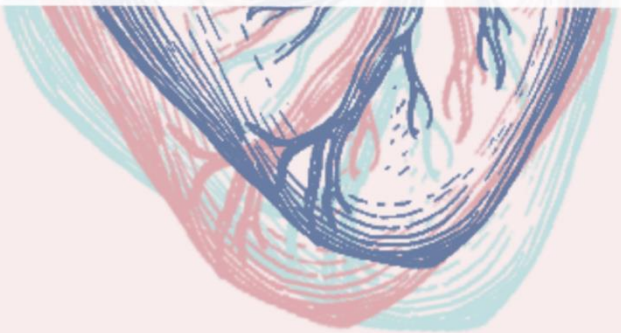
Cardio-Vascular System

4

Pharmacology



Writer: Ameen Alsaras

S.corrector: Safaa Mahfoz

F.corrector: Dena Kofahi

Doctor: Munir Gharaibeh

*In this sheet we will discuss **cardiac arrhythmias,** have fun*

Cardiac Arrhythmias:

- ✓ Overview: They are abnormalities of the cardiac rhythm or electrical activity. As you know, our heart works as a pump which involves both electrical and muscular activity. The nervous control in the heart is maintained by the SA node, AV node, bundle of his, two bundle branches and purkinje fibres, and these will transmit or propagate electrical activity to the muscular component of the heart to produce normal functioning of the heart. Abnormalities in this process are called cardiac arrhythmias which are treated with anti-arrhythmic drugs.
- ✓ Etiology: It could be hereditary or acquired.
- ✓ Types: **1-Abnormalities of Impulse Formation:**
    a) Rate disturbances
    b) Triggered automaticity

2-Abnormalities of Impulse Conduction:

a) Blocks → Blockade of passage of electrical activity through normal conduction pathway.
b) Reentry → Reverberating(repeated) activity along the conduction system.

- ✓ Causes:

1- Cardiac:

a- Ischemic heart disease, Inflammation and Congestive heart failure (these affect the myocardium as well as the conduction system).
b- Trauma e.g. heart surgery (this is the most probable form of trauma to the heart, direct damage from bullet shots for example are much less common).
c- Hypotension (elicits baroceptor reflex which stimulates the sympathetic system, leading to various alterations in the heart and CVS).

2- Non-cardiac:

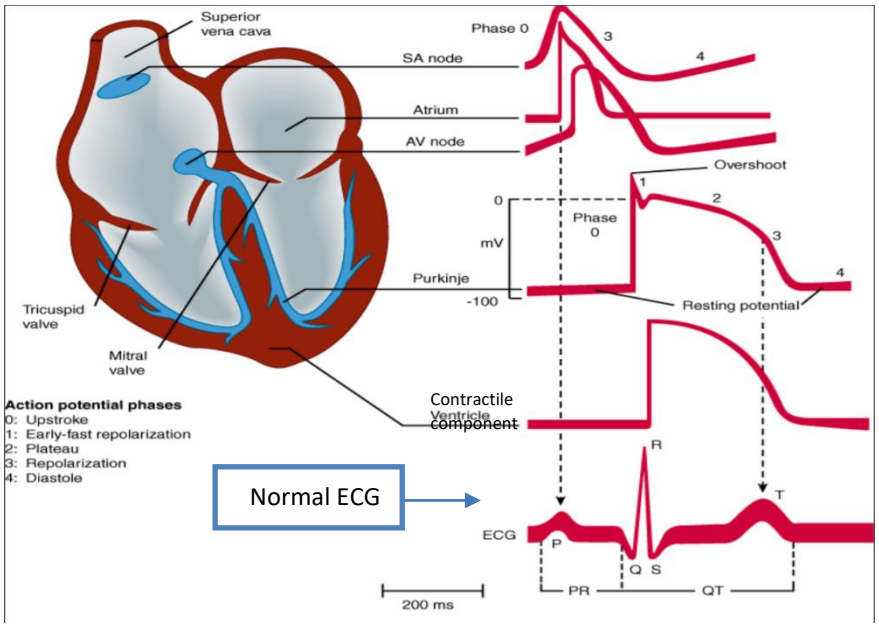
a- Electrolyte imbalance (mainly K^+)
b- Acid-Base imbalance
c- Hypoxia
d- Drugs: Digitalis, anesthetics (many people die from them after successful surgeries), tricyclic drugs (for depression), diuretics, and bronchodilators, most of which are sympathomimetic.
e- Reflexes (from GIT or upper body)

- ✓ Cardiac cells undergo depolarization and repolarization to initiate cardiac action potentials at a rate of 60 times/minute. The shape and duration of each action potential are determined by the activity of ion channel protein complexes in the membranes of individual cells. Ion channel function can be disrupted by inherited mutation(polymorphism), acute ischemia, sympathetic stimulation, or myocardial scarring to create abnormalities of cardiac rhythm, or arrhythmias.

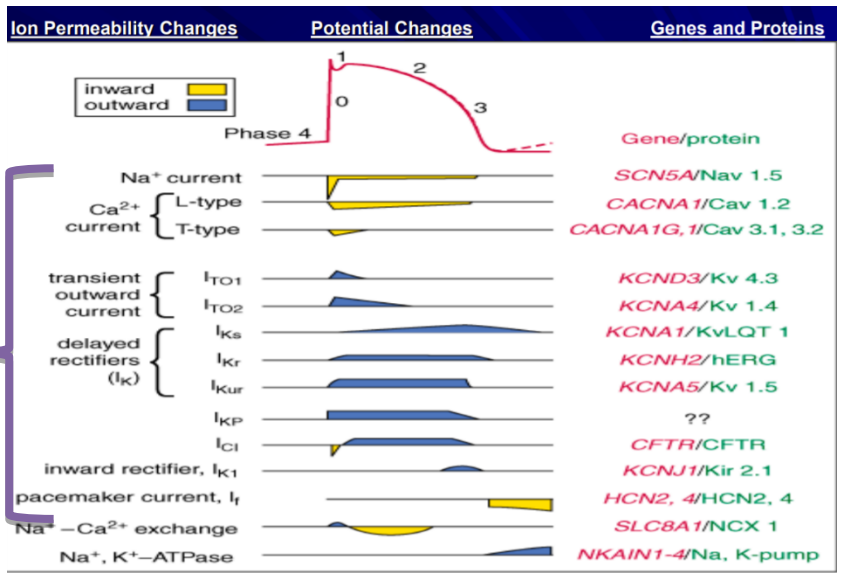
Electrical Activity of the Heart

*In this figure we can see the different action potential in each part of the conduction system. (You know the whole story from physiology)

Electrical activity can be recorded by ECG in humans by putting electrodes on the chest. It is the main method used for cardiac arrythmia diagnosis.



*If we take one of these action potentials, you can see that it is composed of 4 phases and the shape of the action potential depends on movement of ions- either inward or outward. These different ions will move through special channels specific for each ion and thus generate many currents. Channels are proteins → Depend on enzymatic activity and genes for their structure → There is a significant relationship between genetic background and susceptibility to arrhythmias. For example, regarding Na current, which is probably the major current in the heart, there is a gene which is

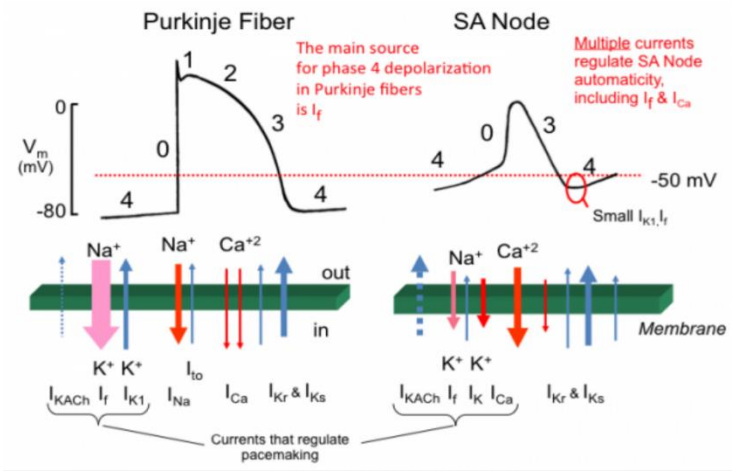


Remember: Na channels can be in resting, activated, or inactivated phase. Briefly, the difference is that: Resting → does not allow Na movement. Activated → allows Na movement. Inactivated → does not allow Na movement because of a conformational change (refractory period).

called SCN5A which produces a protein called and NAV 1.5.You can see in the figure other currents as well as Na/K ATPase.

The following figure illustrates the role of different currents in AP of SA node and purkinje fibers (major depolarization is caused by Ca^{+2} and Na^{+} respectively).

Note: The professor mentioned that contractile myocardium also depends on Ca^{+2} but he probably meant for the plateau phase, as we all know that it depends on Na^{+} for phase 0 (depolarization)

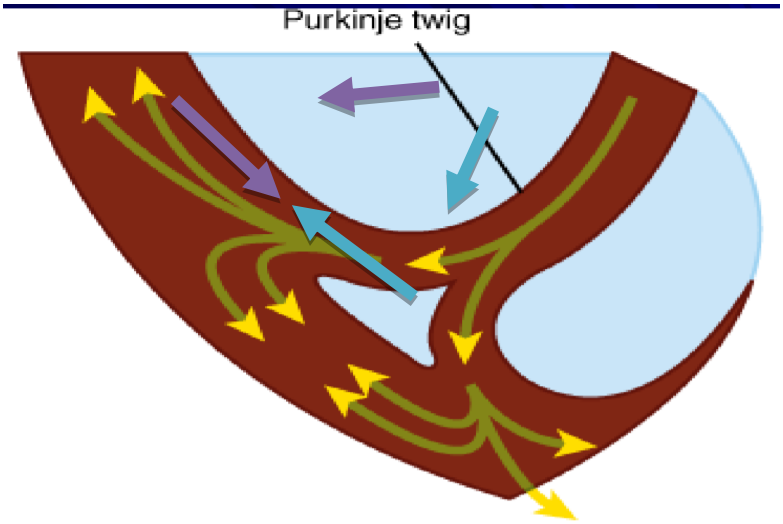


SA Node Automaticity

The SA node is the pacemaker of the heart thanks to its inherent activity to produce (or to reach the threshold for) excitation and reaching the threshold will initiate (or will open the channels for) the AP. **Remember: It is leaky for Na**.

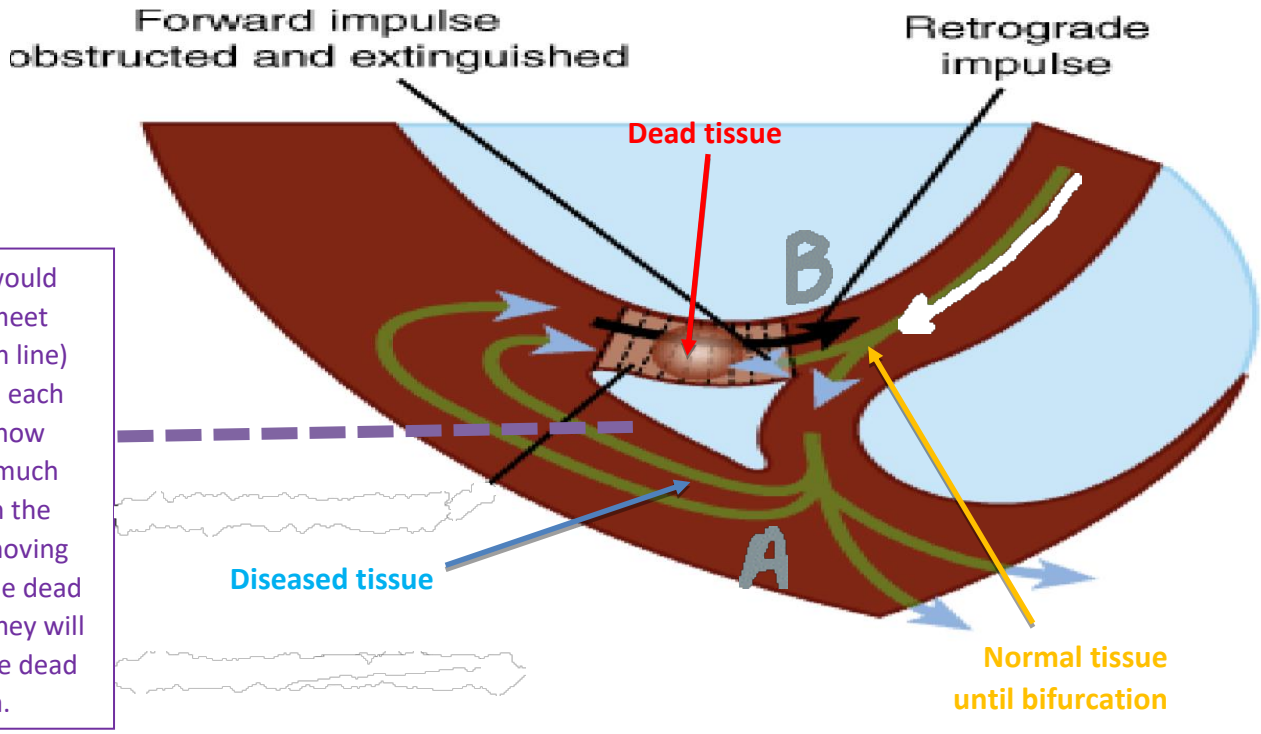
Normal Circuitry and Re-entry Rhythm

Normally, the electrical activity goes through the heart very homogeneously and without any problems. But how does the electrical activity finally terminate? Electrical activity reaches the bifurcation of purkinje fibres which divides the current in **two directions**. Having the same magnitude, these two vectors will eventually meet at a certain point and cancel each other out.



However, for example, in the presence of an ischemic change in one of the terminal passages of these minor currents, we can assume that this ischemic area contains dead

tissues, diseased tissue, and normal tissues. How would that affect the process mentioned above? This is what we call re-entry rhythm or circuit.



Currents would normally meet here (finish line) and cancel each other but now these are much faster than the currents moving through the dead tissue so they will meet in the dead tissue area.

We'll make it a story so we can understand it better.

1. The electrical activity (white currents) will reach the bifurcation as usual –normal fashion, speed, and direction.

2. Now, at the bifurcation point the race starts. Some currents will move in the **diseased tissue (Path A)**. Other loser currents will try to move through the **dead tissue (Path B)** because it's shorter, but they don't know that it is a trap. Only a few of them will succeed (most of them will stop at the dead tissue).

3. The currents moving through path A have won the race and reached the finish line. They haven't found anybody so they continued moving until they've seen the other loser currents stuck at the beginning of dead tissue. As there are very few opposing currents if any, these champion currents can continue moving happily toward the bifurcation

4. When the refractory period ends for the currents of the normal tissue, our currents will propagate even further as a retrograde impulse. Then they can enter the race and repeat the cycle again.

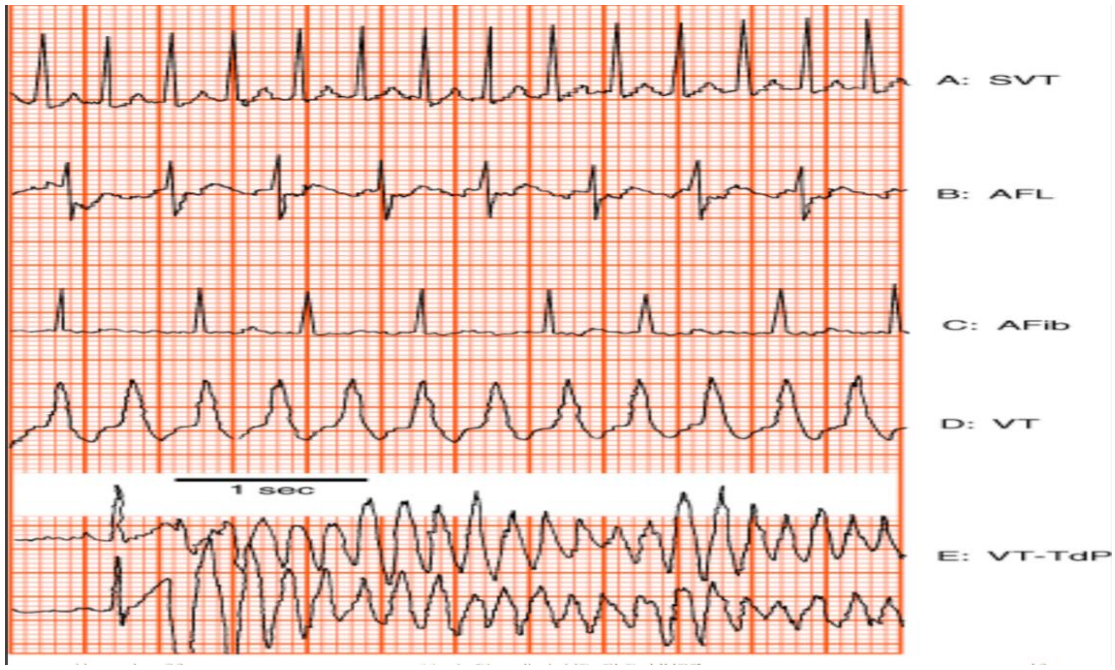
*To sum up: Currents moving in the diseased tissue would move in a circular path (almost), eventually going **back** to the starting point and can even **re-enter** the circuit causing reverberating cycles of cardiac arrhythmia.*

Note: This is what the professor said, and it is a simplified explanation. This topic is a bit more complicated, but this is enough for our level we won't get into more details.

✓ Pre-requisites for Reentry (conditions required for re-entry to occur):

a. Anatomic or physiologic obstacles like dead tissue.
b. Unidirectional block: Notice that in the previous example the dead tissue stopped the forward conduction but it permitted the backward current to move through it.
c. Conduction time around the circuit must be longer than the effective refractory period so the retrograde impulse can form and propagate as we said.

Some Examples of Arrhythmias



A. Supraventricular Tachycardia (SVT): Multiple, very clear p waves occurring at a higher rate in the atria. It is benign and can come for a short period of time and go spontaneously. Patients in this case are healthy but it may occur secondary to over-ingestion of stimulants e.g. coffee or tea, or due to stress and anxiety.
B. Atrial Flutter: Same as A but at a much higher rate than SVT (apparent p waves) .
C. Atrial fibrillation: Atria go crazy and work at an extremely high rate independent of SA node activity. Notice the tiny p waves which denote weak contraction.
D. Ventricular tachycardia: Arrhythmia occurs in the ventricles this time, independent of the activity of atria. Notice that unlike A, B, and C to some extent, there are no P waves this time. So the ventricles take over the electrical activity and contract rapidly.
E. Polymorphic Ventricular Tachycardia-Torsade de Pointes: we will talk about this one in details.

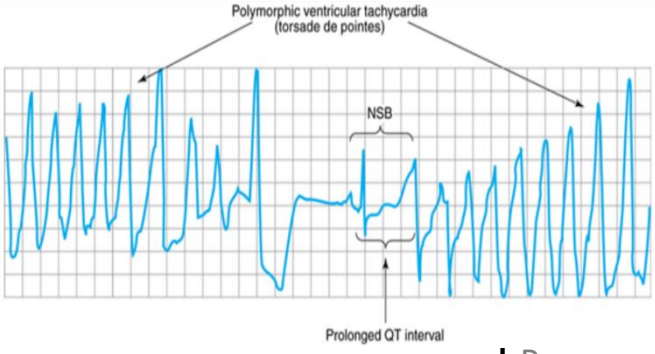
- ✓ Characteristics: Long QT interval, syncope(fainting), sudden death, and it affects very young people.
- ✓ Causes:
  a. Familial long QT interval
  b. Drug - Induced (drugs which prolong AP duration):These drugs are actually used to treat arrhythmias but at some point of time they may cause them.
- ✓ Genetic mutations: 300 different mutations in at least 8 ion channel genes as you can see in the figure below.
- ✓ Mechanisms: Either by increased inward current (called Gain of Function [GF]), or by decreased outward current during the plateau (called Loss of Function [LF]).
- ✓ Risk factors: Bradycardia, hypokalemia, triggered upstrokes, and drugs which increase AP duration. So, even if the causes are there, this condition might not always occur. Risk factors increase the chance of occurrence.
- ✓ Treatment:
  a. Giving K^+ to ensure there are good levels in the body.
  b. Prophylaxis and preventing triggered strokes by giving β-blockers or Mg^{2+}
  c. Decreasing AP duration by an artificial pacemaker or by giving isoproterenol

Genetic abnormalities → protein changes → channel abnormalities → cardiac arrhythmias

*The figure also shows other arrhythmias which have familial or genetic disposition such as CPVT, Brugada syndrome, etc. (It is NOT for memorization). Have a quick look at the defective genes, we will only talk about some of them specifically.

Type	Chromosome Involved	Defective Gene	Ion Channel or Proteins Affected	Result
LQT-1	11	*KCNQ1*	I_{Ks}	LF
LQT-2	7	*KCNH2 (HERG)*	I_{Kr}	LF
LQT-3	3	*SCN5A*	I_{Na}	GF
LQT-4	4	Ankyrin-B[1]		LF
LQT-5	21	*KCNE1 (minK)*	I_{Ks}	LF
LQT-6	21	*KCNE2 (MiRP1)*	I_{Kr}	LF
LQT-7[2]	17	*KCNJ2*	I_{Kir}	LF
LQT-8[3]	12	*CACNA1c*	I_{Ca}	GF
SQT-1	7	*KCNH2*	I_{Kr}	GF
SQT-2	11	*KCNQ1*	I_{Ks}	GF
SQT-3	17	*KCNJ2*	I_{Kir}	GF
CPVT-1[4]	1	*hRyR2*	Ryanodine receptor	GF
CPVT-2	1	*CASQ2*	Calsequestrin	LF
Sick sinus syndrome	15 or 3	*HCN4 or SCN5A*[5]		LF
Brugada syndrome	3	*SCN5A*	I_{Na}	LF
PCCD	3	*SCN5A*	I_{Na}	LF
Familial atrial fibrillation	11	*KCNQ1*	I_{Ks}	GF

Here you can see an ECG for VT-TdP. It is pleomorphic (variable) in many things: strength, rate, and QT interval length. So, you can find normal sinus beats as well as abnormal ones (THE MAJORITY) .



Other Congenital Arrythmias

1. Short QT Syndrome: GF mutations in three potassium channel genes(KCNH2, KCNQ1, and KCNJ2).
2. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT): Stress or emotion-induced syncope. It is caused by mutations in sarcoplasmic proteins that control calcium. Inhibiting RyR2 channels with flecainide appears to prevent CPVT.
3. Sick Sinus Syndrome: Mutations in HCN4 and SCN5A
4. Brugada Syndrome: Ventricular fibrillation, persistent ST elevation, and Bundle branch block (5 in 10,000). Linked to LF mutations in SCN5A
5. Familial Atrial Fibrillation: Linked to GF mutation in the potassium channel gene KCNQ1.

Note: The professor went over the names quickly describing them as 'related to genetic backgrounds', he didn't go into details.

Non-Pharmacologic Therapy

1. Surgery: Can be effective in re-entry rhythms. However, surgery itself can induce trauma and arrhythmia.
2. Radiofrequency Catheter Ablation. استئصال
3. Cryoablation: Using low temperatures in ablation. استئصال بالتبريد
4. Implantable Cardioverter- Defibrillator (ICD): It is used in cases of ventricular tachycardia to prevent repeated or recurrent tachycardia (notice that the external defibrillator can defibrillate cardiac arrhythmias, especially ventricular arrhythmias, from outside but if there is risk of recurrence we use ICD).
5. Gene therapy: Still under development

Anti-Arrhythmic Drugs

✓ Introduction: Available anti-arrhythmic drugs suppress arrhythmias by blocking flow through specific ion channels or by altering autonomic function (mainly by blocking the sympathetic division→ Blockade of many muscular and electrical activities → Rx: by using β-blockers). Anti-arrhythmic drug therapy can have two goals: 1-Termination of an ongoing arrhythmia (acute arrhythmias like ventricular tachycardia). 2-Prevention of the occurrence of an arrhythmia in the future. **Anti-arrhythmic drugs , might help control arrhythmias , but unfortunately also might cause them , especially during long-term therapy**

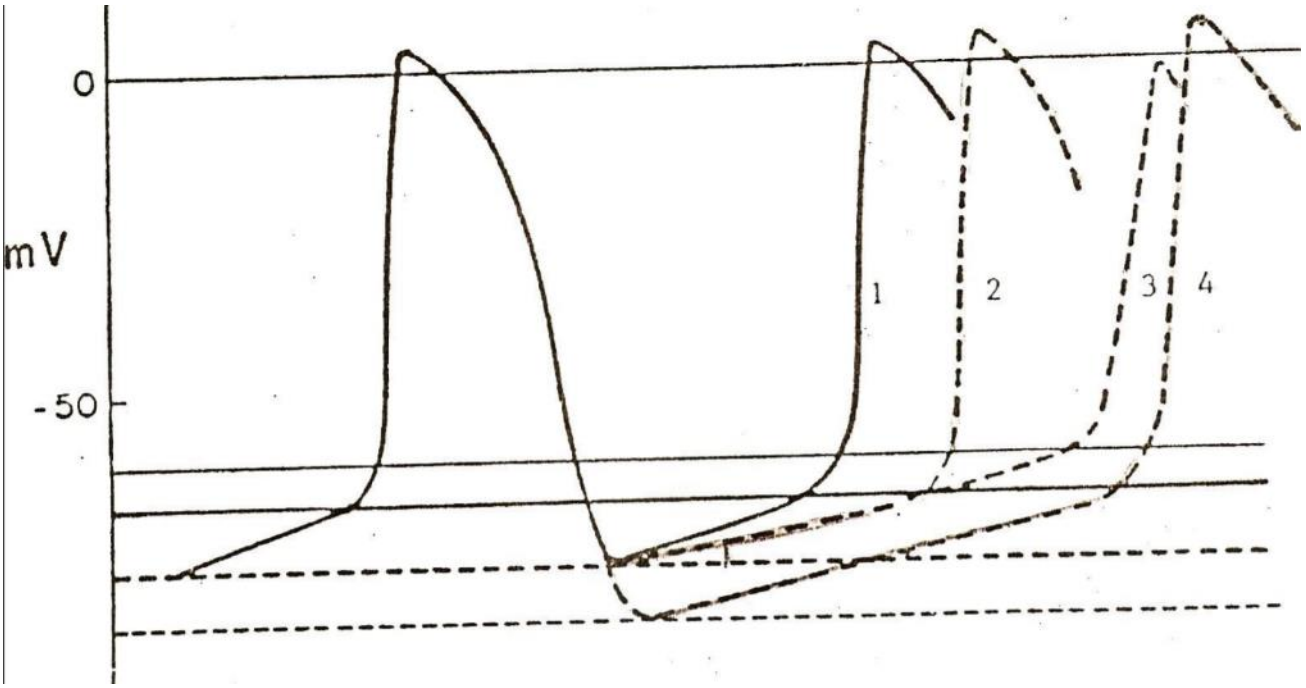
*Remember that the parasympathetic nervous system terminals are poorly presented in the ventricles but richly found in SA node (so, one of atropine effects is increasing the heart rate).

✓ Mechanism of Action Principles:

a. The drugs readily bind to activated channels or inactivated channels but bind poorly to rested channels so they are Use–Dependent or State-Dependent. Channels in normal cells will rapidly lose the drug from the receptors during the resting phase. (This is what we want: to **target** active, arrhythmic cells only).
b. This selectivity is lost with increasing doses (they might be safe at low/therapeutic doses) leading to drug-induced arrhythmias.
c. Also, these drugs may become "proarrhythmic or arrhythmogenic" during fast heart rates (even normal cells would be 'active'), acidosis, hyperkalemia, or ischemia.

✓ Possible Effects on Action Potential:

1. This is the standard AP
2. Decreased phase 4 slope (reaching threshold becomes slower → delay in AP)
3. Higher (less negative) threshold (reaching threshold takes more time due to the increased threshold)
4. Lower (more negative) resting potential and increased threshold leads to a delay in initiation of AP.
5. Increased AP duration can be achieved by increasing plateau duration (not shown in the figure)



✓ Classification of anti-arrhythmic drugs: As you can see in the table below, they are divided into 4 classes: I, II, III, and IV. Class I is further divided into 3

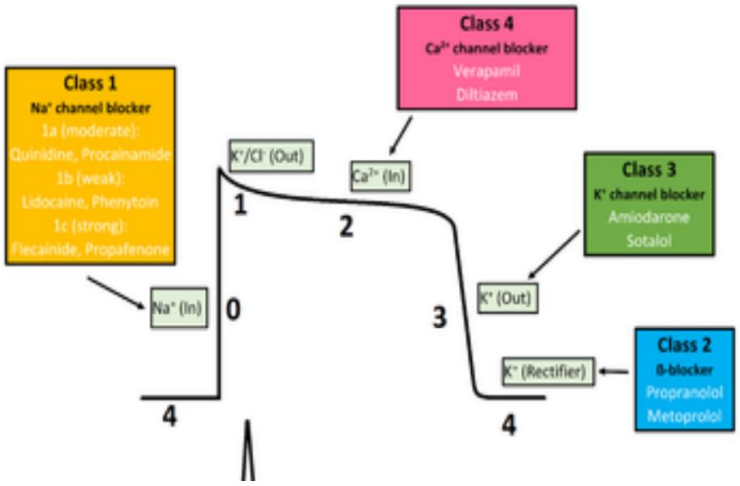
subclasses: a, b, and c (c is not shown in the table). These subclasses vary in dissociation speed from Na channels. You can also see non-classified (miscellaneous) drugs such as digoxin and others. Just have a look at them and details will follow in the next lecture.

Table 17.1 The mechanism of action, the electrophysiological actions and clinical uses of selected antidysrhythmic drugs

		Example	Mechanism of action	Electrophysiological actions	Clinical use
Vaughan Williams classification	Class Ia	Disopyramide	Na^+ channel block	Reduced rate of depolarisation of action potential, increased ERP, decreased AV conduction	Ventricular fibrillation, especially associated with myocardial infarction
	Class Ib	Lidocaine			
	Class II	Propranolol, atenolol	β-Adrenoceptor antagonism	Slowed pacemaker activity, increased AV refractory period	Dysrhythmia prevention in myocardial infarction; paroxysmal atrial fibrillation due to sympathetic activity
	Class III	Amiodarone, sotalol	K^+ channel block	Increased action potential duration and increased ERP	Atrial fibrillation; ventricular fibrillation
	Class IV	Verapamil	Ca^{2+} channel block	Decreased APD, slowed AV conduction	Supraventricular tachycardias; atrial fibrillation
Not classified by system		Adenosine	K^+ channel activation	Slowed pacemaker activity, slowed AV conduction	Given i.v. for supraventricular tachycardias
		Digoxin	K^+ channel activation (vagal action)	Slowed AV conduction (block)	Atrial fibrillation
		Magnesium chloride	? Ca^{2+} channel block		Ventricular fibrillation; digoxin toxicity

In this figure you can see the effect of each class on action potential phases.

**There is a table in slide 32 that shows detailed effects of each drug and its half-life. Refer to it if you want more details (for yourself).*



Good Luck!!