sarcoplasmic reticulum, further increasing the calcium concentration; this is called calcium-induced calcium release (CICR) and is one of the few examples of positive feedback within the body. Therefore, cardiac muscle is less dependent on the t-tubules for excitation-contraction coupling than skeletal muscle.

The length of the action potential produces a desirable property of cardiac muscle: its inability to go into tetanus. The heart acts as a pump only as long as it alternately contracts and relaxes; if it went into tetanus, the heart would expel all the blood within it then stop pumping. The duration of systole is about the same length as the action potential and the refractory period, which is the time when the heart will not respond to a stimulus, corresponds to the action potential. Therefore the heart must relax before it can contract in response to a second stimulus, so it cannot go into tetanus. If an electric shock is applied to the heart in diastole, which is outside the refractory period, an extra beat (extrasystole) will be produced but the extrasystole will have its own refractory period and the heart will relax again before it can give another contraction, so that even a train of stimuli cannot make the heart go into tetanus. However, under certain circumstances the long refractory period can make an irregularity of the heart beat get worse. If the ventricle is stimulated during diastole an extrasystole will be produced that will make the heart be refractory when the next action potential from the sino-atrial node reaches the ventricle and the normal beat will be lost. Therefore the ventricle will not beat again until the following action potential from the sino-atrial node reaches the ventricle, so that the extrasystole will be followed by a very long diastole which is called a compensatory pause.