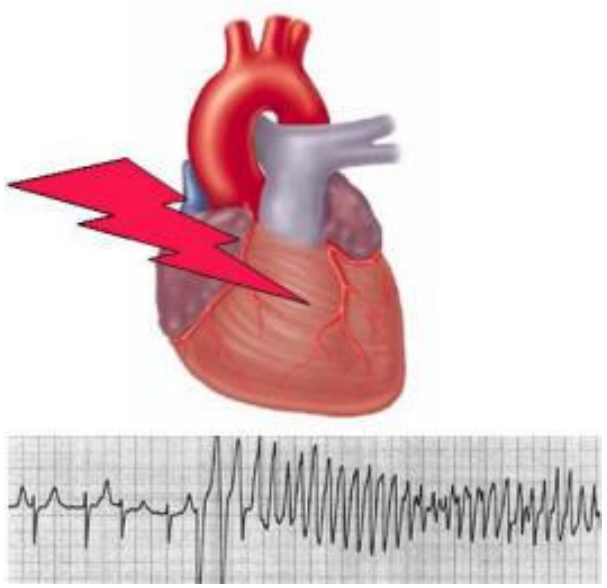
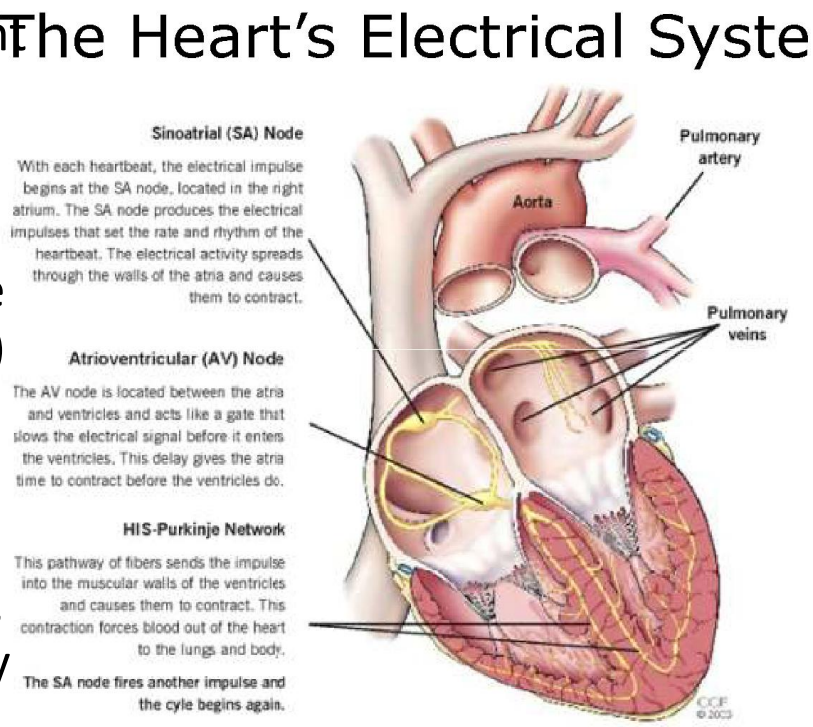
Drugs Used in Cardiac Arrhythmias



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.
- 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.



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:
  - the site of origin of the impulse
  - the rate or regularity of the impulse
  - or the conduction of the impulse.

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

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.

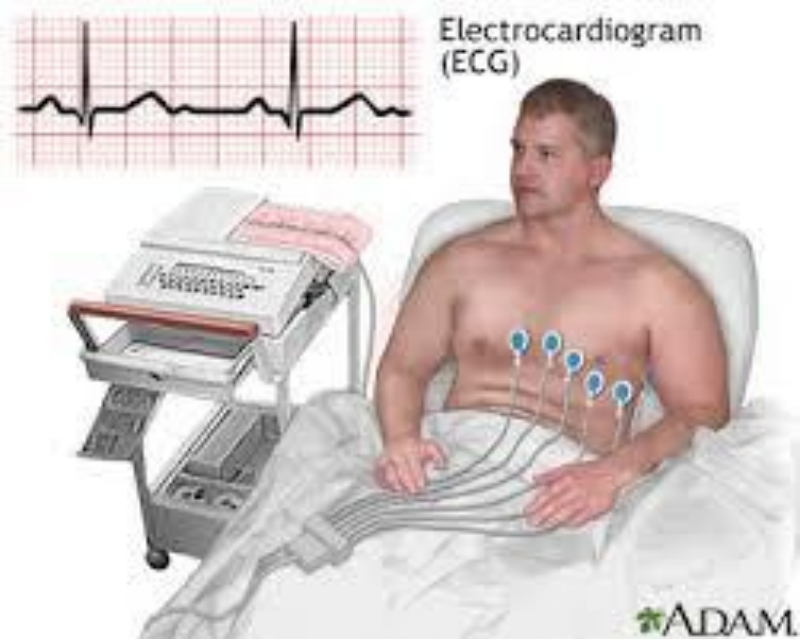
Arrhythmia may decrease cardiac output and disturb perfusion of vital organs.

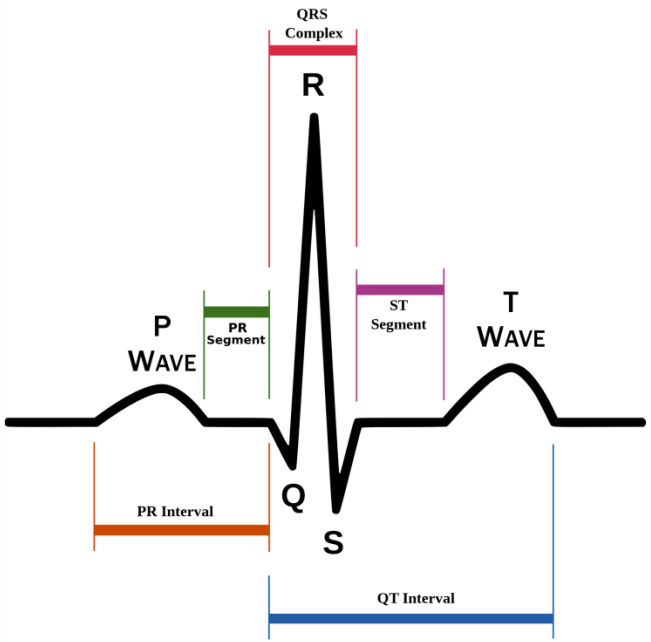
Signs and symptoms that typically accompany arrhythmia:

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

Arrhythmia

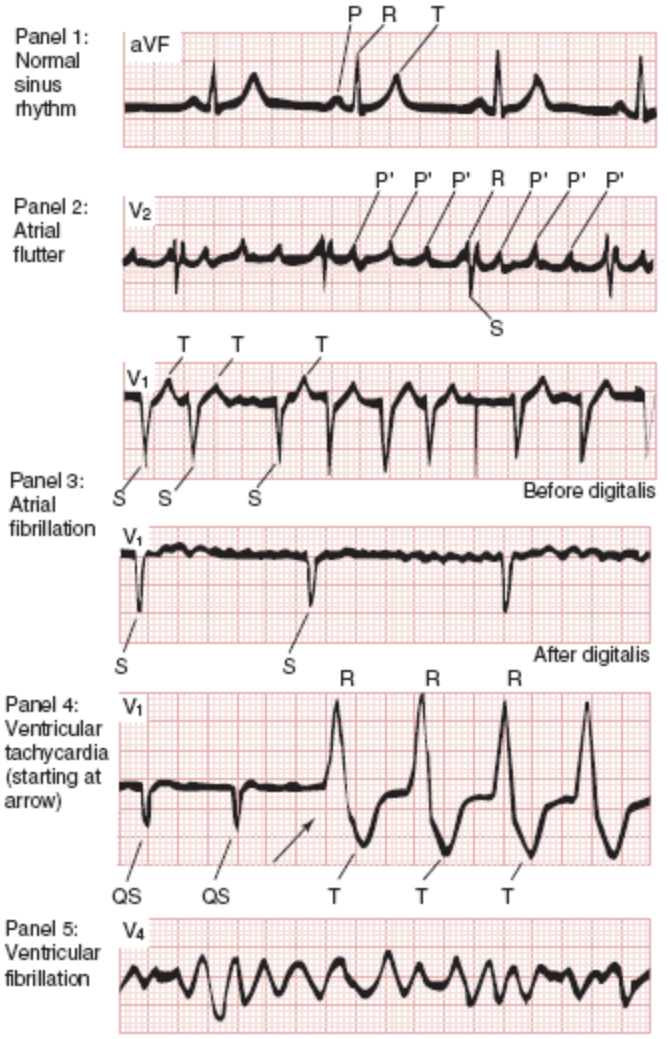
- Although some arrhythmias are silent, most produce signs and symptoms.
- Only ECG can definitively identify an arrhythmia.
- Electrocardiogram (ECG) is a test that show the electrical activity of the heart.





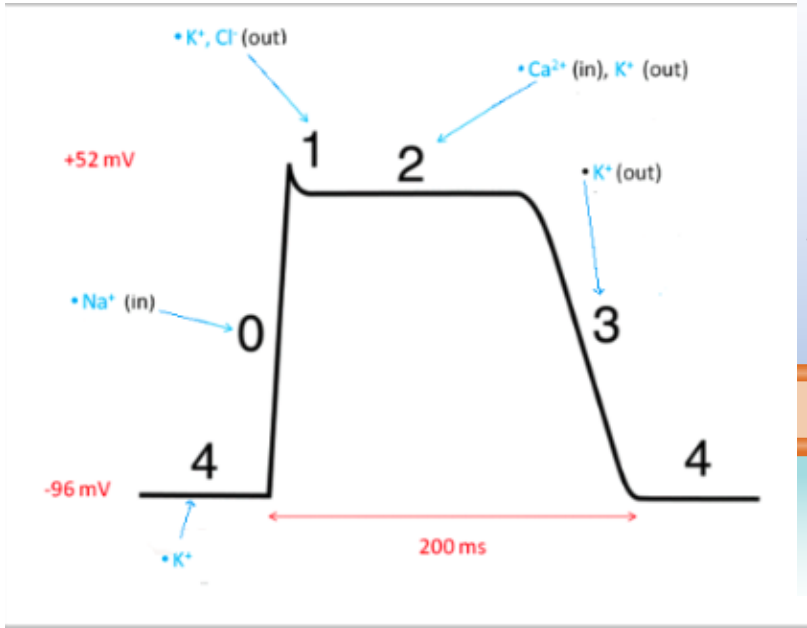
Arrhythmia

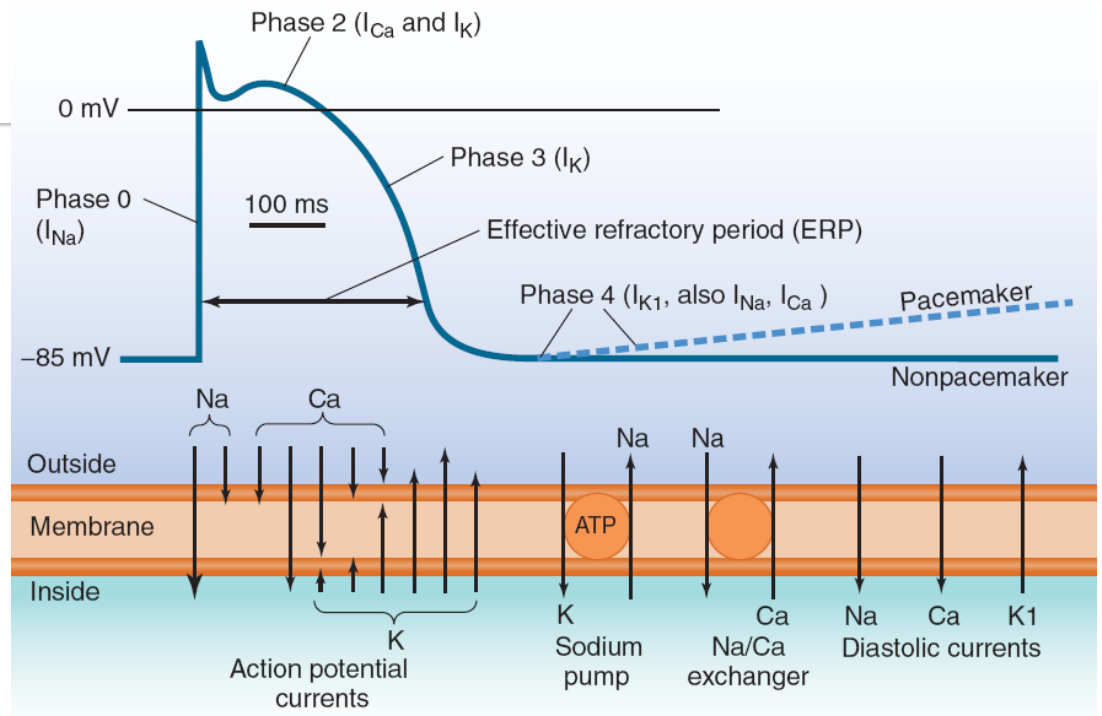
- **Types of arrhythmias:**
- Atrial arrhythmias:
  - Atrial fibrillation
  - Atrial flutter
- Supraventricular tachycardias:
  - AV nodal reentry
  - Acute Supraventricular tachycardia
- Ventricular tachycaria:
  - Acute ventricular tachycardia
  - Ventricular fibrillation



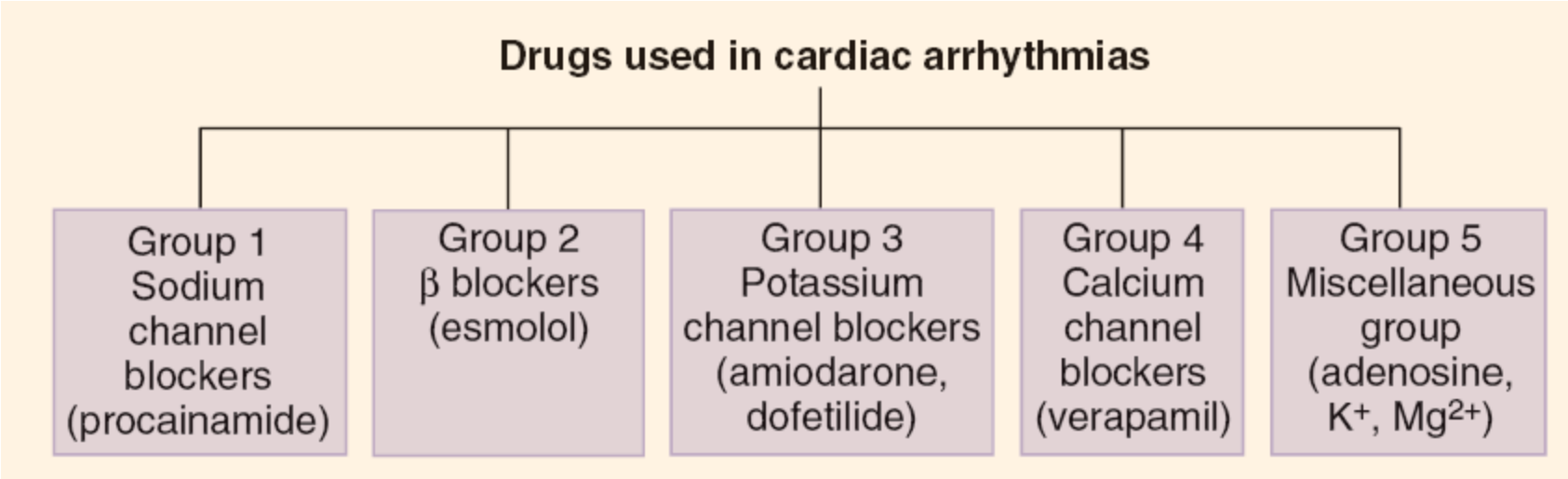
Action Potential of Cardiac Cell

- 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.



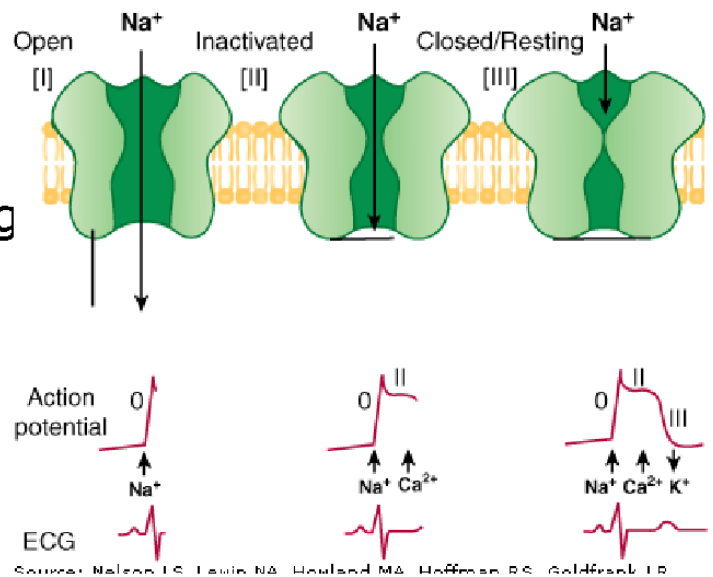


Antiarrhythmic Drugs



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)

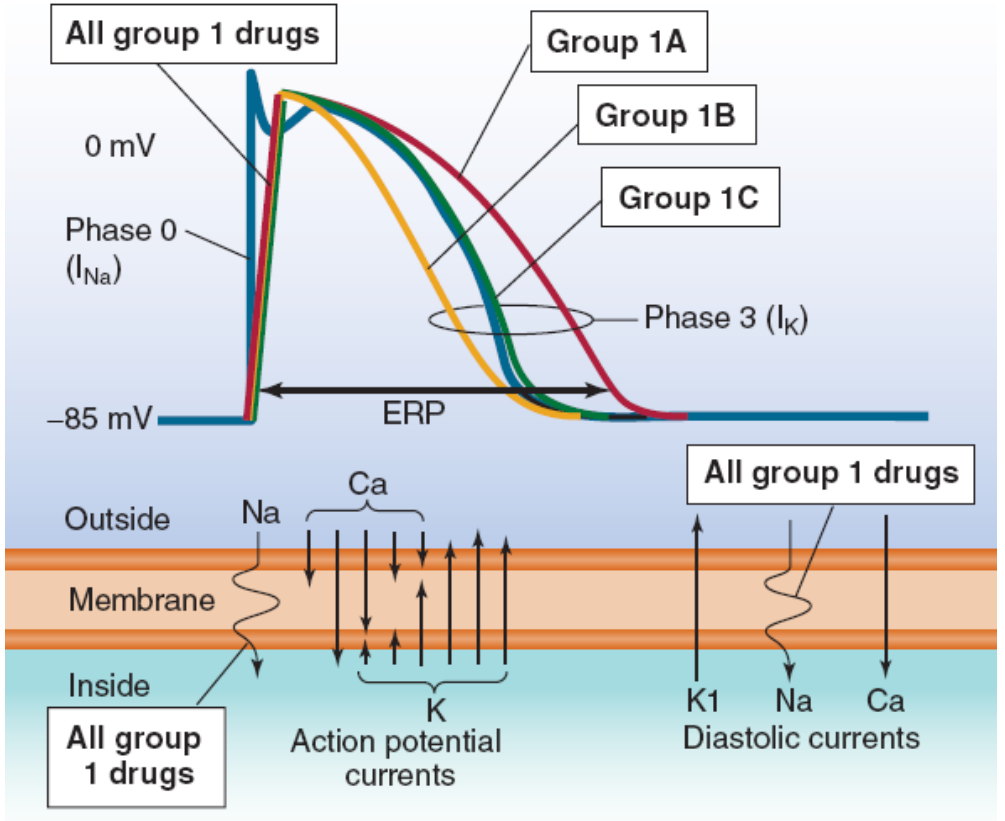
Use-dependence:

- 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.

Group 1 Antiarrhythmics (Sodium Channel Blockers)

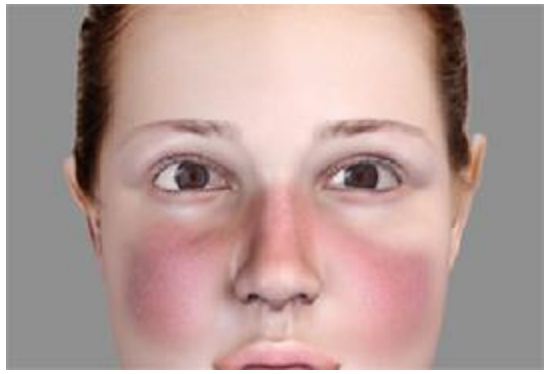
- Group 1 antiarrhythmics decreased rate of entry of sodium which slows the rate of rise of Phase 0 of the action potential.
- The group 1 drugs are further subdivided on the basis of their effects on the action potential (AP) duration:

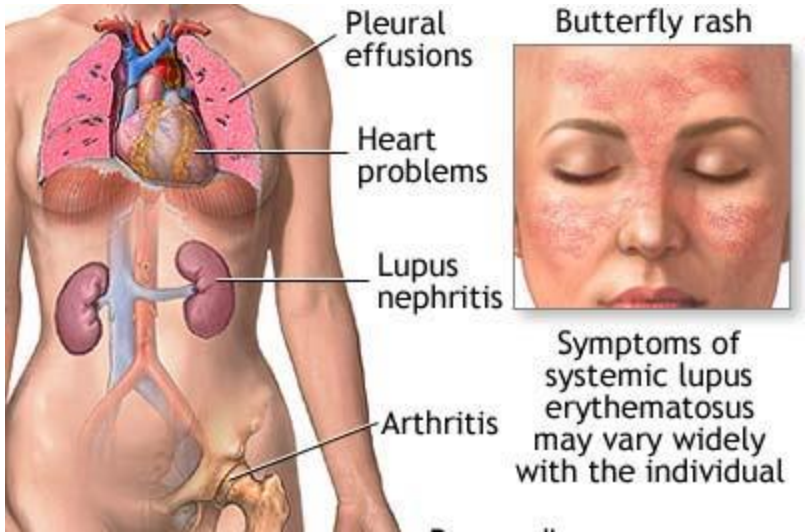
1) Group 1A agents (prototype **procainamide)** prolong the AP.
2) Group 1B drugs (prototype **lidocaine)** shorten the AP in some cardiac tissues.
3) Group 1C drugs (prototype **flecainide)** have no effect on AP duration.



Group 1A Antiarrhythmics

- **Procainamide** is effective against most atrial and ventricular arrhythmias.
- **Procainamide** may cause hypotension and with long-term use a <u>syndrome similar to lupus erythematosus.</u>





Group 1A Antiarrhythmics

- **Quinidine** and **disopyramide** have similar effects to procainamide but are used much less frequently.
- **Quinidine** causes cinchonism (fushed skin, headache, vertigo, tinnitus) and GI upset.
- **Quinidine** reduces the clearance of digoxin and may increase the serum concentration significantly.
- **Disopyramide** has marked antimuscarinic effects and may precipitate heart failure. It is contraindicated in HF and have atropine-like side effects.

  - **Cinchonism** or **quinism** is a pathological condition caused by an overdose of quinidine or its natural source, cinchona bark.

Group 1B Antiarrhythmics

- **Lidocaine** is useful in acute ischemic ventricular arrhythmias. Atrial arrhythmias are not responsive unless caused by digitalis.
- **Lidocaine** is one of the least cardiotoxic of the currently used sodium channel blockers.
- **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 arrhythmias.
- **Phenytoin,** an anticonvulsant, is sometimes classified with the group 1B antiarrhythmic agents. It can be used to reverse digitalis-induced arrhythmias.

Group 1C Antiarrhythmics

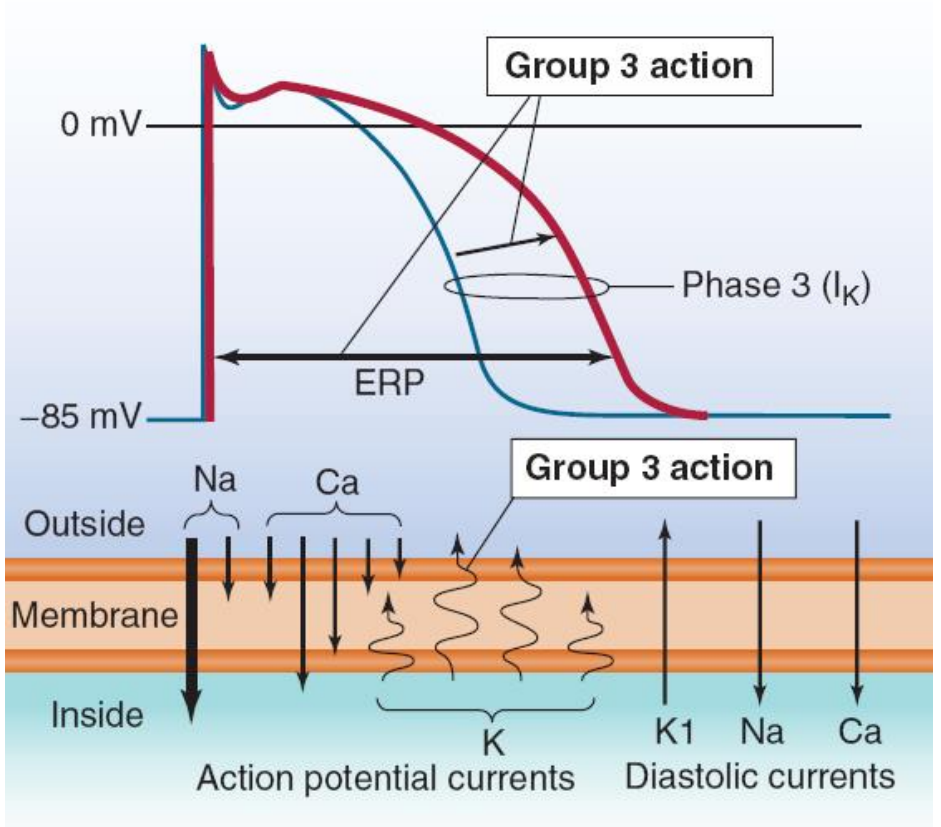
- **Flecainide** is approved only for refractory ventricular and supraventricular tachycardias.
- **Flecainide** is more likely than other antiarrhythmic drugs to exacerbate or precipitate arrhythmias (proarrhythmic effect).
- **Propafenone** has some structural similarities to propranolol and possesses weak β-blocking activity.
- The most common adverse effects are a metallic taste and constipation.

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.
- **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.

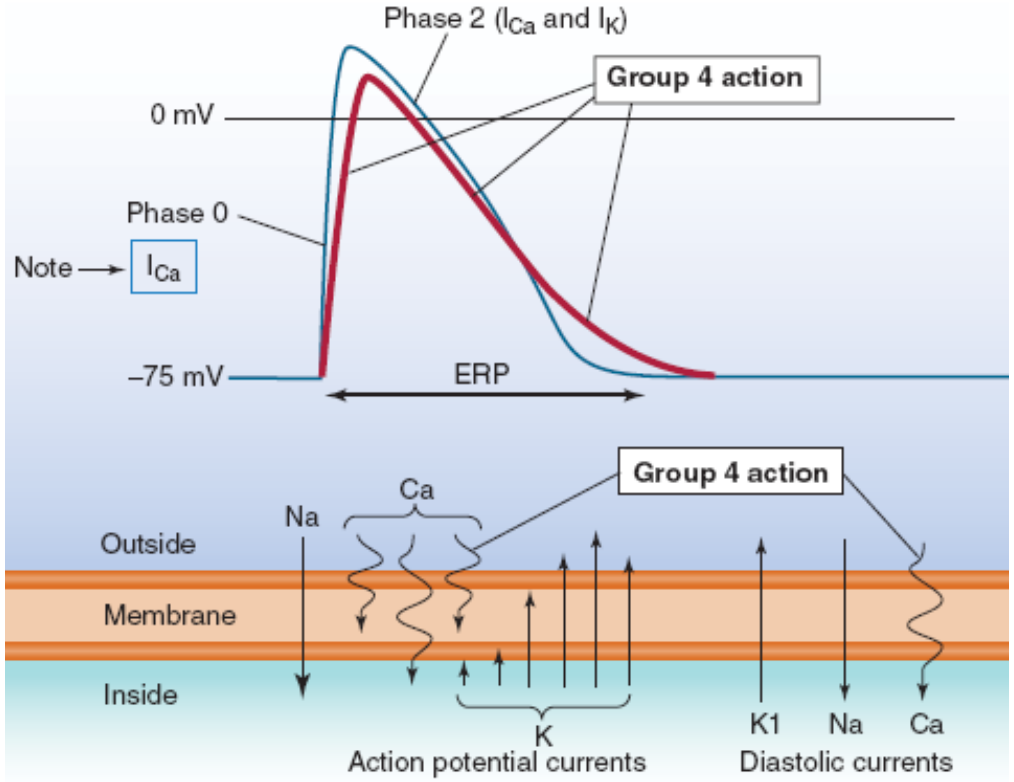


Group 3 Antiarrhythmics (Potassium Channel Blockers)

- **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.
- **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.

Group 4 Antiarrhythmics (Calcium Channel Blockers)

- **Verapamil** is the prototype. **Diltiazem** is also an effective antiarrhythmic drug.
- Nifedipine and the other dihydropyridines are <u>not</u> useful as antiarrhythmics.



Nonpharmacologic Treatment of Arrhythmia

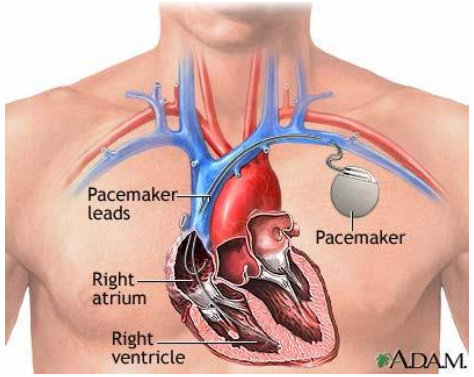
- It should be noted that electrical methods of treatment of arrhythmias have become very important. These methods include:

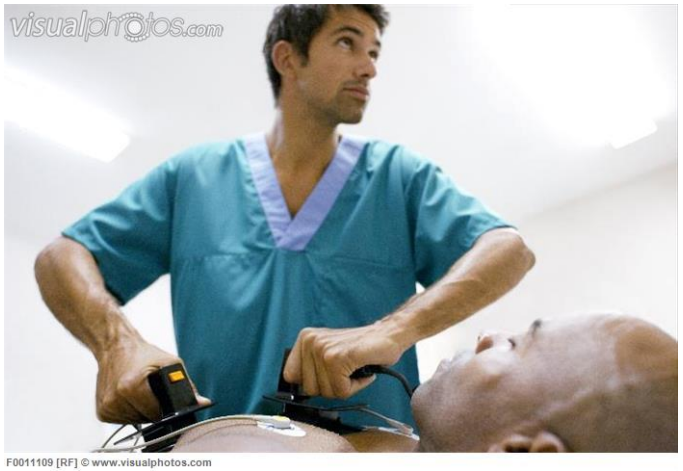
(1) External defibrillation

(2) Implanted defibrillators

(3) Implanted pacemaker

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





Questions??