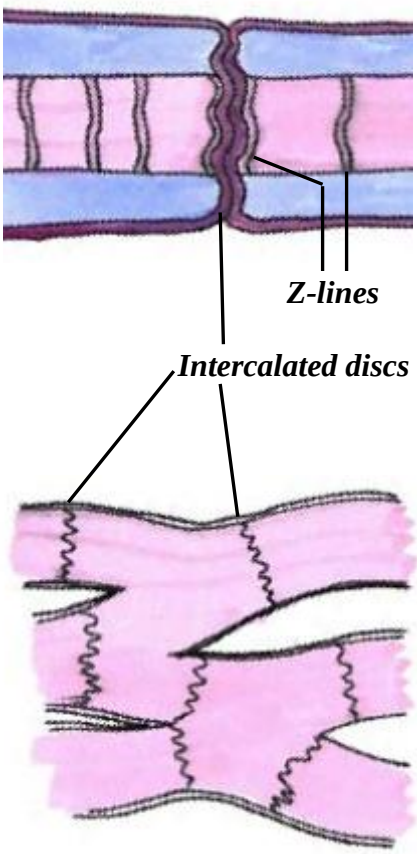
Cardiac Muscle Physiology

Special characteristics of cardiac muscle



- Branching and interdigitating cells
- At their ends, they are connected by INTERCALATED DISCS
- The discs are always at the Z-lines of the myofibrils
- The disc bind the myocytes together and cause them to pull on each other when they contract
- The adjacent fibers also form low-resistance GAP JUNCTIONS
- This way action potentials are transmitted rapidly from one fiber to another
- This permits the myocardium to function as a SYNCYTIUM
- The T-tubules are AT THE Z LINES, not at the A-I junction as they are in the skeletal muscle

- the resting membrane potential of a myocardial cell is about -80mV

CONTRACTILE RESPONSE

- starts just after the start of depolarization
- lasts about 300 msec

MAJOR DIFFERENCE is that instead of being directly attached to the Ryanodine receptor, the L-type "dihydropyridine receptor" calcium channel has to release some calcium into the cell. Seeing as the Ryanodine receptor is a calcium-gated calcium channel, this initiates the release of calcium.

GLYCOSIDE DRUGS

- Eg. Digoxin
- Inhibit Na^+/K^+ ATPase
- Thus, more Na^+ and less K^+ inside the cell
- This reduces the activity of the Na^+/Ca^{++} exchanger (which runs mainly on Na+ concentration gradient)
- Thus, less Ca++ is exchanged out of the cell
- More intracellular Ca^{++} = greater contractility

GLYCOSIDE TOXICITY

Overinhibition of the Na^+/K^+ ATPase results in a partially depolarized cell. This slows conduction and can cause the cell to depolarize spontaneously. Hence, arrhythmias and bradycardia.
… digoxin also competes with K+ ions for the same binding site on the ATPase; thus in hypokalemia, its effect is greater because it has no competition. In hyperkalemia, it may be outcompeted and thus not therapeutic.

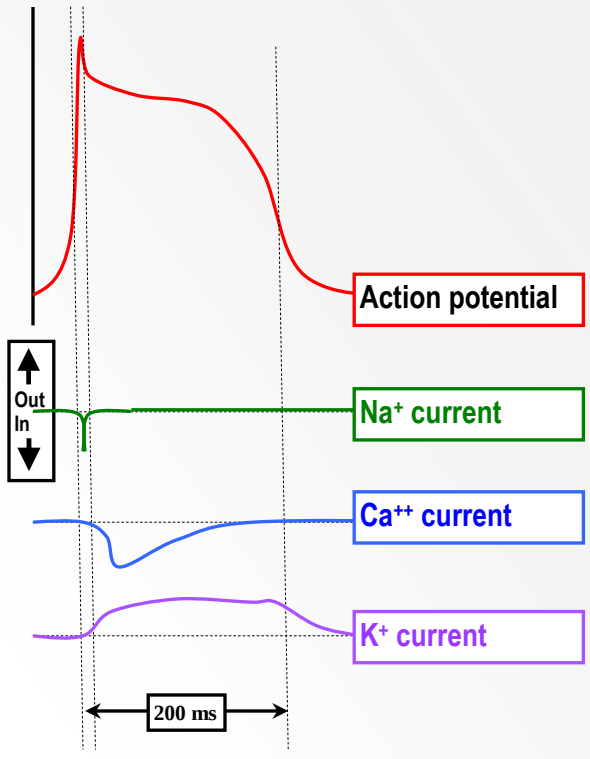
REFRACTORY PERIOD

Phases 0, 1, 2 and most of 3 are refractory to stimulation. In fact, until the membrane reaches -50 mV the myocyte cannot contract again. This is the ABSOLUTE REFRACTORY PERIOD.
Thankfully, it means the cardiac muscle can never suffer tetany.

FIBER TYPES

- oxidative metabolism is the main form here
- ATPase activity is relatively low

The Cardiac Action potential briefly:



Ion Channels of the Myocardial Muscle cell

Extracellular Fluid: poor in K^+, rich in Na^+

Myocardiocyte: rich in K^+, poor in Na^+

The ubiquitous Na^+/K^+ ATPase is the pump that keeps sodium out and potassium in.

The SERCa pump : (sarco/endoplasmic reticulum Ca^{++} pump) constantly sucks calcium into the sarcoplasmic reticulum.

Sarcoplasmic Reticulum (SR)

Ca^{++}

SERCA ATPase

phospholamban

Sympathetic Input: beta-receptors activate phospholamban, which in turn upregulates the calcium pumping. The more calcium in the SR, the more contractility.

K^+

ATP

Na^+

Ca^{++}

ATP

Ca^{++}

Na^+ FAST Na^+

I-R K^+

Trans. K^+

Calcium gated Ca^{++}

O-R K^+

Ca-G K^+

L-type Ca^{++}

GLORY TO THE Na+/K+ ATPase;
Its common to all animals; maintains the potential difference between inside and outside (for myocardial cells, this is about -90 millivolts) Its responsible for much of the RESTING POTENTIAL. For every 3 sodium atoms going out, 2 potassium ions come in.

Thanks to the Na+ /K+ ATPase, the sodium concentration gradient can be used to pump other things, for instance, CALCIUM as in this calcium/sodium exchange pump. You have to keep the calcium out of the myocardiocyte, because too high a concentration will open the calcium-gated calcium channels in the sarcoplasmic reticulum, and cause contraction.

The outward current of calcium is also maintained by the active ATP-powered calcium pump.

FAST VOLTAGE-GATED SODIUM CHANNELS: when the threshold potential is reached, these let the sodium back into the cell in a huge torrent of positivity, thereby depolarizing the cell. They only open for a millisecond, and then close until the cell has repolarised.

RESTING OPEN POTASSIUM CHANNELS:
While the cell is at rest, the potassium channels allow a potassium leak out of the cell. This is driven by the concentration gradient. However, potassium is also being attracted back into the cell by the electrostatic attraction of all that negative charge inside. This negative charge is provided by the predominantly negative large proteins in the cytosol. And so the current of potassium reaches an equilibrium at around -90 millivolts, with the attracting and repelling forces becoming equal at this voltage.

IN ACTUAL FACT, there are several types of potassium channels.

Inward-rectifying:
- open at rest, closed during depolarisation

Outward-rectifying
- closed at rest, open during depolarisation

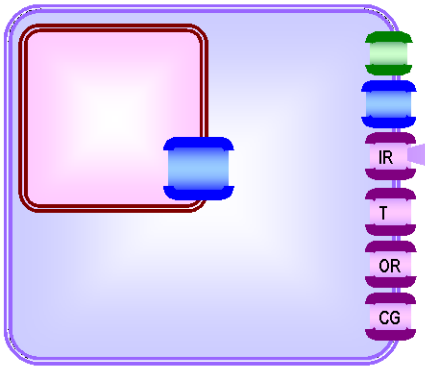
Transient:
- open ONLY during phase 1 – very brief period of action, responsible for the fast down-stroke

Calcium-Gated:
- open at the end of phase 2, when calcium concentration peaks- these are responsible for the end of phase 2

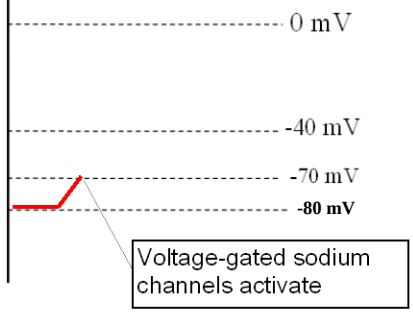
VOLTAGE-GATED CALCIUM CHANNELS: the L-TYPE CALCIUM CHANNELS
These open during the fast upstroke phase, when suddenly the cell becomes less negative; on its way up, at around -40 millivolts, they let calcium back into the cell (it flows along a gradient of concentration). They help trigger the calcium-gated release of… more calcium! From the sarcoplasmic reticulum.

The Action Potential in a Myocardial Muscle Cell

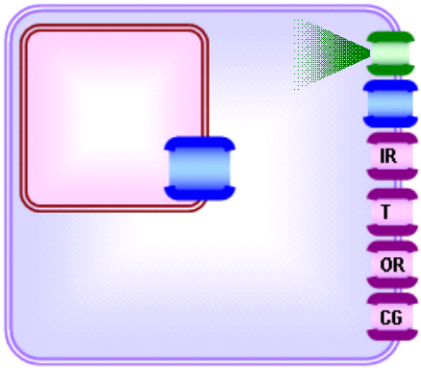
Phase 4



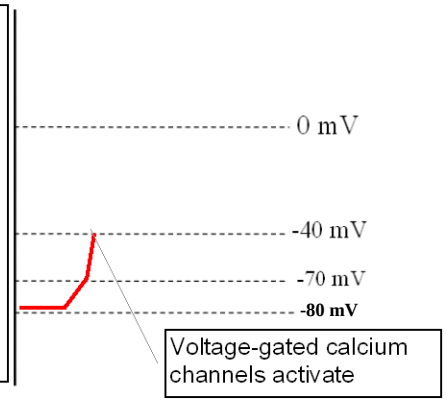
We begin with the myocyte resting;
The pumps are working to maintain the resting potential; they keep the sodium out and potassium in. The open potassium channel allows some potassium to escape so that there isn't too much positive charge inside. The fast sodium channels are ready and waiting, as are the voltage-gated calcium channels. **The tiny upward deflection of voltage is an action potential arriving from a neighbouring cell, bringing the voltage-gated sodium channels to their opening threshold of -70 millivolts**



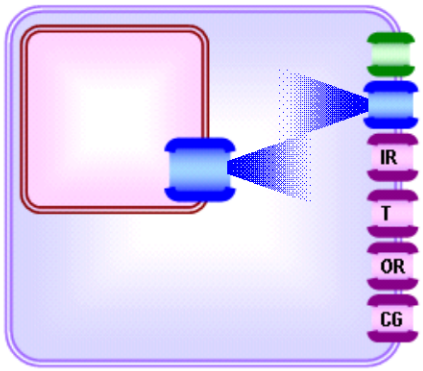
Phase 0



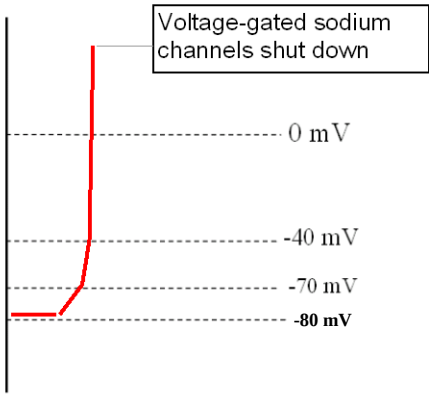
The Fast Sodium Channels Open.
Sodium hoses into the cell. The charge inside the cell rapidly rises.
This is what happens in the atrial muscle, the ventricular muscle, and the Purkinje fibers. The SA and AV nodes don't have such a large voltage across their membranes- they only have about -55mV
At a voltage of -55mV, the sodium channels are locked shut; no action potential can wake them. The inward-rectifying potassium channels close.



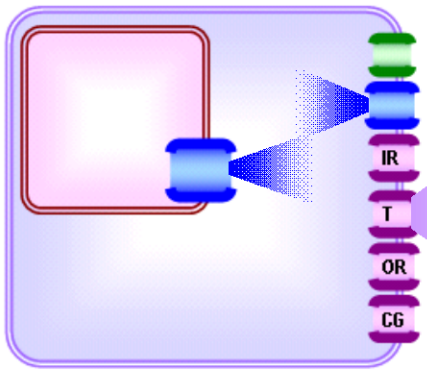
Half-way through phase 0



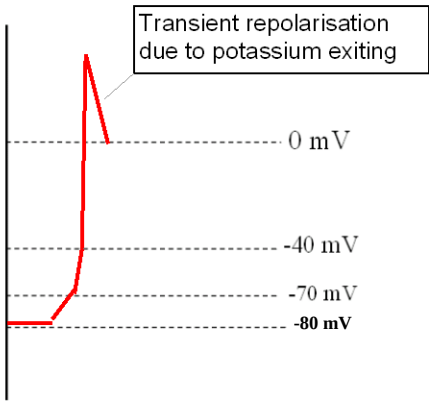
At -40 mV, Calcium channels open:
Calcium rushes into the cell. This adds to the overall trend of rising positivity. Whats more, as the voltage-gated calcium channels open, so do the sarcoplasmic reticulum channels (triggered by a rising calcium concentration.)
After firing for a fraction of a second, the sodium channels shut down and remain inactive until the end of the cycle. That fraction of a second is enough to flood the cell with sodium.



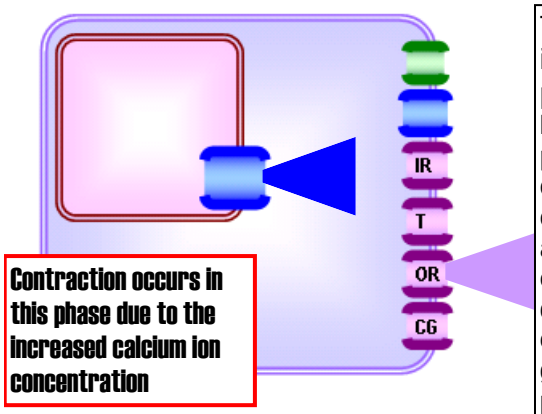
Phase 1



The cell is fully depolarized;
Some positive charge is lost via the transient potassium channels which leak a lot of potassium; as the inside of the cell is now largely positive, the potassium is repelled by this charge. These potassium channels close very soon. The sodium channels are also closed now, but the calcium channels have only just started working, and the ongoing positivity of the cell is due to their action.

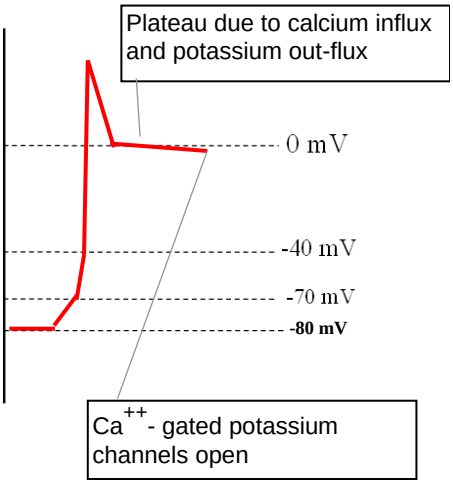


Phase 2

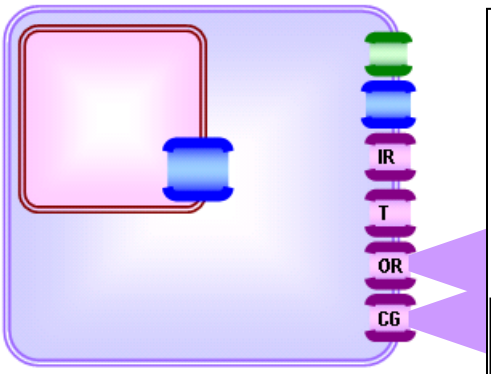


Contraction occurs in this phase due to the increased calcium ion concentration

The longest phase; balance between incoming calcium and outgoing potassium. The potassium continues to leak out via the **outward-rectifying potassium channels,** and the calcium continues to leak in via the L-type calcium channels; the rates of leakage are matched and so in terms of electricity, there is no change in potential difference. Positive ions in, positive ions out. This causes a plateau in the voltage graph. The end of phase 2 is caused by a peak in calcium concentration – this opens the **calcium-gated potassium channels.**

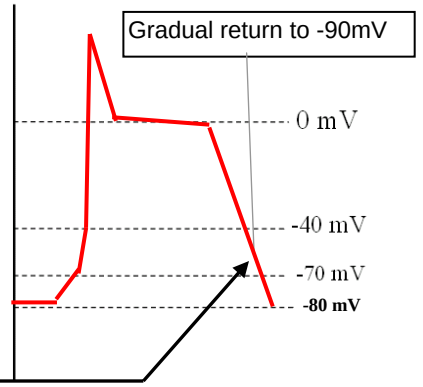


Phase 3



Repolarisation; the L-type calcium channels close, but the outward-rectifying potassium channels (as well as the calcium-gated potassium channels) are still open, and so the cell is slowly brought back to the equilibrium of Phase 4.

The ABSOLUTE REFRACTORY PERIOD ends when the membrane reaches around -50 mV.



ADDITIONALLY:

Contrary to my puerile diagrams, the ion channel picture is far from simple. There are throngs of ion channels besides those mentioned above.

Acetylcholine-activated Potassium Channels are activated by the actions of the parasympathetic nervous system; it stands to reason – if you want to slow down the heart, you make it more difficult to reach threshold by hyperpolarizing the cell. This hyperpolarity is achieved by opening these Ach-gated potassium channels, and letting even more potassium exit the cell during the resting phase. **Confusingly, these are also activated by Adenosine. – but via a different receptor , the purine A1.**

Arachidonic Acid-activated Potassium Channels allow fatty acids to shorten the action potential, for example during an ischaemic event. Acidosis opens these channels, and as a consequence phases 2 and 3 are shorter (repolarisation is faster)

ATP-sensitive Potassium Channels are inactive at normal ATP concentration; however as soon as the concentration drops (i.e. in ATP-depleted fatigued heart muscle, or during a coronary artery occlusion). They shorten the action potential and therefore shorten systole. Apparently that plays a protective factor to the ATP-depleted myocytes, by reducing demand. However it also kills people with heart failure and pulmonary oedema.

Why do we obsess over electrolytes?

That requires a topic all of its own

- **Changes in external K+ concentration affect the resting membrane potential;**
- **Changes in external Na+ concentration affect the MAGNITUDE of the action potential**
- **This stands true for all excitable tissues**
-

Cardiovascular Physiology, 6th Edition. David E. Mohrman, Lois Jane Heller. From CIAP
http://proxy14.use.hcn.com.au/resourceTOC.aspx?resourceID=64
Arnold M. Katz **Cardiac Ion Channels, NEJM Volume 328:1244-1251April 29, 1993 Number 17**
Guyton and Hall, 2006 Textbook of Medical Physiology 11th edition. Henry Gray (1825–1861). Anatomy of the Human Body. 1918.

MECHANICAL CHARACTERISTICS

- Like in skeletal muscle, there is a resting length at which the contraction of the cardiac muscle is maximal
- The initial length of the fibers is determined by the degree of diastolic filling (that's what stretches the sarcomeres)
- The pressure these fibers develop when they contract increases along with the filling pressure – up to a point. Then it decreases again.
- The stretching of fibers causes Troponin C to increase its affinity for calcium, which in turn increases contractility.
- HOWEVER the decrease in contraction strength is NOT due to a decrease in the number of cross-bridges like it is in skeletal muscle. A stupidly dilated heart still hasn't got to that point.
- Instead the decrease is due to disruption of the myocardial fibers- they come apart at the intercalated discs.

AUTONOMIC FACTORS INFLUENCING CONTRACTILITY

- Beta-1 receptors affect the contractility of the heart by influencing Ca^{++} homeostasis:
    - They produce cAMP, which in turn activates Protein Kinase A, which in turn phosphorylates voltage-gated calcium channels, forcing them to spend more time in the open state.
    - Protein Kinase A also phosphorylate phospholamban, which causes the SERCA pump to concentrate more potassium in the sarcoplasmic reticulum, and the result is more calcium release during the contraction.
    - Increased SERCA activity also means shortened relaxation time, which is important if the heart rate is increased (a nicely relaxed ventricle permits better diastolic filling)
- The heart also has Beta-2 receptors, but they are not innervated, and are concentrated in the atria

CARDIAC METABOLISM

- Our hearts have an insanely generous blood supply, numerous mitochondria, and they have a higher concentration of myoglobin.
- Normally, less than 1% is produced by anaerobic metabolism; in states of great strive this can go up to 10%, but that's about it. Under anaerobic conditions no contraction is possible.

Normally, the heart is a fat-burning organ

- 35% of the caloric needs are satisfied by CARBOHYDRATES
- 5% by KETONES
- **60% by FAT**
- Of tis fat, 50% is in the form of circulating free fatty acids

References: Ganong Review of Medical physiology, 23rd ed, chapter 5