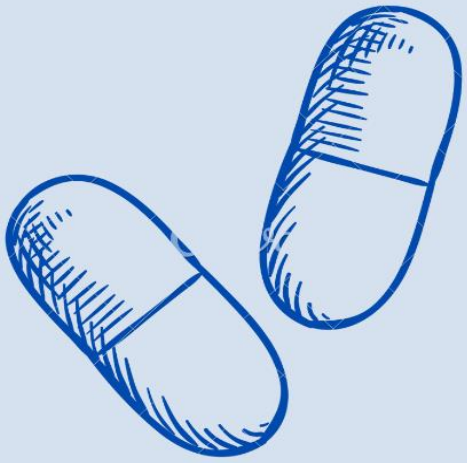


CVS
pharmalcololgy

Writer: Aya Kotkot

corrected by: Naemah Abuhantash

Doctor: Dr. Alia Shatanawi

قال تعالى: يَوْمَ لَا يَنفَعُ مَالٌ وَلَا بَنُونَ(88) إِلَّا مَنْ أَتَى اللَّهَ بِقَلْبٍ سَلِيمٍ(89).

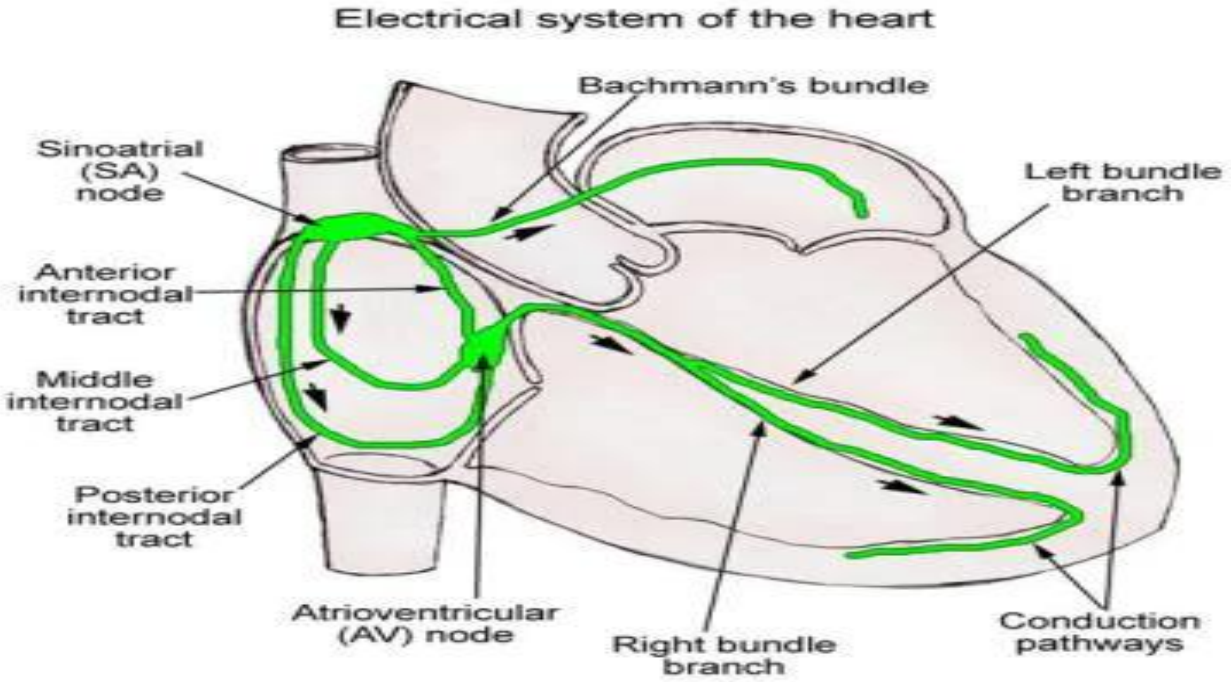
A heart arrhythmia	**an irregular heartbeat**.

Anti-arrhythmic Drugs

Topic 1:medical terms to understand

AS a quick recap:

-The conduction in the heart is initiated by the SA node then transmits to AV node ,going down to the left and right bundles in the septum ,all the way to reach purkinje fibers then spreads the conduction to each part of the heart.



-Normal rate of SA node equals 60-100, Above(tachycardia/tachyarrhythmia) or below(bradycardia/bradyarrhythmia).

-we have atria and ventricle, anything above the line of ventricles is called supraventricular arrythmia and it's the same as atrial arrythmia.

-sinus rhythm is the same as SA node rhythm which is the normal rhythm of the heart ,if there's an increase in the firing of the sinus it's called sinus tachycardia

-SA node has automaticity effect (initiates the conduction),if any other area in the atria tries to make the conduction ,it's called triggered automaticity.

If the triggered automaticity happens in

- *One region:it's called focal atrial tachycardia*
- *More than one region it's called Multifocal atrial tachycardia*

-Atrial fibrillation: It's a form of tachyarrhythmia where we have increase of firing in certain (area/fossi) of the atrium, characterized by higher HR >100bpm. The ECG changes are irregular ,it's not synchronized ,some parts of the heart are beating faster than others.

in atrial fibrillation, the atria beat irregularly. In atrial flutter, the atria beat regularly, but faster than usual and more often than the ventricles

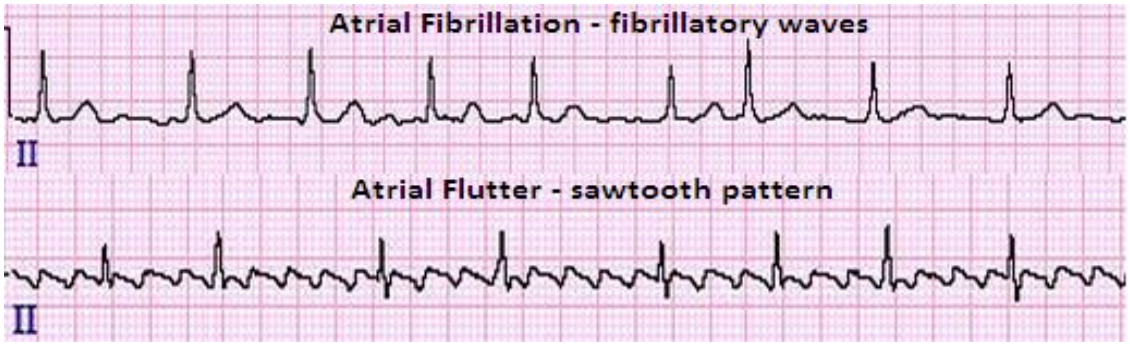
Results of non-synchronized depolarization!?"WE ARE TALKING ABOUT "A FIB""

- *Let me simplify it to you: imagine having someone's heart ,and you start to twist it in a different ways ,definitely you'll end up with a thrombus formation(cuz you kept twisting the muscles stupid ,so the blood flow will decrease therefore it will accumulate & form a clot),this can predispose to a formation of an either:*

1. *Emboli→ pulmonary trunk→lungs*
2. *Emboli→reach the brain →Stroke*

Conclusion: atrial or ventricular fibrillation patients need to take not only anti-arrhythmic drug ,but also anti-coagulant, ok doctors!

-Atrial flutter: it's also tachyarrhythmia, but it's higher than that of atrial fib, so sometimes it's more than 250 or more than 350 bpm.
The ECG changes (let's say for ex; R wave) it's equal in different depolarizations



- AVNRT: atrioventricular nodal re-entry tachycardia

-AVRT: atrioventricular re-entry tachycardia

- *(In the AV node)*
- *When there's a block in the way of electrical conduction and it's not allowing it to propagate properly*
- *Occurs because of re-entry circuit, they're called paroxysmal supraventricular tachycardia(PCVT).*

-Sinus tachycardia could be benign, meaning that the patient couldn't feel any symptoms ,so no need to prescribe anti-arrhythmic medications, why ??
→because anti-arrhythmic drugs are pro-arrhythmic ,meaning that they could induce arrythmia by altering the ion movements mainly:

- *K+*
- *Na+*
- *Ca+2*

-The most important one is K+ ion, due to having the closest resting membrane potential (-94) to the resting state of cardiac muscles(-90),that's why any change mainly in the potassium concentration has the major effect ,so in case of hypokalemia this can triggered automaticity.

-You remember Nernst equation regarding K+ concentration? NO! me neither But it's talking about the concentration of ions outside and inside ,if we change one of these parameters ,the resting membrane potential will change ,which will change the ions move.

-Definition of cardiac arrhythmia :irregularities in the heart rate(which is a serious condition and could lead to a sudden death).

ALL OF THE ABOVE ABOUT CARDIAC ARRHYTHMIA ; NOW WE WILL BE TALKLING ABOUT NON CARDIAC CAUSES OF ARRYTHMIAS

Topic 2: Non-cardiac causes of arrythmia(acquired)

1- Electrolyte imbalance. *(in plasma concentration of these electrolytes like Na+/K+/Ca+2 ,this can initiate or predispose a condition of arrythmia)*

2- Acid-Base imbalance.

3-Hypoxia.

4-Drugs:

- Digitalis / Digoxin→*it blocks Na/K Atpase ,which stablishes the equilibrium of these electrolytes, used in heart failure(will be discussed later inshallah)*
- Anesthetics • Tricyclic • Diuretics
- Bronchodilators: sympathomimetic (*beta2 agonist ;salbutamol used in asthma): they're sympathomimetic agents so they're going to effect the heart and sinuses inducing arrythmias, you may think how! & what happened to selectivity?!*

Remember: The major rule for selectivity, is the dose; increase the dose, you lose the selsctivty,also beta2 are located in the heart too ,but predominate in the lungs .

5-Reflexes (GI, Neuronal)

##There's a mnemonic to memorize the drugs that induce arrythmia(anti-ABCDE)+the ones that we mentioned above :

1. *Anti-Arrhythmic*
2. *Antibiotics(macrolides;azithromyocin,clarithromyocin)*
3. *Anti-psychotics ;haloperidol*
4. *Anti-Depressants*
5. *Anti-Emetics*

Topic 3: Cardiac causes of arrythmia(acquired)

• Ischemic heart disease. →***necrosis/fibrosis/scare of the area ,affecting the conduction transmission causing block, which will predispose to a kind of arrythmia called Re-entry circuit.***

• Inflammation of the heart

• Trauma e.g. heart surgery; ***open heart surgery ,catheter insertion***

• Congestive heart failure.

• Hypotension; ***will be discussed inshallah….***

Topic 4: Other causes of arrythmia(inherited)

Certain individuals have mutation in the ion channels ,resulting In either

- ***Inactive: loss of function mutation***
- ***Overactive: gain of function mutation***

قال تعالى:فَإِنّ معَ العُسرِ يُسرا إنّ مَعَ العُسْرِ يُسرَا(5)

Topic 5: Electrical activity of the heart

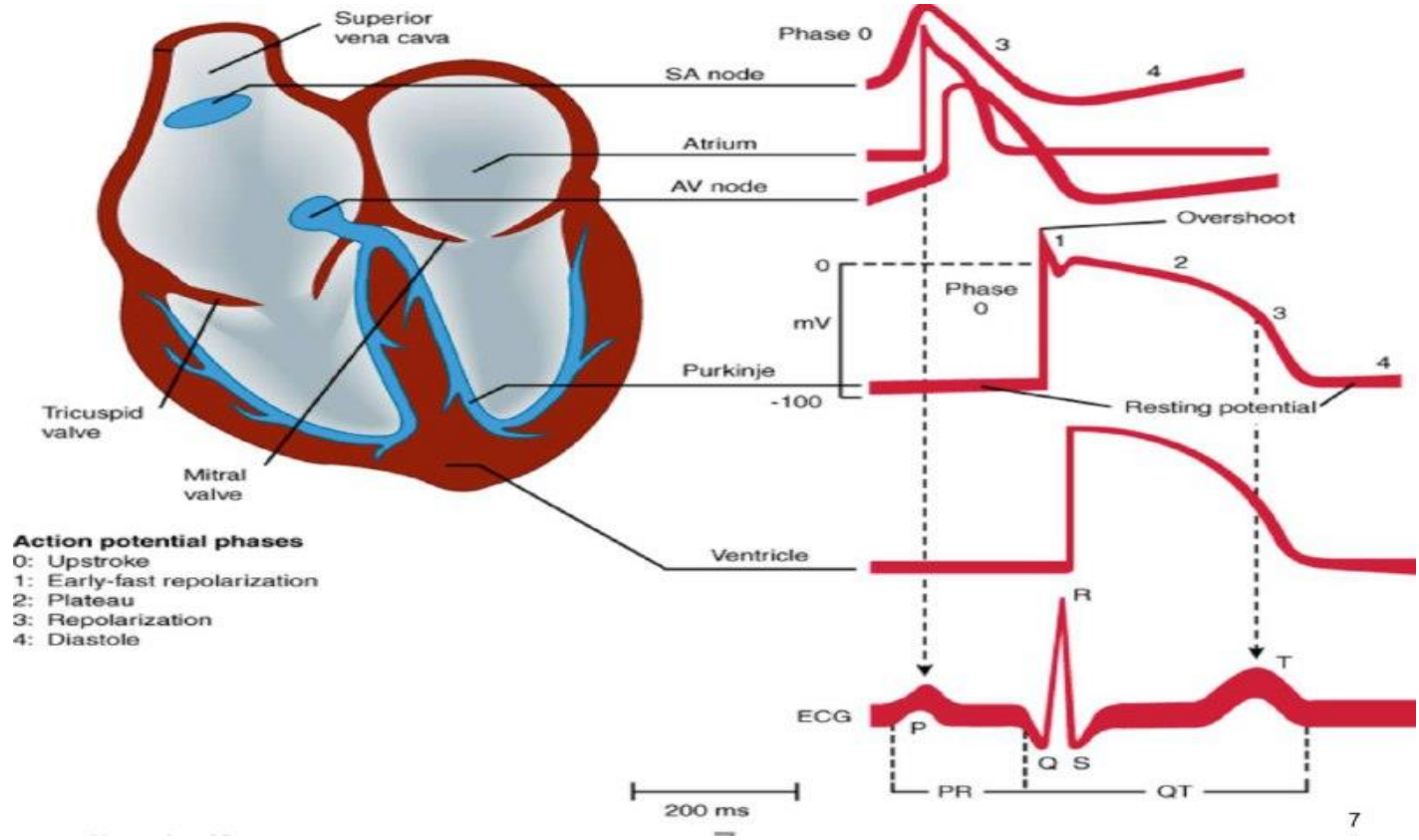
• Cardiac cells undergo depolarization and repolarization to initiate cardiac action potentials: 60 times/ minute.

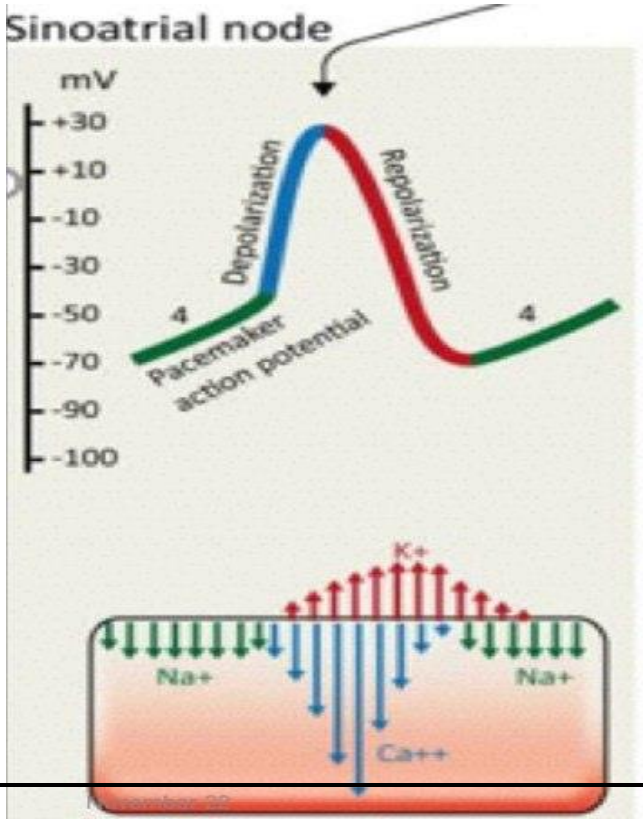
• The shape and duration of each action potential are determined by the activity of ion channel protein complexes in the membranes of individual cells.

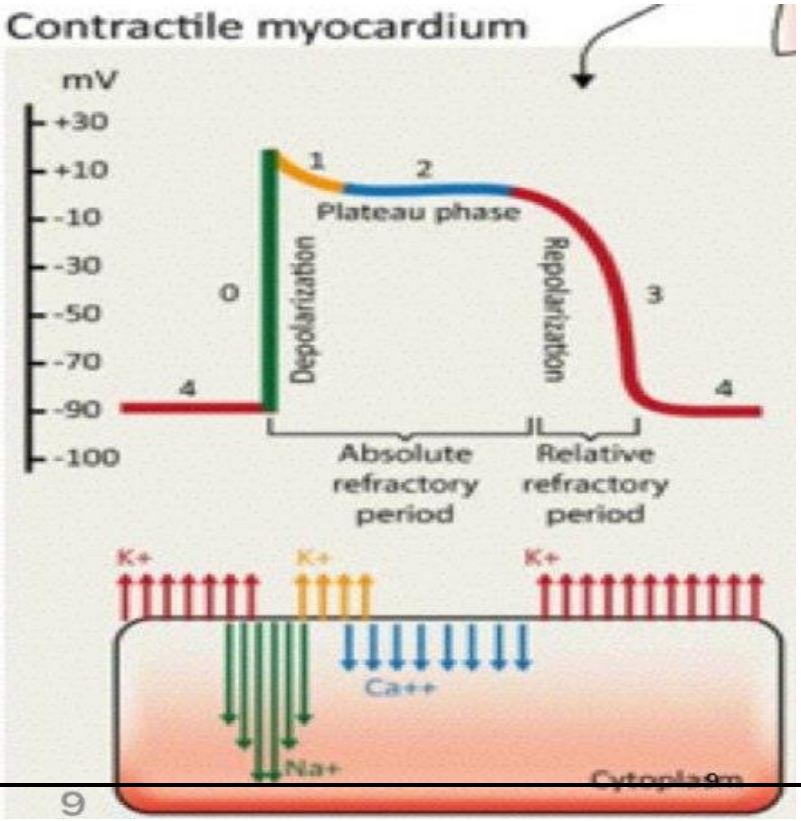
• Ion channel function can be disrupted by inherited mutation/polymorphism, acute ischemia, sympathetic stimulation, or myocardial scarring, to create arrhythmias

Myocardial scarring is **the accumulation of fibrous tissue resulting after some form of trauma to the cardiac tissue**

Topic 6: differences between automaticity of SA node & Action potential phases







Please take care of these notes, cuz according to them you'll diagnose your patient & prescribe a suitable drug inshallah(ما تفضحنا مع طلاب الصيدلة)

General notes for both potentials:

- ***-Na+ channels in inward current (gets inside the cell)***
- ***-Ca+2 channels in inward current (gets inside the cell)***
- ***-K+ channels in outward current***

The differences between them:

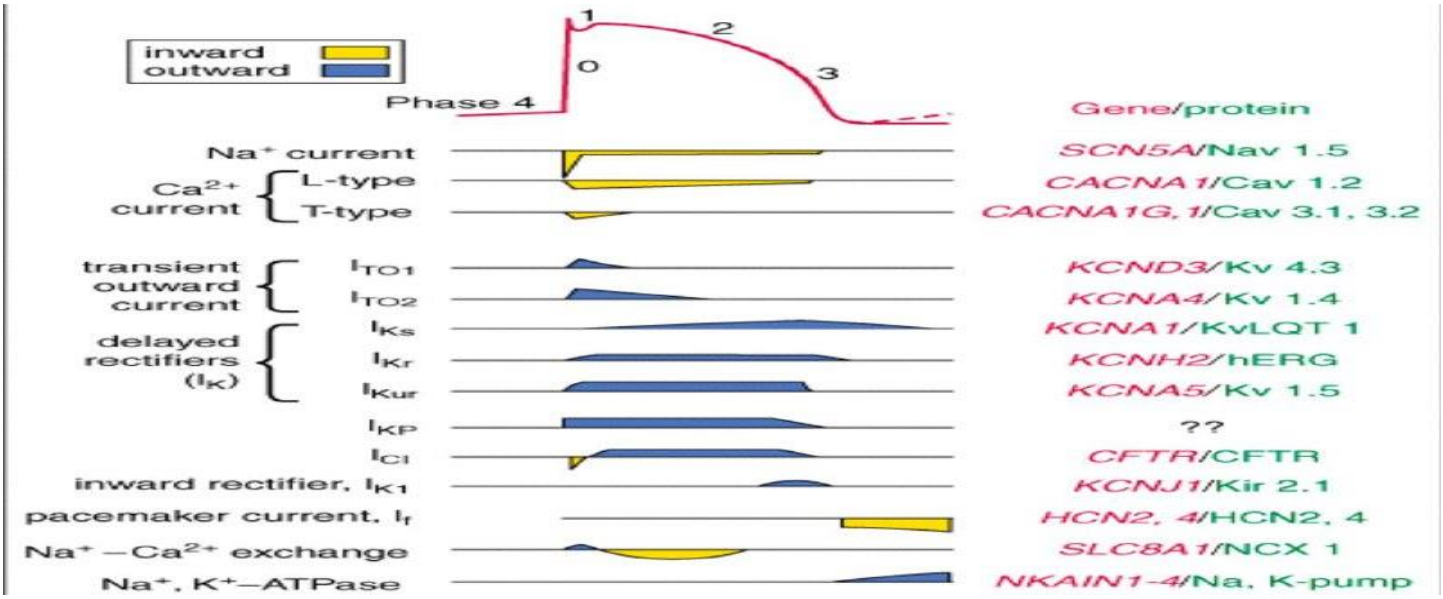
-the pacemaker current are called funny current; we have leakage of Na and Ca ions that will allow slow depolarization to occur when you reach the threshold, we have opening of Ca channels then entry of Ca+2 ions making a specific characteristic for the Sa node.

-another difference is the upstroke of the action potential due to Na+ entry(depolarization),so we will discuss a drugs affecting the upstroke in action potential ,and the automaticity of SA node.

-phase 1 in AP (mainly caused by the K+ ions)

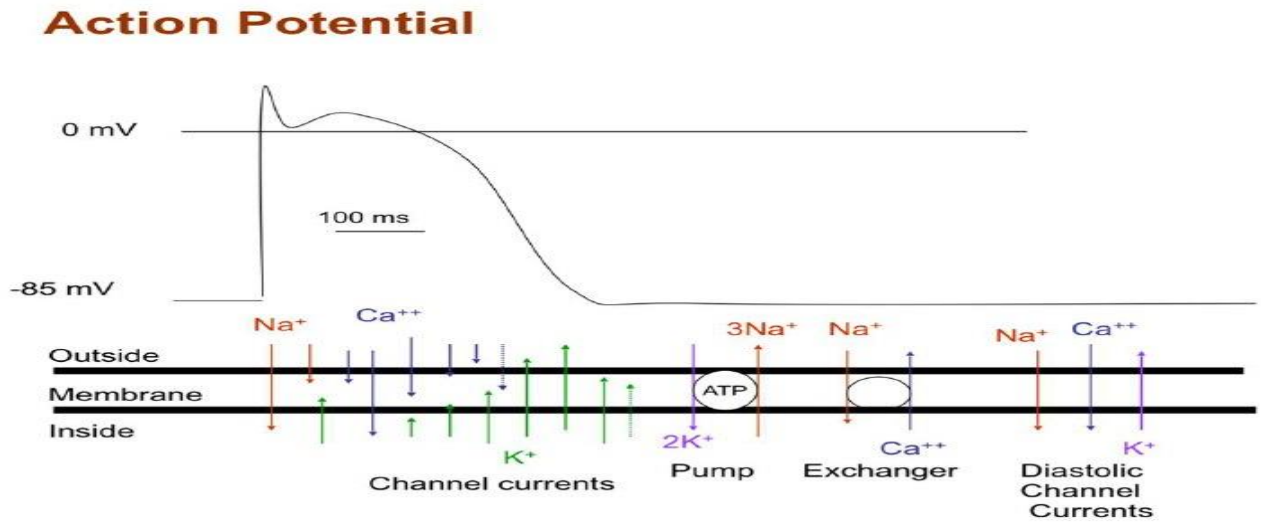
-plateau phase in AP(caused by Ca inward & K outward)

Important note :the slope of phase 4 (depolarization by Na+ ions) is responsible for the heart rate, if it increases or decreases .



Action Potential

- Phase 0: rapid depolarization due to influx of Na+ via voltage dependent sodium channels.
- Phase 1: partial repolarization due to inactivation of Na+ channels
- Phase 2: plateau from slow Ca2+ influx via L-type voltage sensitive Ca2+ channels
- Phase 3: repolarization due to inactivation of Ca2+ and efflux of K+ due to activation of K+ channels
- Phase 4: the pacemaker potential) inward movement of Na+ and Ca2+



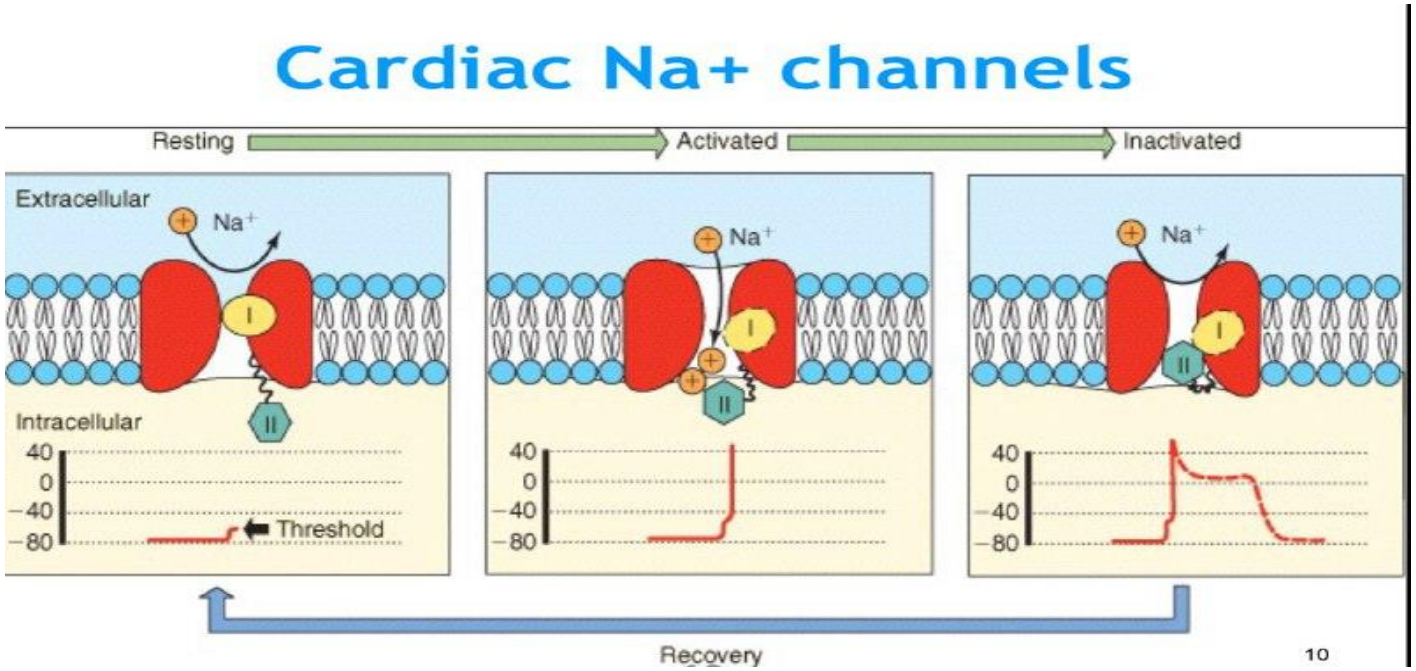
Most important channels:

-Na/K ATPas: maintains the electrochemical gradient .

**3Na+ outward *2K+ inward*

-Na/Ca exchanger .

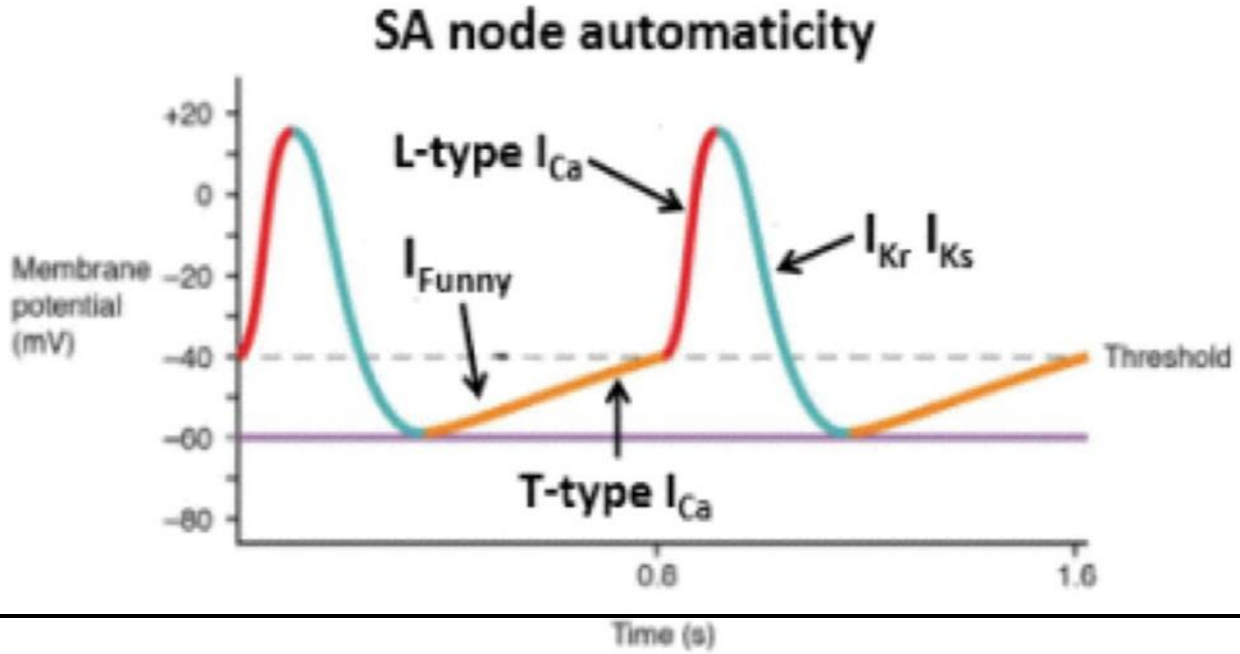
Topic 7:Na+ channels states



The sodium channel is present in three conformations; opened / closed and activated/inactivated finally, resting state

The difference between inactivated and rested?

Inactivated: it's in the refractory period, so no other AP is allowed to be generated, this is not really that important in our topic, but what really matters that we found there's a various drugs acting on a different conformational sates of the sodium channels, to re-emphasize the current (will be discussed inshallah).



Topic 8: Cardiac electrophysiology

A. Resting Membrane Potential (RMP) - A voltage difference (about -90 mV) exists across the surface membrane of all cardiac cells due to uneven distribution of ions. This is created primarily by active cell membrane transport of Na+ (3 out) and K+ (2 in) by Na+, K+-ATPase.

B. Action Potential (AP) - When cardiac cells are electrically excited, a sequence of voltage changes (depolarization and repolarization) occurs as a function of time. These changes in voltage are due to changes in conductance of ions (mainly Na+, Ca++, and K+) across the cell membrane.

Topic 9: Distribution of Ions

potassium-sparing diuretics are one type of diuretic. They are **weak diuretics usually prescribed in combination with other types of diuretics**. They are used to increase the amount of fluid passed from the body in urine, whilst also preventing too much potassium being lost with it

"It's going to make missing with ions distribution"

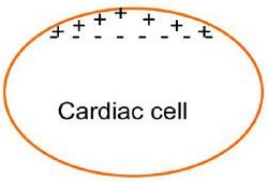
-we have different type of acting:

- ***K+ sparing diuretic: they retain the K ions, causing hyperkalemia***
- ***Other Diuretic: excreting K+ ions renally leading to hypokalemia***

both of them will miss up the normal distribution, result in predisposition of cardiac arrythmias

Distribution of ions at rest [mM]

Ion	Intracellular	Extracellular
Na^+	10	145
K^+	140	4
Cl^-	4	115
Ca^{++}	<0.001	2



Topic 10: ventricular arrythmia

-we talked about supraventricular(atrial) ,let us talk about ventricular arrythmia now:

As atrial, we also have ventricular fibrillation and ventricular flutter

Same as atrial fib, what u most do is as follows:

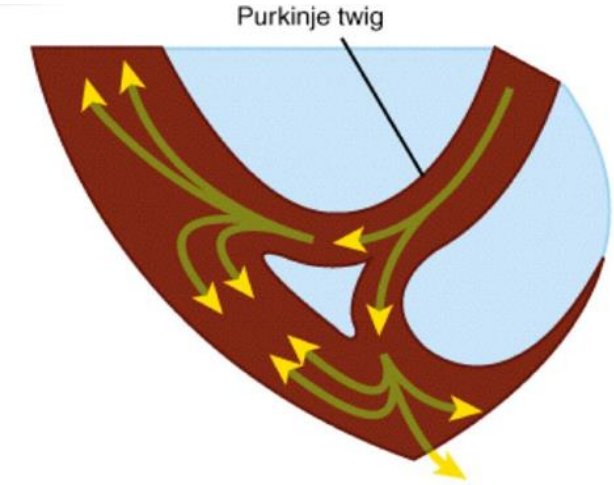
COPPY THE LINK AND WATCH THE VIDEO TO IMAGINE WHAT IS GOING ON :

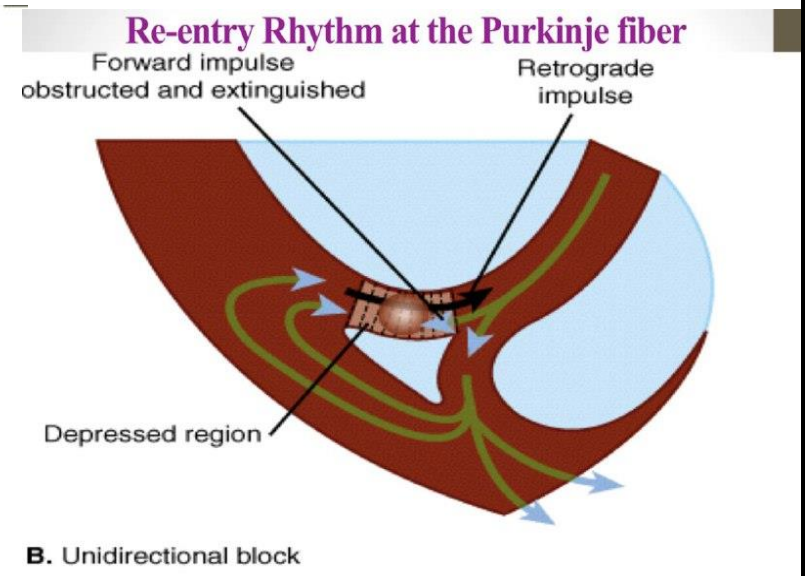
http://hobartcardiology.com.au/conditions/atrioventricular-nodal-reentry-tachycardia-avnrt/

1-anti-arrhythmic

2-anti-coagulant

3-look for the cause of this ventricular fib





B. Unidirectional block

In a normal situation the conduction is transmitted as follows

SA → AV → LF/RT bundles → purkinje fibers → each part of the heart.

If the signal faces a block, it's going to separate and split in 2 paths :

- *Complete its normal pathway to other side*
- *Will re-enter its previous pathway as shown above*

-In the left figure (normal circuit), after splitting the signal, they will meet and delete each other.

-In the right figure (diseased heart): having obstructed region, the signal (beta) goes to the bifurcation, which is the normal pathway, the other signal (alpha) goes to the disease pathway facing an obstacle & it would be hardly transmitted. The retrograde signal is going to turn around, and meet up in the depressed area(obstacle).

-The alpha arm (that went on the diseased area right after splitting) is impeded and slowed after facing the block therefore ,the AP generated by alpha has a short refractory period, the retrograde signal is going to be able to generate a new AP,and this what we call Rr-entry circuit, it will always be ready for another stimulus .

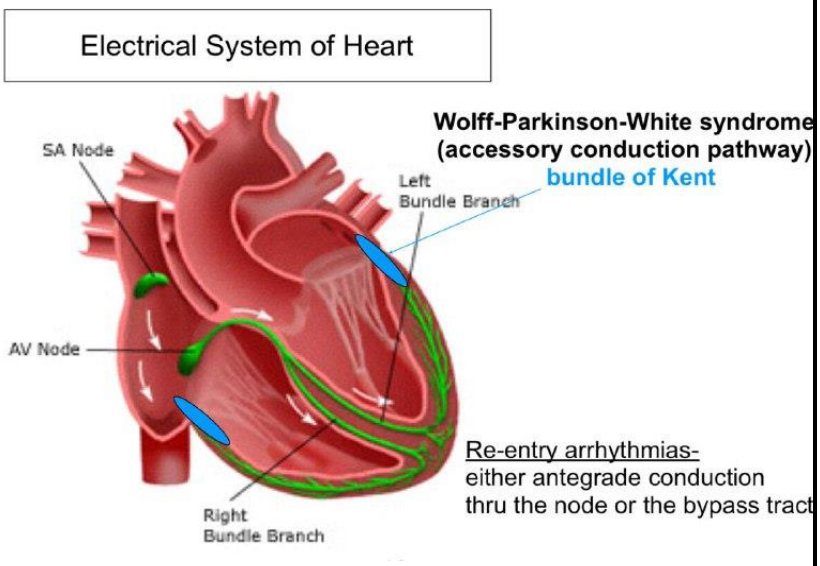
-The block could be; a drug-induced ,Scar formation after heart surgery, congenital diseases , drugs that decrease conduction (beta blockers)

Topic 11: Bundle of Kent

Bundle of Kent is **an abnormal pathway present in a small percentage of the general population that results in a condition known as Wolff-Parkinson-White syndrome (WPW)**.

-If this loop (re-entry circuit) happens in the bundle of Kent, it's an accessory part of the normal electrical conduction ,it's nonfunctioning until something abnormal happens to the heart

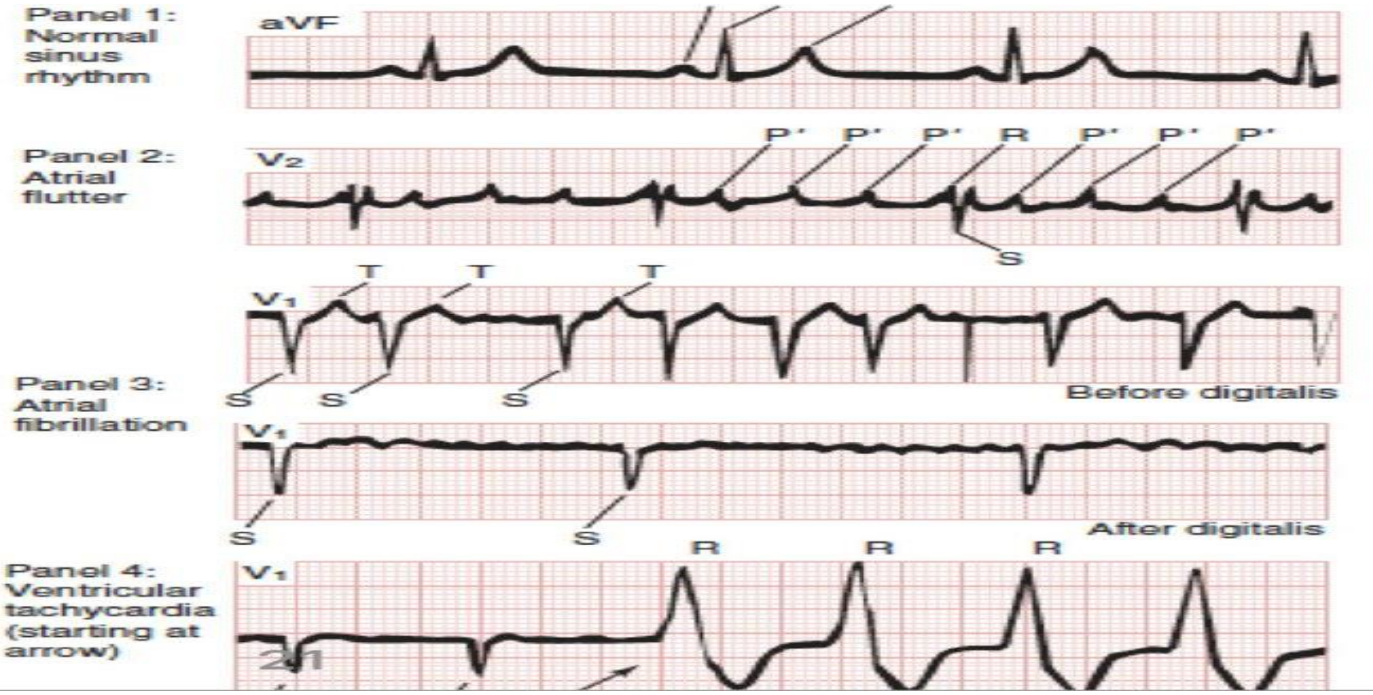
Wolff-Parkinson-White syndrome *is an inherited disease ,causes a defect in the bundle of Kent it's a form of re-entry circuit & a type of arrythmia.*



Topic 11: Pre-requisites for Reentry (Circus Movement)

Anatomic or physiologic obstacle.
-Unidirectional block.
Conduction time around the circuit must be longer than the effective refractory period.

Topic 12: ECG of some arrythmias



-panel 3: Notice in A.fib that we have more irregularities (the distance between the 2 waves is shorter than the normal), which is more serious.
-panel 4: Notice that the (P) wave is missing, meaning that the conduction starts from the ventricles, we're no more listening to the SA node
Note: V.fib is almost lethal (dangerous condition of all types of arrythmia)

Torsade(*twisting*) de Pointes Polymorphic*(multiple forms)* Ventricular Tachycardia
LQT, syncope, and sudden death. Causes:

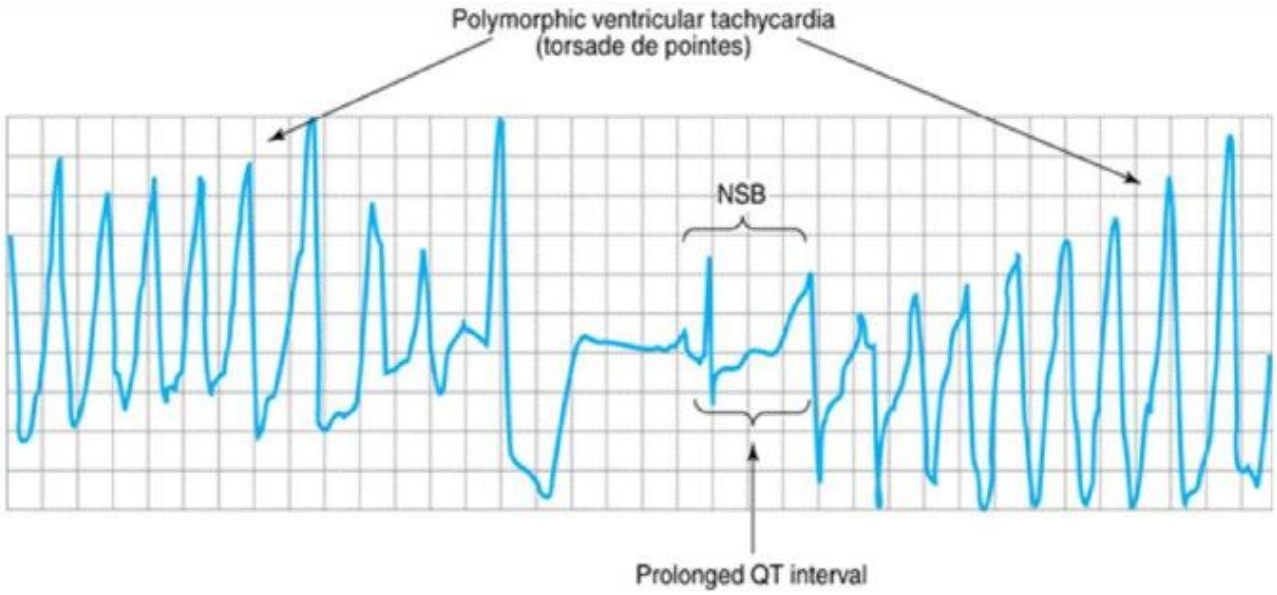
Torsade de pointes is an uncommon and distinctive form of polymorphic ventricular tachycardia (VT) characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line

- Familial long QT interval
- Drug - Induced (drugs which prolong APD).
- Genetic mutations: 300 different mutations in at least 8 ion channel genes.

Mechanisms:

- Increased inward current (GF), or
- Decreased outward current (LF) during the plateau.

-Now we need to diagnose it!



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

-Prolonged Q-T interval is a characteristic of this disease, it's serious &cause a sudden death in young age, it's a genetic mutation of one pf these ion channels(a mutation in gene SCN5A, which disrupts fast inactivation of the cardiac sodium channel (I Na))

-Trx: discovered by accident & start taking beta blockers,& need a genetic screening for relatives
-Polymorphic: different length of waves
-Ventricular: due to missing (p) wave
-Be a good doctor and wait for the long Q-T to diagnose your patient.

TABLE 14–1 Molecular and genetic basis of some cardiac arrhythmias.

Type	Chromosome Involved	Defective Gene	Ion Channel or Proteins Affected	Resul
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* 23	I_{Ks}	GF

Torsade de Pointes Risk Factors:

- Bradycardia.
- Hypokalemia.
- Triggered upstrokes.
- Drugs which ↑ APD.

Treatment:

- K+
- ↓ Triggered upstrokes (β Blockers or Mg++)
- ↓ APD (Pacemaker or isoproterenol).