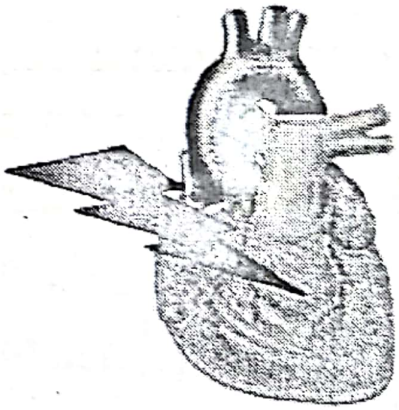
Artery Academy

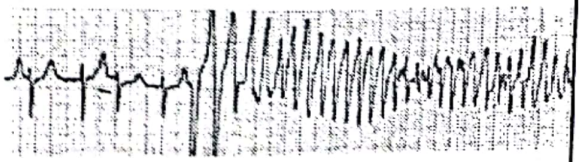
Ayah Rabba'

Drugs Used in Cardiac Arrhythmias

Pharmacology I

Dr. Heba Khader





« اللهمّ إني أسألك حين المسألة ، وحين الدعاء ما وحين النجاح ، اللهم ثبت المعلومة في صدري ، ما جعلني قويّ الحافظة وأحيي القلب » .

↳ Controlled by electrical signals from SA node.

Normal Sinus Rhythm

Normal electrical cardiac function **(normal sinus rhythm, NSR)** is dependent on generation of an impulse in the normal sinoatrial (SA) node pacemaker usually at a frequency of 60–100 bpm. (beat per minute)

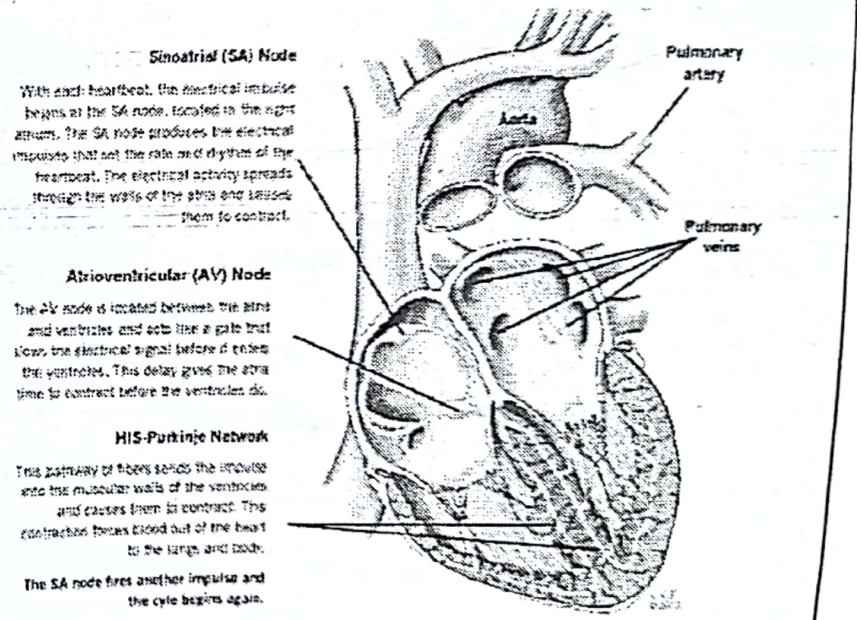
This impulse spreads rapidly through the atria and enters the atrioventricular (AV) node, which is normally the only conduction pathway between the atria and ventricles.

Conduction through the AV node is slow, requiring about 0.15 seconds. (This delay provides time for atrial contraction to propel blood into the ventricles.) The impulse then propagates over the His-Purkinje system and invades all parts of the ventricles.

electrical signals

الوحيد للانتقال Pathway هو (AV node) انه! هم نعرف

The Heart's Electrical System



↳ irregular heart beat or (heart rythm)

Arrhythmia

- Arrhythmias (also called dysrhythmia) consist of cardiac depolarizations that deviate from the above description in one or more aspects; there is an abnormality in:
  1. the site of origin of the impulse → electrical signal يصير في أكثر من مكان لانتاج
  2. the rate or regularity of the impulse → خطأ في سرعة أو انتظام النبض
  3. or the conduction of the impulse. → مشكلة في انتاج electrical signal.

- Many factors can precipitate or exacerbate (تفاقم) arrhythmias: ischemia (1), hypoxia (2), acidosis or alkalosis (3), electrolyte abnormalities (4), excessive catecholamine exposure (5), drug toxicity (eg, digitalis or antiarrhythmic drugs (6)).

↳ cases in which the arrhythmia is complication.

in chronic Digoxin toxicity.

Arrhythmia

Cardiac arrhythmias are a common problem in clinical practice, occurring in up to 25% of patients treated with digitalis, 50% of anesthetized patients, and over 80% of patients with acute myocardial infarction.

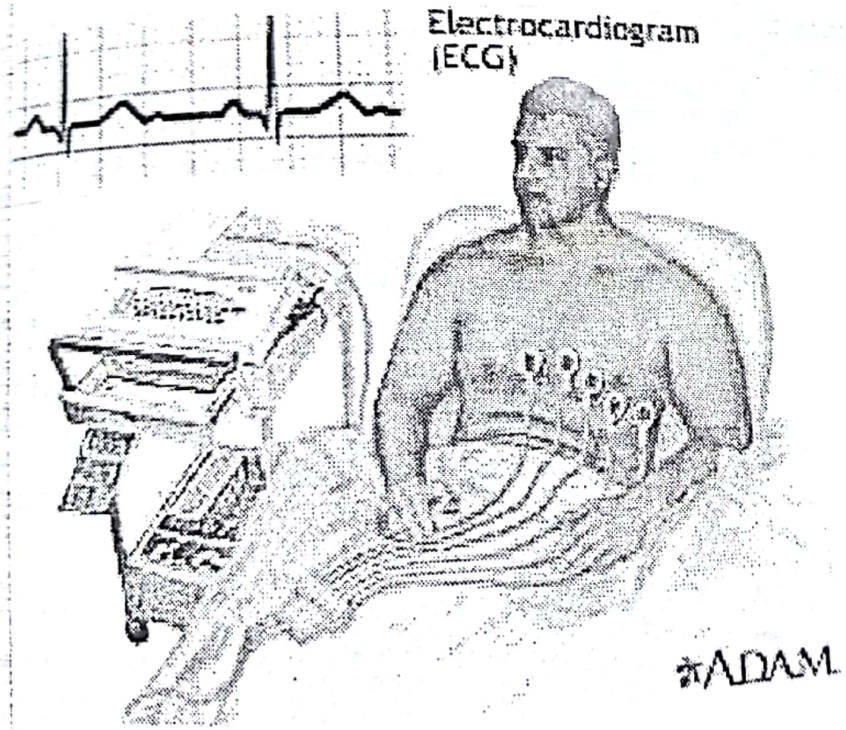
Arrhythmia may decrease cardiac output and disturb perfusion of vital organs.

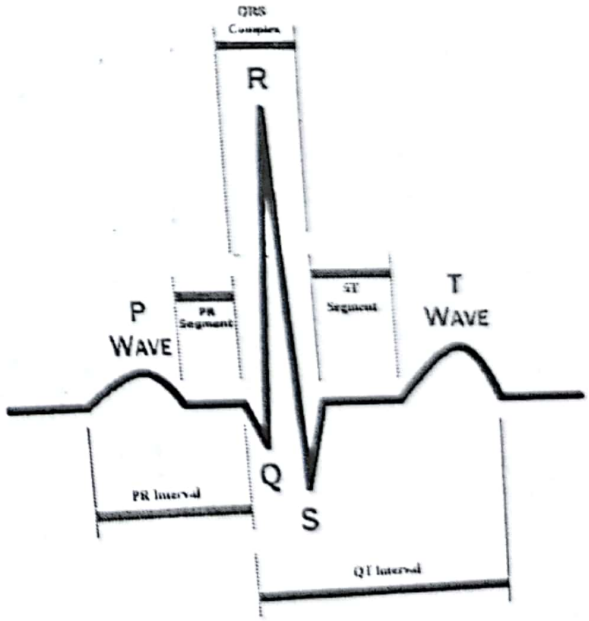
Signs and symptoms that typically accompany arrhythmia:

1. Chest pain
2. Anxiety and confusion (from reduced brain perfusion)
3. Abnormal pulse rate or rhythm
4. Reduced blood pressure

Arrhythmia

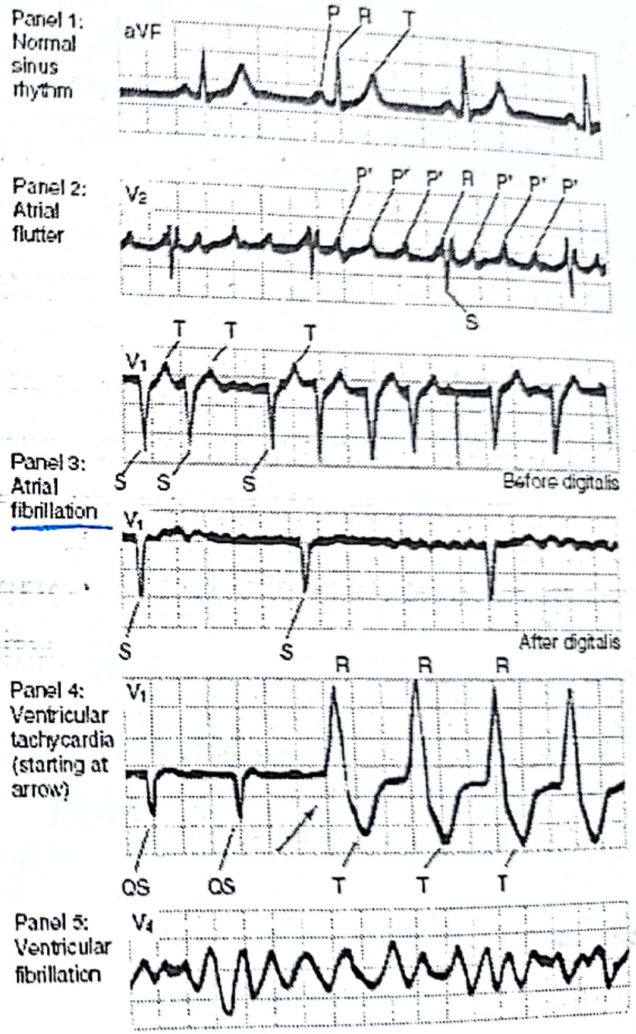
- Although some arrhythmias are silent, most produce signs and symptoms.
- Only ECG can definitively identify an arrhythmia.
- Electrocardiogram (ECG) is a test that show the electrical activity of the heart.





Arrhythmia

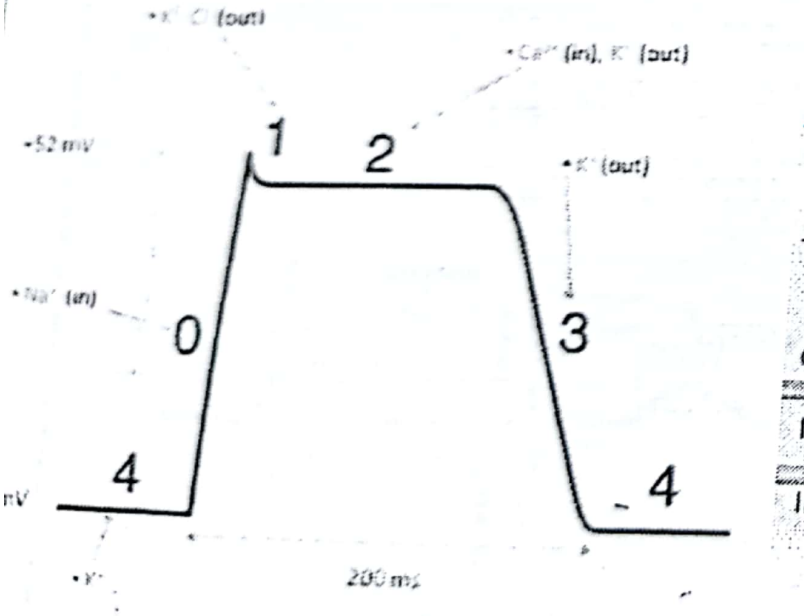
- **Types of arrhythmias:**
- Atrial arrhythmias:
  - Atrial fibrillation → (Blood stasis) clot
  - Atrial flutter
- Supraventricular tachycarias:
  - AV nodal reentry → (مكان ثاني بحفز AV node)
  - Acute Supraventricular tachycardia
- Ventricular tachycaria:
  - Acute ventricular tachycardia
  - Ventricular fibrillation (death)

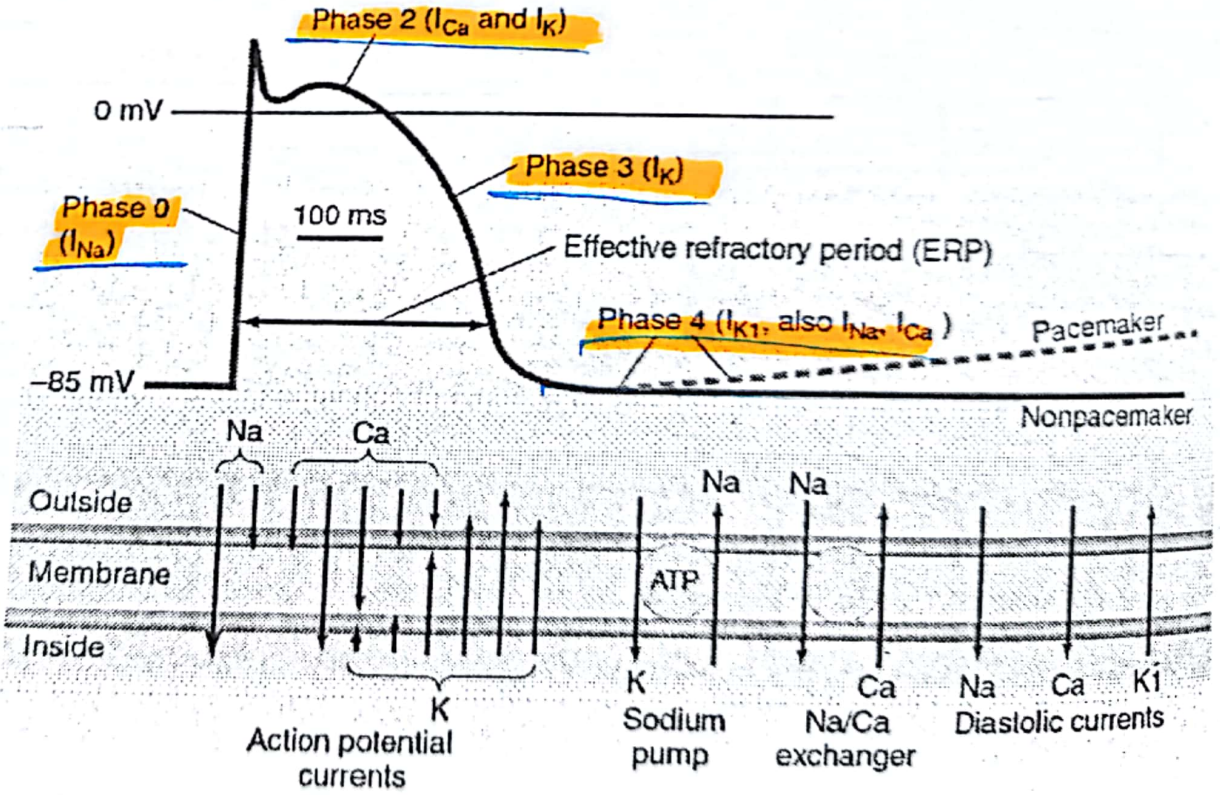


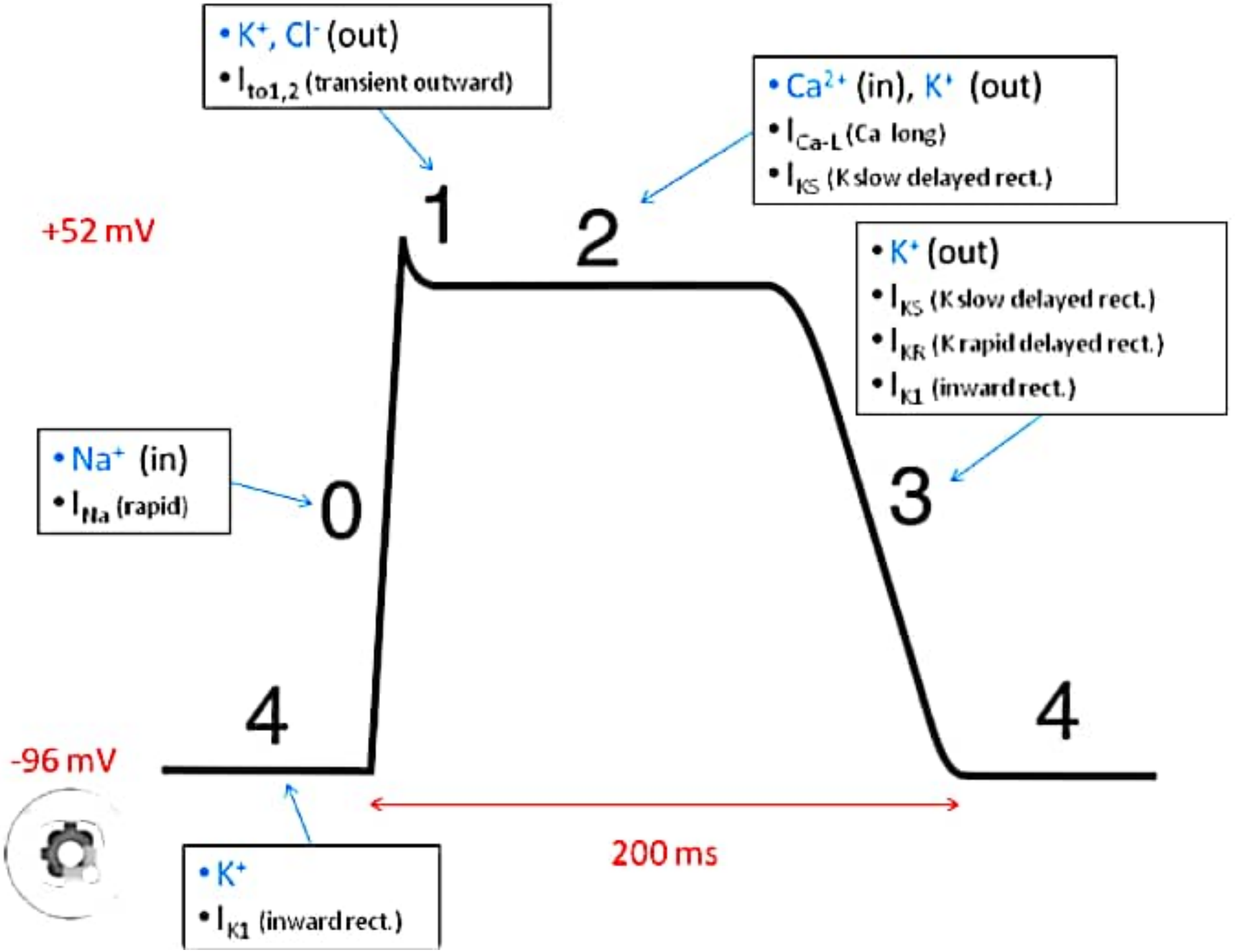
AV nodal reentry & وجود مكان ثاني بينتج electrical signals.

Action Potential of Cardiac Cell

- The cellular action potentials are the result of ion fluxes through voltage-gated channels and carrier mechanisms.
- Antiarrhythmic drugs act on 1 or more of the 3 major currents (I_{Na}, I_{Ca}, I_K) or on the β adrenoceptors that modulate these currents.






• K+, Cl- (out)
• Ito1,2 (transient outward)
• Ca2+ (in), K+ (out)
• ICa-L (Ca long)
• IKS (K slow delayed rect.)
+52 mV
1
2
• K+ (out)
• IKS (K slow delayed rect.)
• IKR (K rapid delayed rect.)
• IK1 (inward rect.)
• Na+ (in)
• INa (rapid)
0
3
4
4
-96 mV
200 ms
• K+
• IK1 (inward rect.)

* بداية AP في (phase 0)
* دخول Na^+ داخل الخلية يتبع فرق الجهد بين طرفي الخلية عشان الخلية. (Na^+ channel open)

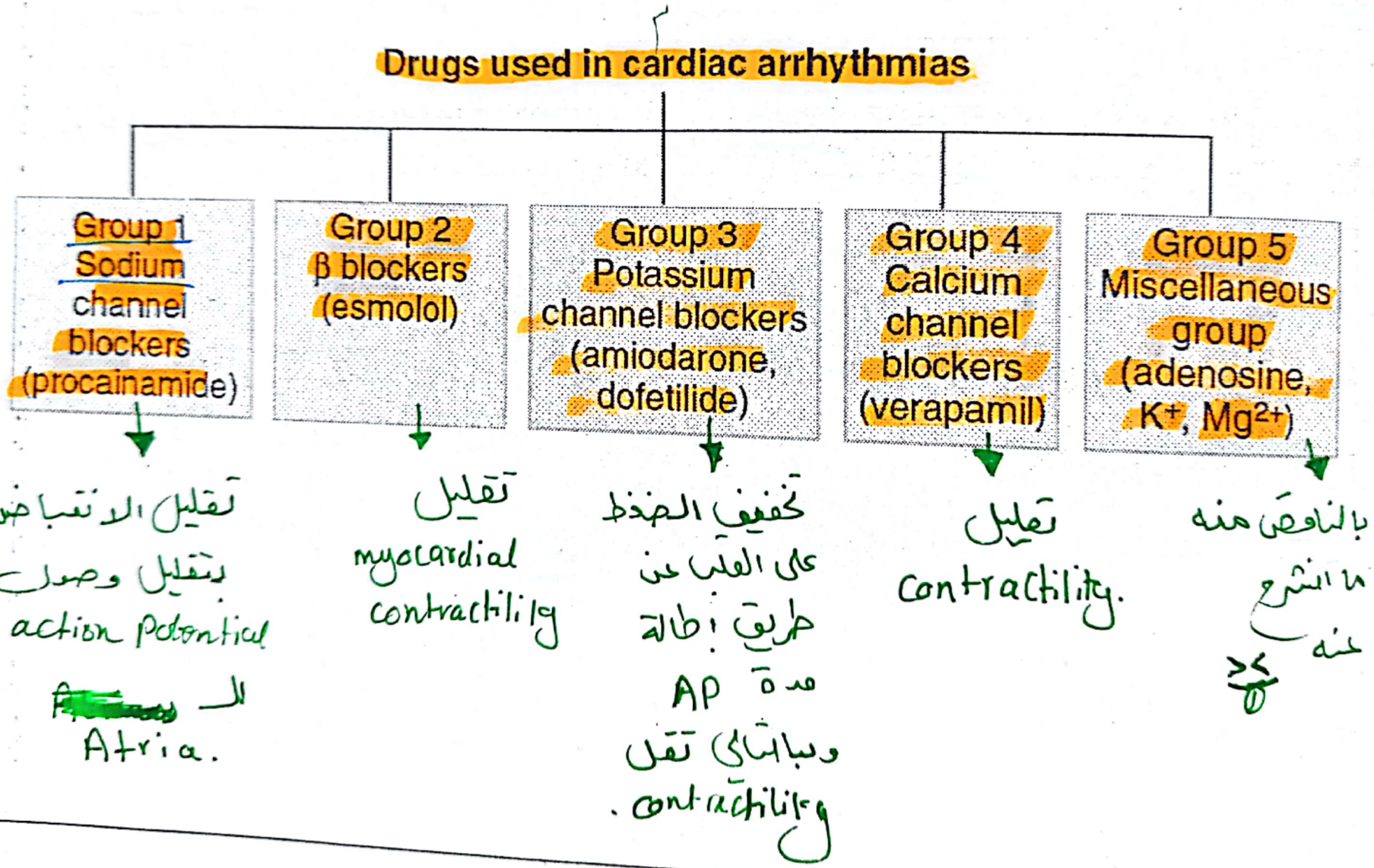
- يعالج arrhythmia عن طريق تقليل دخول Na^+ إلى الخلية ← prolong AP ← Na^+ channel Blocker

* phas 2 من AP :
* دخول Ca^+ داخل الخلية عبر Ca^{+2} channel وخروج K^+ من الخلية إلى خارجها.

- عكن أقلل contractility عن طريق تقليل دخول Ca^+ إلى الخلية ← تقليل contraction ← prolong AP ← Ca^+ channel Blockers.

* phase 3 من AP :
- خروج K^+ خارج الخلية ووصول الخلية لمرحلة repolarization
- بدي أطول فترة QT (AP) ← K^+ channel Blocker

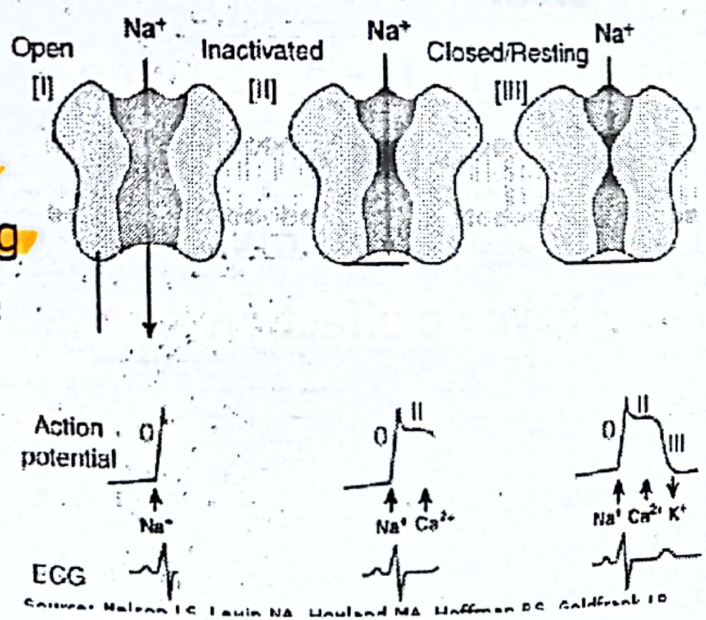
Antiarrhythmic Drugs



atrium. الـ action potential سرعة توصيل *

Group 1 Antiarrhythmics (Sodium Channel Blockers)

- All antidysrhythmics in class 1 (A, B, and C) alter Na^+ conductance through cardiac voltage-gated Na^+ channels. These drugs bind to the Na^+ channels and slow their recovery from the open or inactivated state to the resting, or closed, state.
- This conversion must occur before the channel can reopen and participate in another depolarization. Consequently, as the proportion of drug-bound Na^+ channels increases, fewer of these channels are capable of reactivation on the arrival of the next depolarizing impulse. As a result, by reducing the excitability of the myocardium, abnormal rhythms are prevented.



Group 1 Antiarrhythmics (Sodium Channel Blockers)

Use-dependence: (selective on open Na+ channels) (inactivated)

- Group 1 drugs bind more rapidly to open or inactivated sodium channels than to channels that are fully repolarized following recovery from the previous depolarization cycle.
- Therefore, these drugs show a greater degree of blockade in tissues that are frequently depolarizing (for example, during tachycardia, when the sodium channels open often).
- This property is called use-dependence (or state-dependence) and it enables these drugs to block cells that are discharging at an abnormally high frequency, without interfering with the normal, low-frequency beating of the heart.

مع

* يرتبط هذا الدواء على Na+ channels في حالة inactivate or open قبل ما يصرلها closing

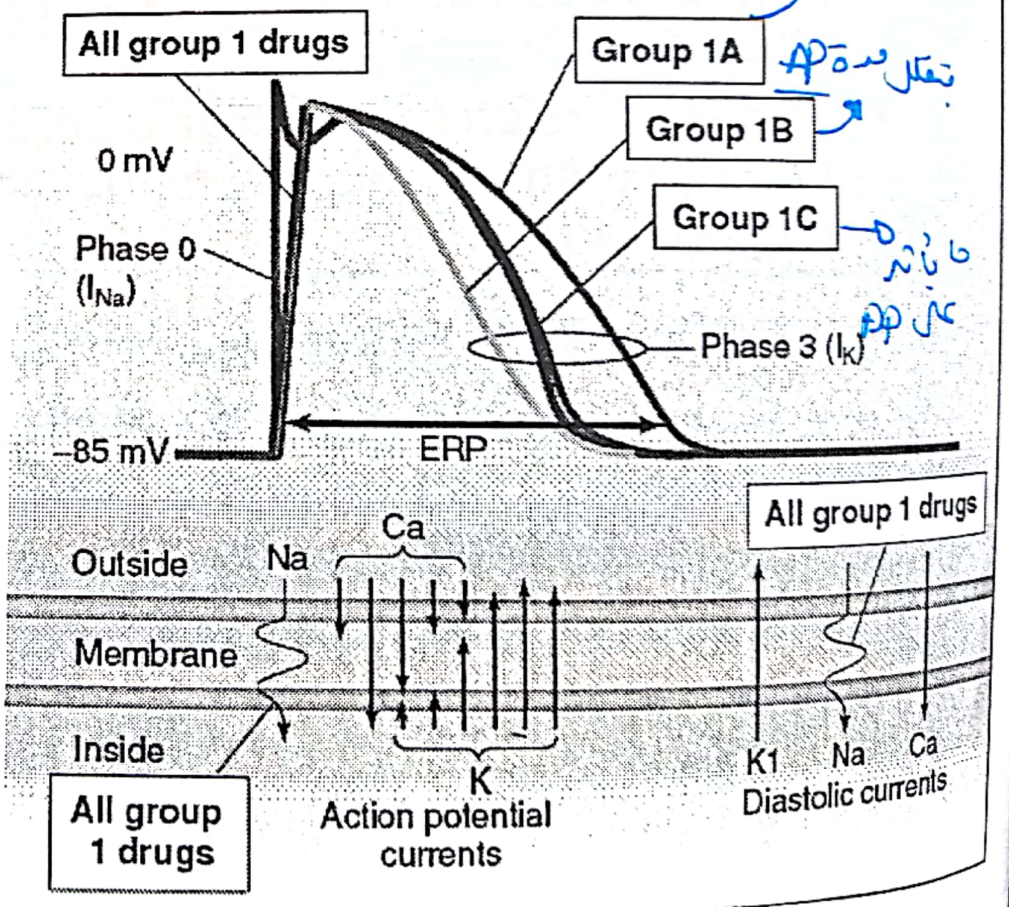
عشان تمنع اذ تأخر depolarization

- لانه في حالة closed channels ما بتستجيب لانها في حالة resting

Group 1 Antiarrhythmics (Sodium Channel Blockers)

- Group 1 antiarrhythmics decreased rate of entry of sodium which slows the rate of rise of Phase 0 of the action potential.
- The group 1 drugs are further subdivided on the basis of their effects on the action potential (AP) duration:

1) Group 1A agents (prototype procainamide) prolong the AP.
2) Group 1B drugs (prototype lidocaine) shorten the AP in some cardiac tissues.
3) Group 1C drugs (prototype flecainide) have no effect on AP duration.



Group 1A Antiarrhythmics

- Procainamide is available in an intravenous formulation only and may be used to treat acute atrial and ventricular arrhythmias.
- However, electrical cardioversion or defibrillation and amiodarone have mostly replaced procainamide in clinical use.

- Procainamide may cause hypotension.

Group 1A Antiarrhythmics

- **Quinidine** is used in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular tachyarrhythmias.
- Quinidine sulfate or gluconate is rapidly and almost completely absorbed after oral administration. (oral)
- **Quinidine** causes cinchonism (fushed skin, headache, vertigo, tinnitus) and GI upset. (SE)
- Drug interactions are common with quinidine since it is an inhibitor of both CYP2D6 and P-glycoprotein.
- **Quinidine** reduces the clearance of digoxin and may increase the serum concentration significantly. (cause digoxin toxicity).
  - **Cinchonism** is a pathological condition caused by an overdose of quinidine or its natural source, cinchona bark.

Group 1A Antiarrhythmics

- **Disopyramide** is used in the treatment of ventricular arrhythmias as an alternative to procainamide or quinidine
- **Disopyramide** has marked antimuscarinic effects.
- Both quinidine and disopyramide are substrates for CYP3A4 and should be used with caution with potent inhibitors of CYP3A4.
  - grap fruit.
  - Ca^+ channel Blockers.

Group 1B Antiarrhythmics

- **Lidocaine** is useful in acute ischemic ventricular arrhythmias. Atrial arrhythmias are not responsive unless caused by digitalis.
- **Lidocaine** is usually given intravenously, but intramuscular administration is also possible. It is never given orally because it has a very high first-pass effect and its metabolites are potentially cardiotoxic.
- **Mexiletine** has similar actions and is given orally for chronic treatment of ventricular arrhythmias, often in combination with amiodarone.
- **Mexiletine** has a narrow therapeutic index and caution should be used when administering the drug with inhibitors of CYP2D6.
- **Phenytoin**, an anticonvulsant, is sometimes classified with the group 1B antiarrhythmic agents. It can be used to reverse digitalis-induced arrhythmias.

→ not given with quindine as a combination.

Group 1C Antiarrhythmics

- **Flecainide** is useful in the maintenance of sinus rhythm in atrial flutter or fibrillation in patients without structural heart disease (left ventricular hypertrophy, heart failure, atherosclerotic heart disease) and in treating refractory ventricular arrhythmias.
- **Flecainide** has a negative inotropic effect and can aggravate chronic heart failure.
- **Flecainide** is more likely than other antiarrhythmic drugs to exacerbate or precipitate arrhythmias (proarrhythmic effect).

الكشف عن Arrhythmia قبل ظهور الأعراض بسبب خاصية

Remember ⇒

- negative inotropic ⇒ ↓ myocardial contractility ↓ heart rate.

Group 1C Antiarrhythmics

- **Propafenone** has some structural similarities to propranolol and possesses weak β-blocking activity.
- Use of propafenone is restricted mostly to atrial arrhythmias.
- **Propafenone** may also cause bronchospasm due to its β-blocking effects. It should be avoided in patients with asthma.
- Propafenone is also an inhibitor of P-glycoprotein.
- Both **flecainide** and **propafenone** should be used with caution with potent inhibitors of CYP2D6.
  - Quinidine

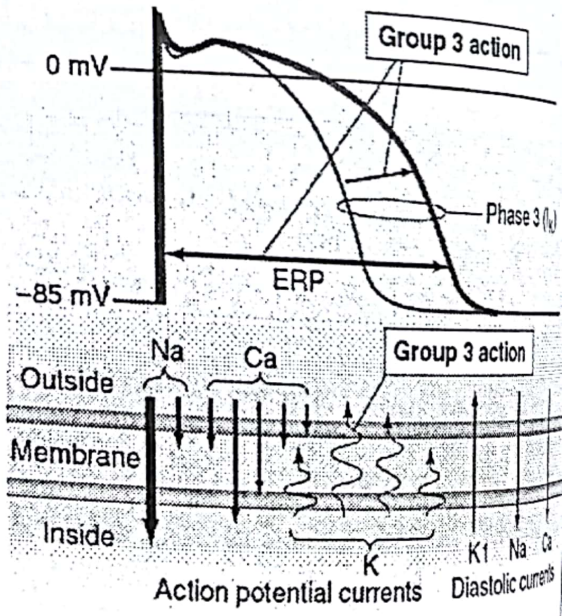
Group 2 Antiarrhythmics (Beta Blockers)

- Their mechanism in arrhythmias is primarily cardiac beta adrenoceptor blockade.
- **Esmolol,** a very short-acting beta blocker for intravenous administration, is used exclusively in acute arrhythmias that occur during surgery or emergency situations..
- **Propranolol, metoprolol,** and **timolol** are commonly used as prophylactic drugs in patients who have had a myocardial infarction.
- The toxicities of beta blockers are the same in patients with arrhythmias as in patients with other conditions.
- **Sotalol** and **amiodarone,** generally classified as group 3 drugs, also have group 2 beta-blocking effects.

Group 3 Antiarrhythmics (Potassium Channel Blockers)

- **Dofetilide** and **ibutilide** are typical group 3 drugs.
- The hallmark of group 3 drugs is prolongation of the AP duration. This AP prolongation is caused by blockade of potassium channels, chiefly the ones are responsible for the repolarization of the AP.
- **Sotalol** is a chiral compound (ie, it has 2 optical isomers). One isomer is an effective beta blocker, and both isomers contribute to the group 3 antiarrhythmic action. The clinical preparation contains both isomers.
- They are effective for atrial arrhythmias.

→ also have group 2 drugs effects.



Group 3 Antiarrhythmics (Potassium Channel Blockers)

- **Amiodarone** is usually classified as a group 3 drug because it blocks the same potassium channels and markedly prolongs AP duration. However, it also blocks sodium and calcium channels and beta receptors.
- Despite its adverse effect profile, **amiodarone** is the most commonly employed antiarrhythmic and thought to be the least proarrhythmic of the class I and III antiarrhythmic drugs.
  - Amiodarone is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias. Amiodarone has been a mainstay of therapy for the rhythm management of atrial fibrillation or flutter.

الدعامة الأساسية

[redacted]

* group 1 and 2 and 3 drugs.

Group 3 Antiarrhythmics (Potassium Channel Blockers)

- **Amiodarone** adverse effects include:
  - pulmonary fibrosis
  - Neuropathy
  - Hepatotoxicity
  - Corneal deposits
  - optic neuritis
  - blue-gray skin discoloration
  - hypo- or hyperthyroidism.
- However, use of low doses and close monitoring reduce toxicity, while retaining clinical efficacy.
- Amiodarone is subject to numerous drug interactions, since it is metabolized by CYP3A4 and serves as an inhibitor of CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein.

↳ high drug-drug interaction.

Group 4 Antiarrhythmics (Calcium Channel Blockers)

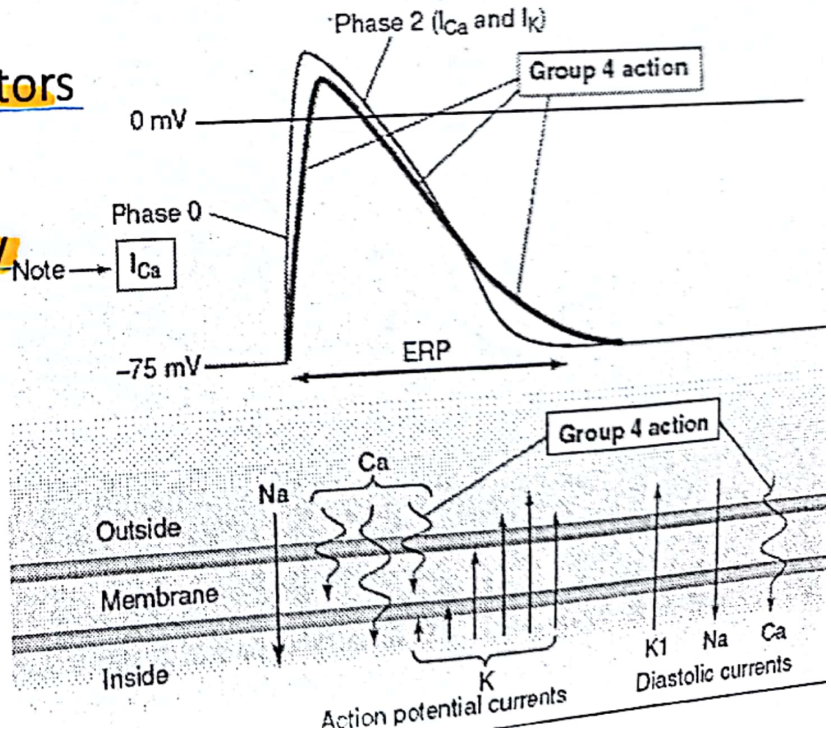
(non hydropyridine)

Verapamil is the prototype. **Diltiazem** is also an effective antiarrhythmic drug.

These agents are more effective against atrial than against ventricular arrhythmias.

Nifedipine and the other dihydropyridines are not useful as antiarrhythmics.

Both agents are substrates and inhibitors of CYP3A4, as well as substrates and inhibitors of P-glycoprotein. As such, they are subject to many drug interactions.



Nonpharmacologic Treatment of Arrhythmia

- It should be noted that electrical methods of treatment of arrhythmias have become very important. These methods include:

(1) External defibrillation

(2) Implanted defibrillators

(3) Implanted pacemaker

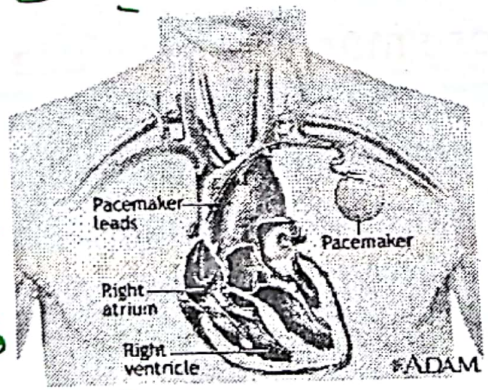
(4) Radiofrequency ablation of arrhythmogenic foci via a catheter.

سا محوني على هاد التفريخ، بسا ما انكون عنه تفاصيل كثيرة، اددسو السلايدات وللا تتعبوا ♥

Good Luck ALL ♥

كي

* حكينا انه من أسباب arrhythmia يكون في مكان تاني بيعمل electrical signals على انتاج



في هاي الحالة بيكون العلاج كي وحتى هاد المكان فيتوقف منه electrical signal انتاج