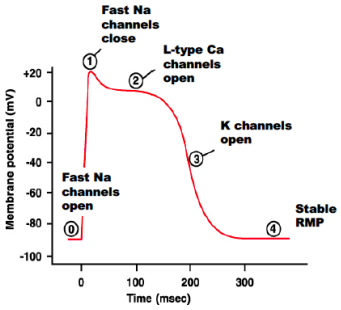
Lecture 2: Cardiac muscle cell - Electromechanical coupling

Ventricular Electrical Activity



- When the AP spreads across the cardiac muscle, it changes the electric field.
- This influences fast Na+ channels and allows Na+ into the cell which causes it to depolarise.
- The fast Na+ channels stay open for a certain amount of time before inactivation of the channel occurs which leads to the closure of these channels.
- Large-type Ca2+ channels open creating the plateau of the AP.
- The L-type Ca2+ channels stay open for a certain amount of time before inactivation occurs.
- K+ channels open which causes the repolarisation of the cell.

- Measuring ion movement:
  - Membrane permeability (cm/s)
  - Ion conductance (1/R)
  - Current flow (amps)

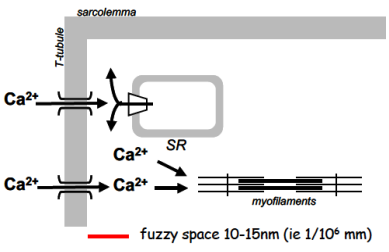
- Transmembrane Na+ and K+ gradients:
  - ECF [K+] = 5mM
  - ICF [K+] = 140mM
    - The concentration of K+ is higher inside the cell.
    - Opening a K+ channel results in K+ to leave the cell which will hyperpolarisation of the cell.
  - ECF [Na+] = 145mM
  - ICF [Na+] = 10mM
    - The concentration of Na+ is higher outside the cell.
    - Opening a Na+ channel results in Na+ to enter the cell which will depolarisation of the cell.
- Transmembrane Ca2+ gradients:
  - ECF [Ca2+] = 2 mM
  - ICF [Ca2+] = 100 nM
  - SR [Ca2+] = 1mM
    - Due to the large difference in Ca2+ concentration gradients, there is a huge drive for Ca2+ to move into the ICF in the cell.
    - Ca2+ concentration differences = Potential energy stored for contraction initiation.
    - Having a concentration difference in a place between compartments provides for 'signalling' potential and 'work' potential.
    - Building and rebuilding the Ca2+ concentration gradients costs energy directly and indirectly, and also electrical stability.

Excitation-contraction coupling

- Ionic transporters maintain transmembrane gradients.
  - Pumps cost energy, exchangers are energy free.
  - Pumps go one way, exchangers are the reverse.
  - Electrogenic transporters alter membrane potential.

CA2+ IN

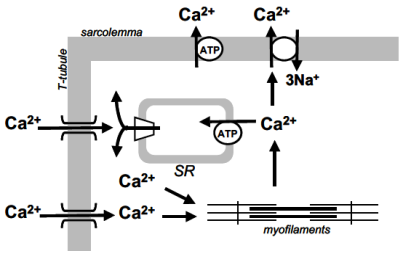
- AP spreads down T-tubule which causes the opening of L-type Ca2+ channels and allows Ca2+ to enter the cell.
- Ca2+ goes directly to the myofilaments.
- In the fuzzy space, some Ca2+ triggers the opening of SR Ca2+ release channels/ryanodine receptor which causes more Ca2+ release which will go the microfilaments.
- Cardiac muscle cell contracts.



- Ca2+ influx to cytosol for contraction:
  - About 20% via L-type Ca2+ channels from the outside of the cell.
  - About 80% from SR in the inside of the cell.

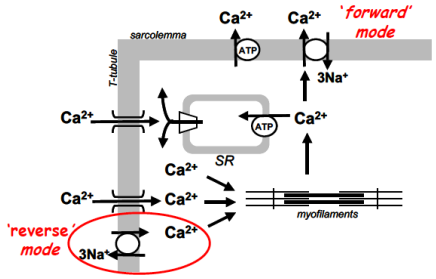
CA2+ OUT

- Ca2+ efflux from cytosol for relaxation:
  - About 19% via Na+ Ca2+ exchanger/NCX.
    - Indirect energy costs which affects resting membrane stability.
    - Closer to resting threshold trigger - risk of arrhythmia.
  - About 1% via sarcolemmal Ca2+ pump.
    - Direct energy costs
  - About 80% uptake by SR Ca2+ pump/SERCa2.
    - Direct energy costs
- On a beat to beat basis, we need to have a steady state.
- Over a long time frame, gradual shifts result in pathological consequences.



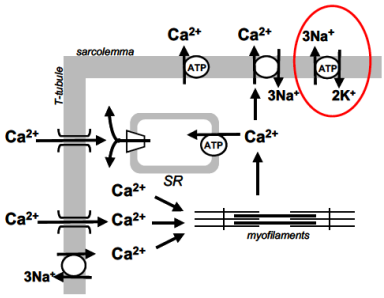
CA2+ GOING BOTH WAYS

- Forward mode of Na+ Ca2+ exchanger
  - In relaxation, Ca2+ is exiting the cell while 3Na+ enter the cell.
  - Ca2+ exit by Na+ Ca2+ exchanger is dominant.
  - 2+ out, 3+ in = 1+ overall
    - This depolarises the membrane which makes it a potential problem in relaxation because the cell is trying to repolarise.
    - Causes destabilisation of membrane potential.
- Reverse mode of Na+ Ca2+ exchanger
  - At the beginning of the AP, Na+ enters the cell via fast Na+ channels.
  - The high concentration of Na+ inside the cell allows Ca2+ to enter the cell.
    - Normal: Small amounts of Ca2+ entry
    - Pathological problem: Bigger amount of Ca2+ entry.



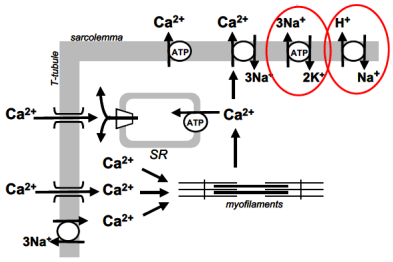
RESTORING NA+ LEVELS

- Na+/K+ ATPase
  - Ubiquitous transporter - most cells have this transporter.
  - 3+ out, 2+ in = -1 overall
    - This hyperpolarises the cell and helps bring the membrane potential down.
    - Counteracts the effects of Na+ Ca2+ exchanger.



DEALING WITH METABOLIC ACID PRODUCTION

- Metabolism causes the production of H+ which comes from glucose and lipid substrates.
  - There is lots of mitochondria in cardiac muscle cells.
- Na+/H+ exchanger
  - Removes H+ from the cell throughout the cycle.
    - Brings in Na+ which is removed by Na+/K+ ATPase.
  - The concentration of H+ will always be lower than the outside of the cell because it is constantly washed by blood.
  - 1+ out, 1+ in = 0 overall
    - Non-electrogenic transporter



- Ca2+ efflux via Na+ Ca2+ exchanger and metabolic H+ efflux via Na+/H+ exchanger makes myocyte Na+ load.
- Na+ is extruded via Na+/K+ ATPase.
  - Delayed repayment of energy debt.
- Some Na+ exit via NCX reverse mode may occur early when Na+ level is high and may provide some activator Ca2+ influx.

KEEPING THE ELECTRICAL BALANCE

- Na+ Ca2+ exchanger is an electrical liability because of its electrogenic nature which depolarises the cell.