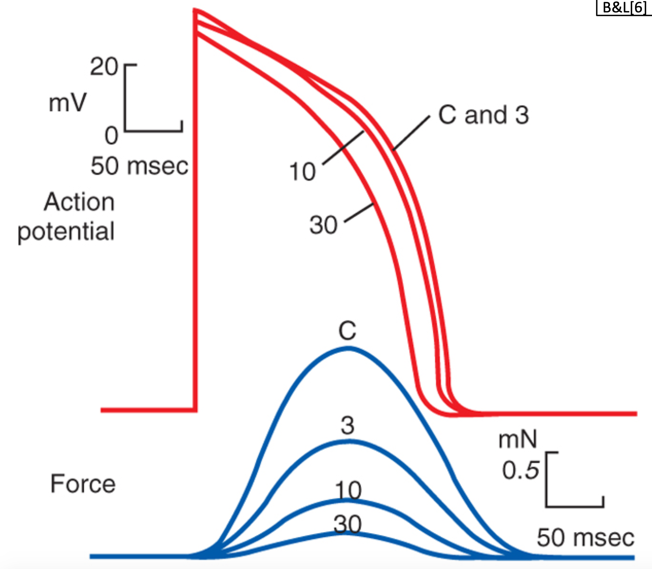
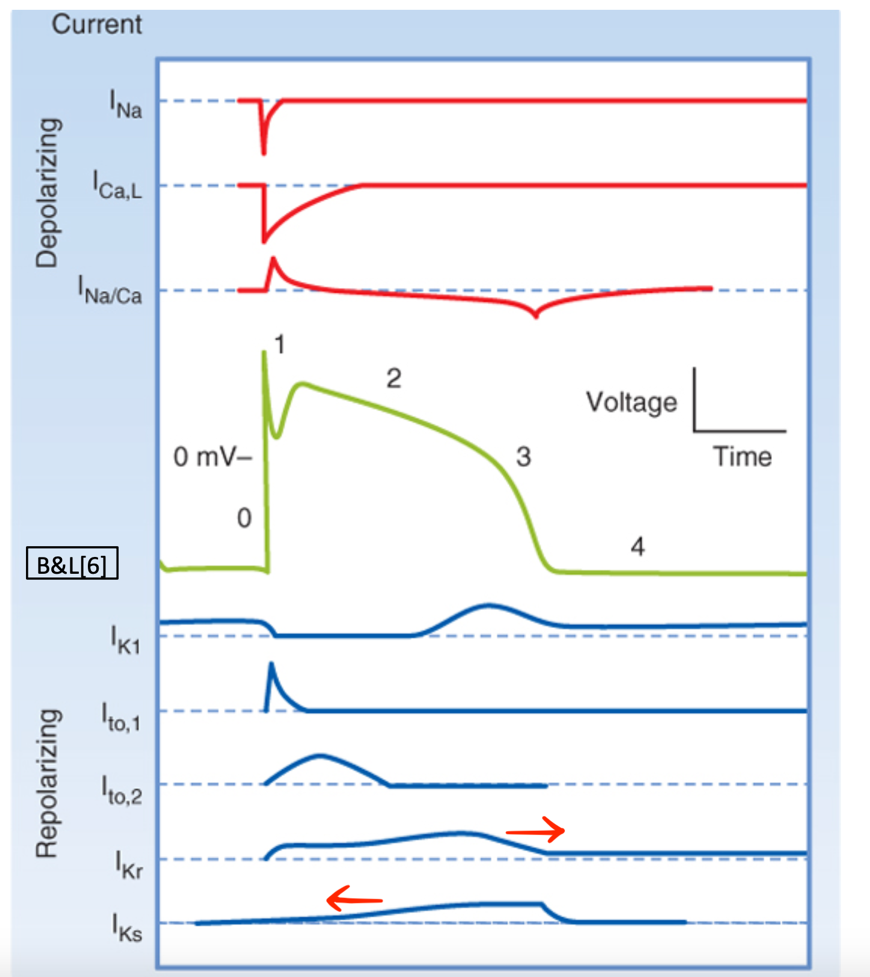
Discussion Question 1  
In an experiment in which cardiac fast action potentials were measured it was observed that administration of a particular drug resulted in a decrease in the duration of phase 2 along with more of a “droop” (negative slope) in phase 2. Please provide a possible explanation for these observations. Answer individually;

The phase of the cardiac fast action potential, during which the membrane potential declines slowly, is known as plateau phase or phase 2. It is the result of a balance between an influx of Ca2+ entering the cell through calcium channels and the efflux of potassium moving out of the cell through delayed rectifier channels. If the influx calcium is reduced, the efflux of K+ becomes to dominate and will change the duration of phase 2 and a “droop” in phase 2. Compared to T-type calcium channels, L-type calcium channels are more common, remain open longer, and contribute to phase 2. We can assume that this particular drug blocks L-type channels. As the drug blocks L-type calcium channels, less calcium ions enter the cell altering the balance. Phase 2 duration becomes shortened and slope is more negative (Fig.1).

We can also imagine that the drug instead of blocking calcium channels, increases potassium conductance by increasing either the duration of the rapid current IKr or delaying less the slowing activating current IKs which then rises earlier during phase 2 (Fig.2). More potassium ions move out of the cell and the influx of Ca2+ is counterbalanced less in time and in duration by the efflux of K+.



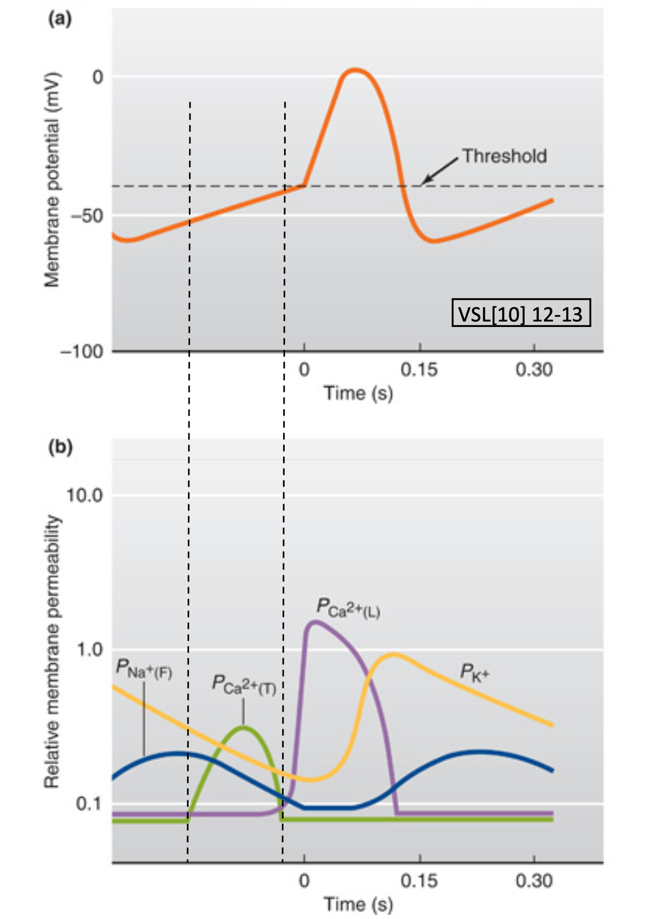
**Fig. 1**: With increase concentrations of diltiazem, the plateau duration diminishes and the plateau voltage becomes less positive (slope increasing negatively) (video 3, slide 3)



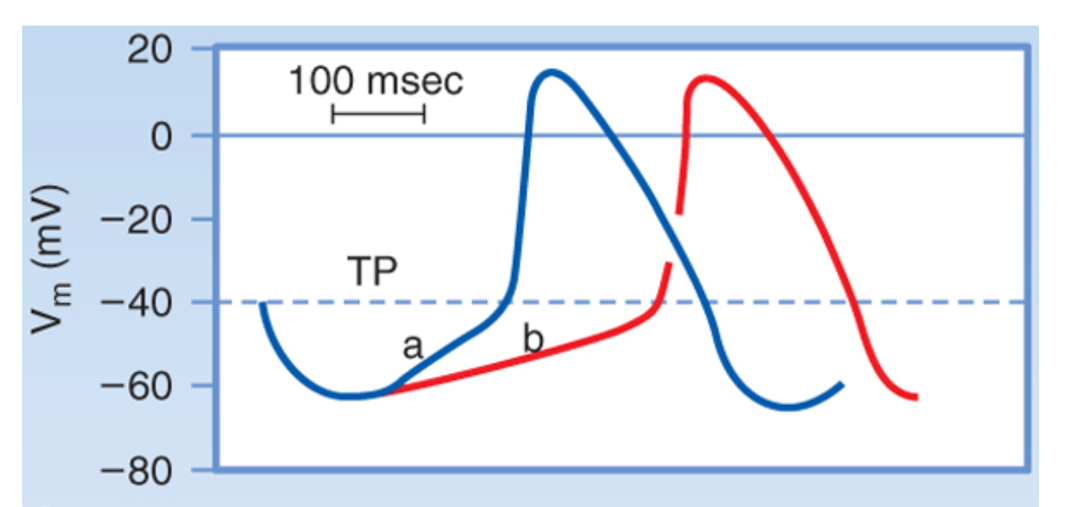
**Fig.2:** delayed rectifier K+ currents IKr , being extended later into the early recovery phase and IKs starting earlier during the phase 2.

Discussion Question 2  
What would be the effect of a drug that reduces T-type Ca2+ current on the time to reach threshold in a cardiac pacemaker potential? Briefly explain. Answer individually;

The T-type Ca2+ current participates at the end of the slow depolarization leading to the threshold of the action potential (Fig. 1). The drug reducing T-type Ca2+ current affects the slope of the end of phase 4 of the cardiac pacemaker action potential reducing it like in figure 2 as less calcium ions enter the cell and depolarizing it more gradually. It takes longer to reach action potential threshold, which in turns decreases the frequency of pacemaker firing thus slowing the heart rate (Fig. 2).



**Fig. 1**: Membrane potential and ionic movements in each phase VSL [15] 12-16



**Fig 2**: For the same threshold potential (TP), decrease in T-type Ca2+ current from [a] to [b] reduces the slope of the pacemaker action potential, resulting in slower depolarization of phase 4 (Video 4, slide 5).Discussion Question 3  
What would be the effect of a drug that reduced L-type Ca2+ current in AV nodal cells on the timing of the EKG waveform? Briefly explain. Answer individually;