Pharmacology

Dentistry Department

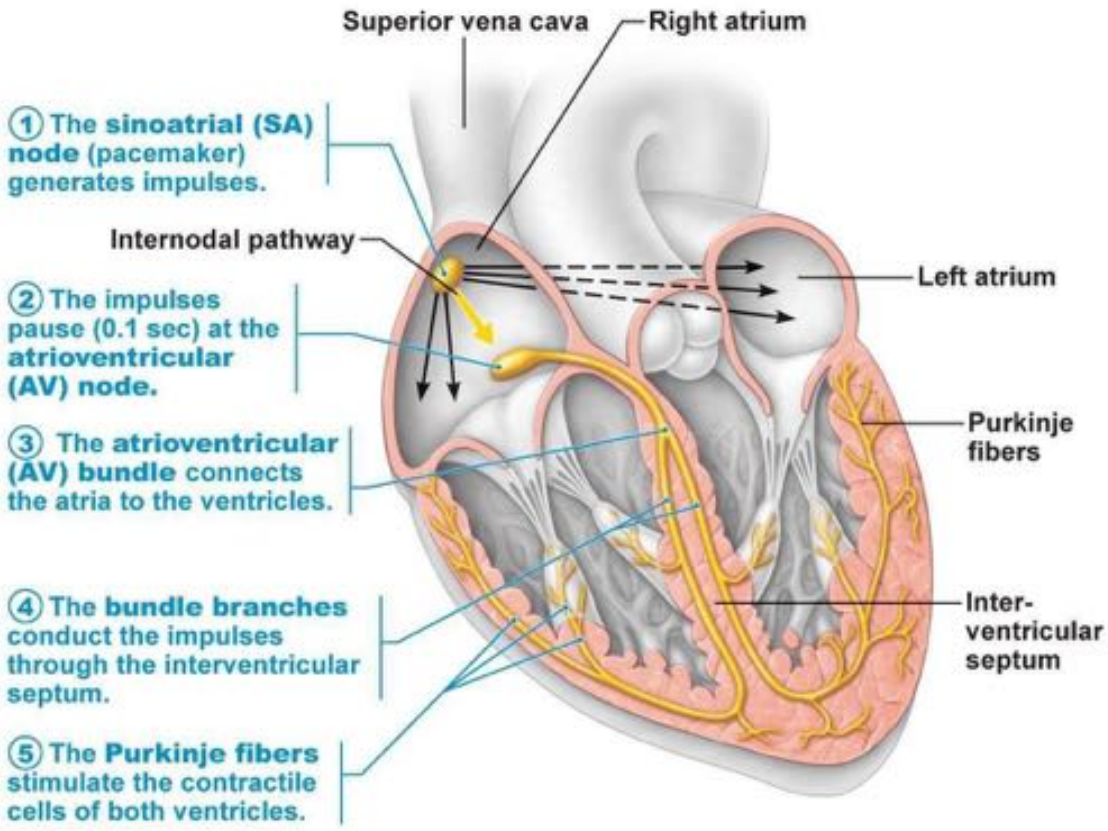
3rd Grade

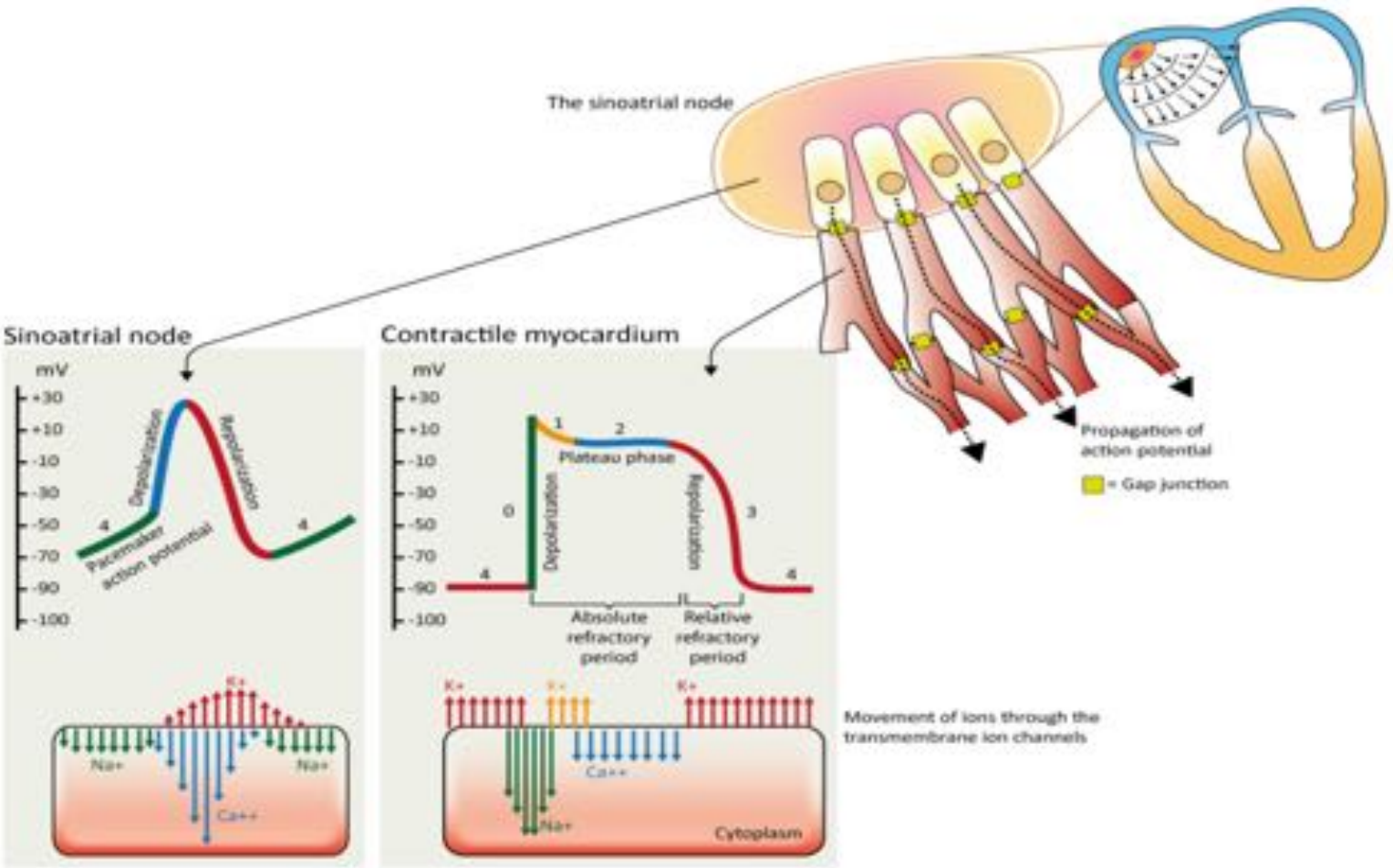
Antiarrythmics Drugs

Dr. Ali Al-Athari

Overview:

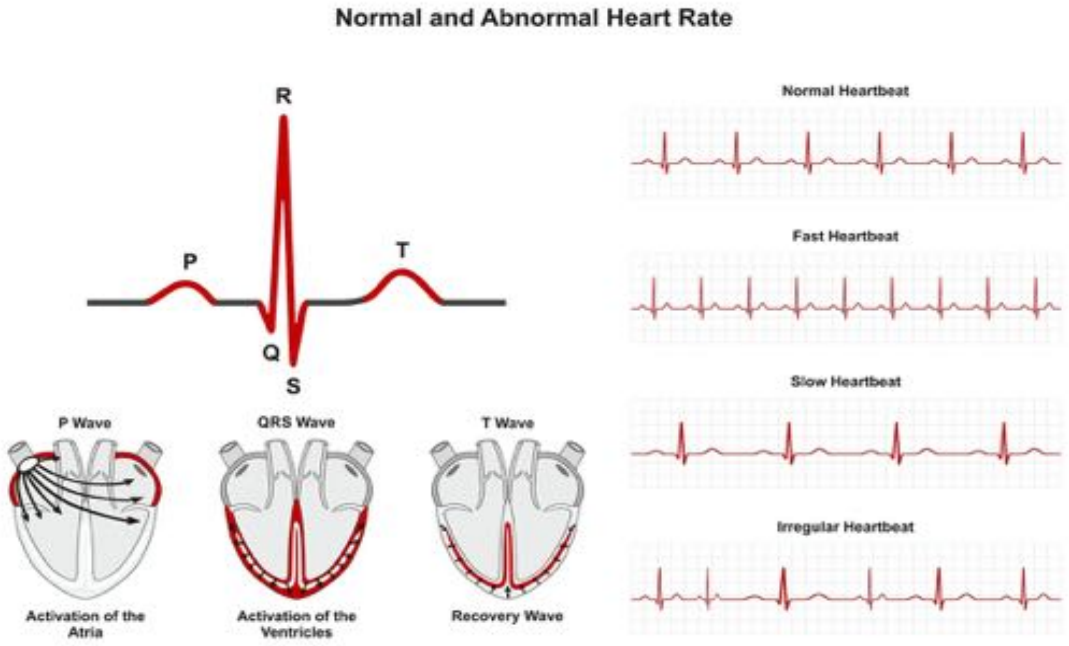
- In contrast to skeletal muscle, which contracts only when it receives a stimulus, the heart contains specialized cells that exhibit **automaticity**. That is, they intrinsically generate rhythmic action potentials in the absence of external stimuli.
- These "**pacemaker**" cells differ from other myocardial cells in showing a slow, **spontaneous depolarization during diastole (phase 4)**, caused by an **inward positive current carried by sodium and calcium ions**. This depolarization is fastest in the sinoatrial **(SA) node** (the normal initiation site of the action potential), and it decreases throughout the normal conduction pathway through the atrioventricular **(AV) node** to **the bundle of His and the Purkinje system**.
- **Dysfunction of impulse generation or conduction** at any of a number of sites in the heart can cause an **abnormality in cardiac rhythm**.




The sinoatrial node
Propagation of action potential
= Gap junction
Sinoatrial node
mV
+30
+10
-10
-30
-50
-70
-90
-100
Depolarization
Repolarization
4
4
Pacemaker action potential
Contractile myocardium
mV
+30
+10
-10
-30
-50
-70
-90
-100
1
2
Plateau phase
0
3
4
4
Depolarization
Repolarization
Absolute refractory period
Relative refractory period
K+
Na+
Na+
Ca++
K+
K+
K+
Ca++
Na+
Cytoplasm
Movement of ions through the transmembrane ion channels

Arrhythmias:

- **Arrhythmias** are dysfunctions cause abnormalities in **impulse formation and conduction in the myocardium.**
- Most arrhythmias arise either from **aberrations in impulse generation (abnormal automaticity) or from a defect in impulse conduction**.

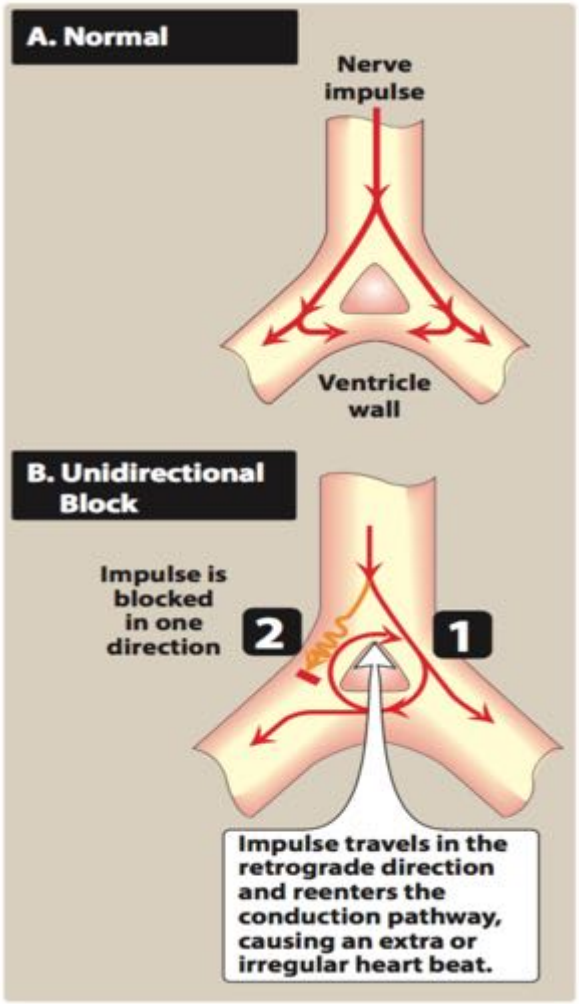


Causes of arrhythmias:

1. Abnormal automaticity:

- The **SA node** shows the fastest rate of **phase 4 depolarization** and, therefore, exhibits a higher rate of discharge than that occurring in other pacemaker cells exhibiting automaticity. Thus, the **SA node normally sets the pace of contraction for the myocardium**. **If cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmias may arise.**
- **Most of the antiarrhythmic agents suppress automaticity by blocking either Na+ or Ca2+ channels to reduce the ratio of these ions inside the cell.** This decreases the slope of phase 4 (diastolic) depolarization and/or raises the threshold of discharge to a less negative voltage. Antiarrhythmic drugs cause the frequency of discharge to decrease. This effect is more pronounced in cells with ectopic pacemaker activity than in normal cells.

2. Abnormalities in impulse conduction: Impulses from higher pacemaker centers are normally conducted down pathways that **bifurcate to activate the entire ventricular surface** .A phenomenon called **reentry** can occur if a **unidirectional block caused by myocardial injury or a prolonged refractory period results in an abnormal conduction pathway.** Reentry is the most common cause of arrhythmias, and it can occur at any level of the cardiac conduction system. This short-circuit pathway results in re-excitation of the ventricular muscle, causing premature contraction or sustained ventricular arrhythmia. Antiarrhythmic agents prevent reentry by slowing conduction (class I drugs) and/or increasing the refractory period (class III drugs), thereby converting a unidirectional block into a bidirectional block.



Antiarrhythmic drugs

- **Antiarrhythmic drugs** can **modify impulse generation and conduction to prevent arrhythmias from occurring or to reduce symptoms associated with arrhythmias.**
- Unfortunately, **many of the antiarrhythmic agents** are known to have dangerous **proarrhythmic actions** that is, **to cause arrhythmias**. For example Inhibition of potassium (K+) channels (typically thought of as class III activity) widens the action potential and can, thus, prolong the QT interval. If prolongation is excessive, these drugs increase the risk of developing life-threatening ventricular **tachyarrhythmias (torsades de pointes).**

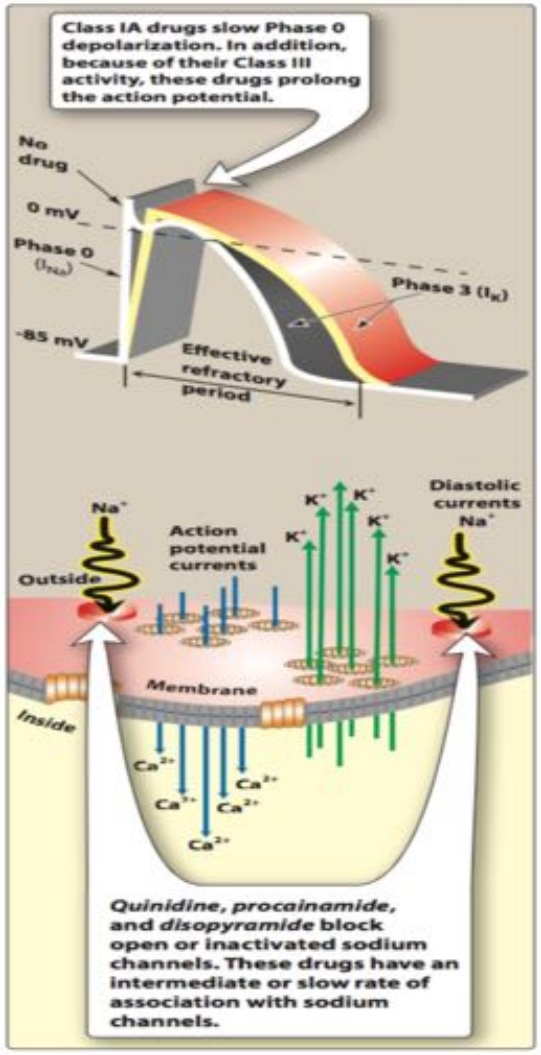
CLASS I ANTIARRHYTHMIC DRUGS:

- **Class I antiarrhythmic drugs** act by blocking **voltage-sensitive sodium (Na+) channels.** The use of sodium channel blockers has declined due to their **proarrhythmic effects, particularly in patients with reduced left ventricular function and ischemic heart disease**.
- **Use dependence: Class I 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. 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.**
- The class I drugs have been subdivided into three groups according to their effect on the duration of the ventricular action potential.

Class IA antiarrhythmic drugs: Quinidine, procainamide, and disopyramide

Mechanism of action:

- Class IA drugs bind to **open and inactivated sodium channels and prevents sodium influx**, **thus slowing the rapid upstroke during phase 0** . They decrease the slope of phase 4 spontaneous depolarization, inhibits potassium channels, and blocks calcium channels. Because of these actions, **They slow conduction velocity and increase refractoriness.**
- These drugs produce a **negative inotropic effect**, particularly **Disopyramide** thus they may produce a clinically important decrease in myocardial contractility in patients with systolic heart failure.
- Because of their **concomitant class III activity, they can precipitate arrhythmias** that can progress to ventricular fibrillation.



Therapeutic uses:

Class IA antiarrhythmic drugs are used in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular arrhythmias.

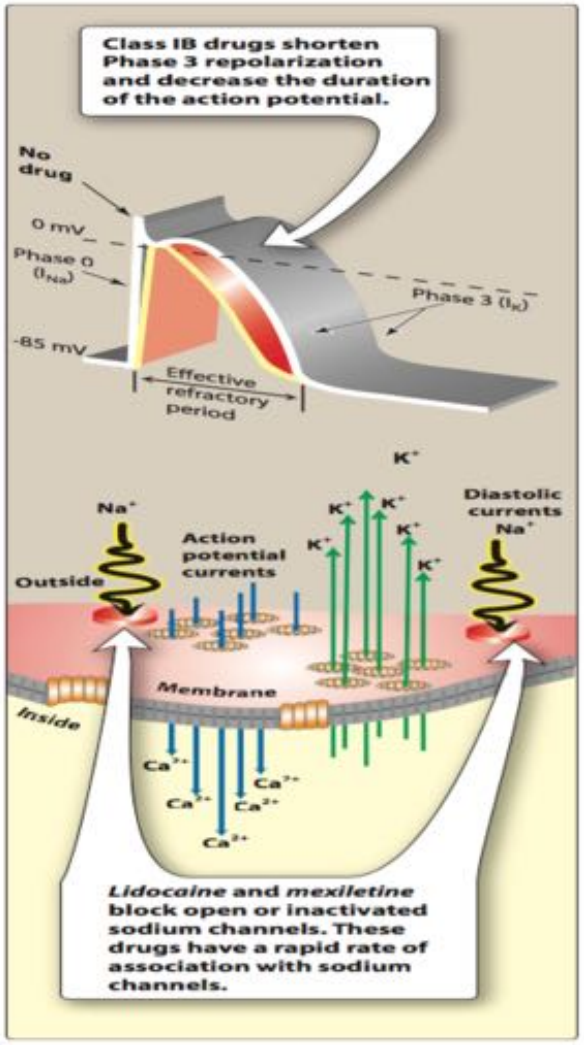
Adverse effects:

- Large doses of ***quinidine*** may induce the symptoms of **cinchonism (blurred vision, tinnitus, headache, disorientation, and psychosis).**
- ***Disopyramide*** has the **strongest anticholinergic adverse effects** of the class IA drugs (for example, **dry mouth, urinary retention, blurred vision, and constipation**).
- Both ***quinidine*** **and** ***disopyramide*** should be used with caution with potent inhibitors of CYP3A4.

Class IB antiarrhythmic drugs: Lidocaine and mexiletine

Mechanism of action and therapeutic uses:

- **In addition to sodium channel blockade, *lidocaine* and *mexiletine* shorten phase 3 repolarization and decrease the duration of the action potential**
- The class IB agents rapidly associate and dissociate from sodium channels. Thus, the actions of class IB agents are manifested when the cardiac cell is depolarized or firing rapidly.
- The class IB are useful in treating **ventricular arrhythmias**.
- **Lidocaine has no negative inotropic effect**.



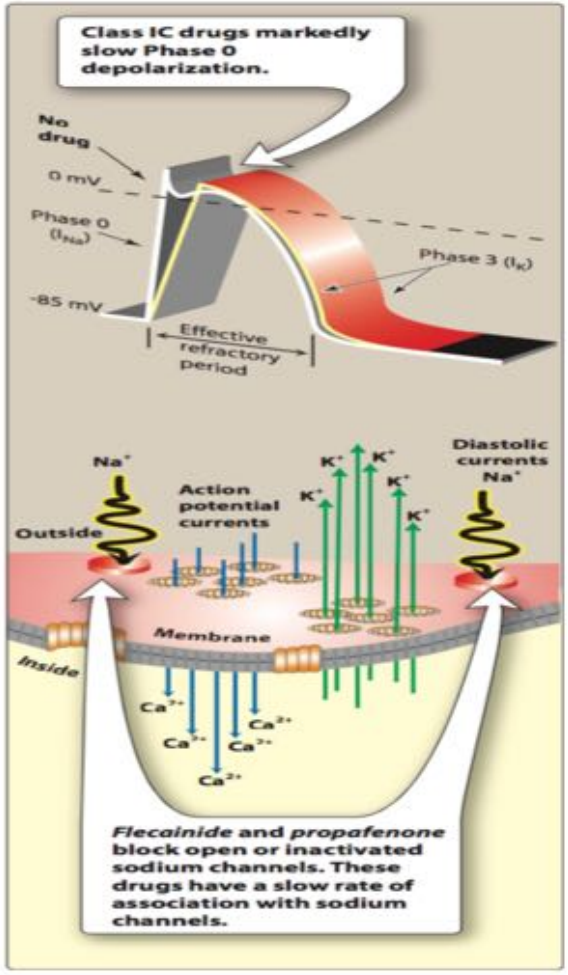
Adverse effects:

- ***Lidocaine*** has a fairly **wide therapeutic index**. It shows little impairment of left ventricular function and has no negative inotropic effect. Central nervous system (CNS) effects include **nystagmus** (early indicator of toxicity), drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions, which often limit the duration of continuous infusions.
- ***Mexiletine*** has a **narrow therapeutic index** and caution should be used when administering the drug with inhibitors of CYP2D6. **Nausea, vomiting, and dyspepsia** are the most common adverse effects.

Class IC antiarrhythmic drugs: Flecainide and propafenone

Mechanism of action:

- ***Flecainide*** **suppresses phase 0 upstroke in Purkinje and myocardial fibers. This causes marked slowing of conduction in all cardiac tissue**.
- **Automaticity is reduced by an increase in the threshold potential, rather than a decrease in slope of phase 4 depolarization.**
- ***Flecainide*** **also blocks potassium channels leading to increased action potential duration.**
- ***Flecainide*** has a **negative inotropic effect** and can aggravate chronic heart failure.
- ***Propafenone*** like *flecainide*, **slows conduction in all cardiac tissues but does not block potassium channels**.



Therapeutic uses:

- ***Flecainide and propafenone*** are 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).

Adverse effects:

- ***Flecainide*** is generally well tolerated, with blurred vision, dizziness, and nausea occurring most frequently**.**
- ***Propafenone*** has a similar side effect profile, but it may also cause **bronchospasm due to its β-blocking effects. It should be avoided in patients with asthma.**

CLASS II ANTIARRHYTHMIC DRUGS: Metoprolol, propranolol and Esmolol

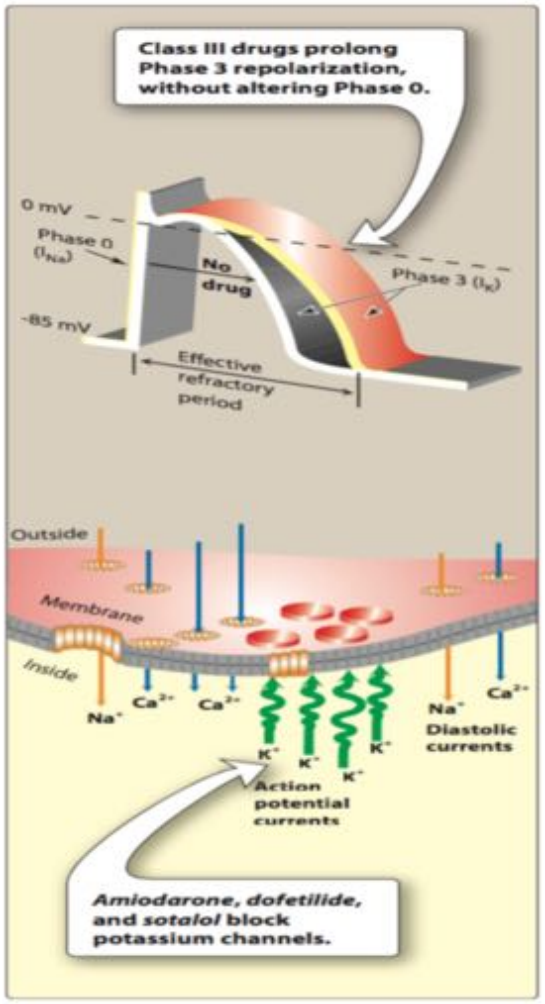
- **Class II agents are β-adrenergic antagonists**, or **β-blockers**.
- **These drugs diminish phase 4 depolarization and, thus, depress automaticity, prolong AV conduction, and decrease heart rate and contractility.**
- **Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity.** They are also used for atrial flutter and fibrillation and for AV nodal reentrant tachycardia. In addition, β-blockers prevent life-threatening ventricular arrhythmias following a myocardial infarction.
- ***Metoprolol*** is the β-blocker most widely used in the treatment of cardiac arrhythmias. Compared to nonselective β-blockers, such as *propranolol* ,it **reduces the risk of bronchospasm**.
- ***Esmolol*** is a very-short-acting β-blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations. It has a fast onset of action and a short half-life, making it ideal for acute situations and also limiting its adverse effect profile.

CLASS III ANTIARRHYTHMIC DRUGS:

Class III agents block potassium channels and, thus, diminish the outward potassium current during repolarization of cardiac cells. These agents prolong the duration of the action potential without altering phase 0 of depolarization or the resting membrane potential . Instead, they prolong the effective refractory period, increasing refractoriness. All class III drugs have the potential to induce arrhythmias.

A. Amiodarone :

Mechanism of action: *Amiodarone* contains iodine and is related structurally to thyroxine. It has complex effects, **showing class I, II, III, and IV actions, as well as α-blocking** activity. **Its dominant effect is prolongation of the action potential duration and the refractory period by blocking K+ channels.**



Therapeutic uses:

- ***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.**
- 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.**

Pharmacokinetics:

- ***Amiodarone*** is incompletely absorbed after **oral administration**. The drug is unusual in having **a prolonged half-life of several weeks**, and it distributes extensively in adipose tissue.
- Full clinical effects may not be achieved until months after initiation of treatment, unless loading doses are employed.

Adverse effects:

- *Amiodarone* shows a variety of toxic effects, including **pulmonary fibrosis, neuropathy, hepatotoxicity, corneal deposits, optic neuritis, blue-gray skin discoloration, and hypo- or hyperthyroidism.**

B. Dronedarone

- ***Dronedarone*** **is an *amiodarone*** derivative, which is **less lipophilic, has lower tissue accumulation, and has a shorter serum half-life than *amiodarone*.**
- It **does not have the iodine moieties that are responsible for thyroid dysfunction associated with *amiodarone*.**
- Like *amiodarone*, **it has class I, II, III, and IV actions**.
- *Dronedarone* has a better adverse effect profile than *amiodarone* but may still cause **liver failure.**
- The drug is **contraindicated** in those with symptomatic **heart failure** due to an increased risk of death.
- Currently, *dronedarone* is used to maintain sinus rhythm in **atrial fibrillation or flutter,** but it is less effective than *amiodarone*.

C. Sotalol

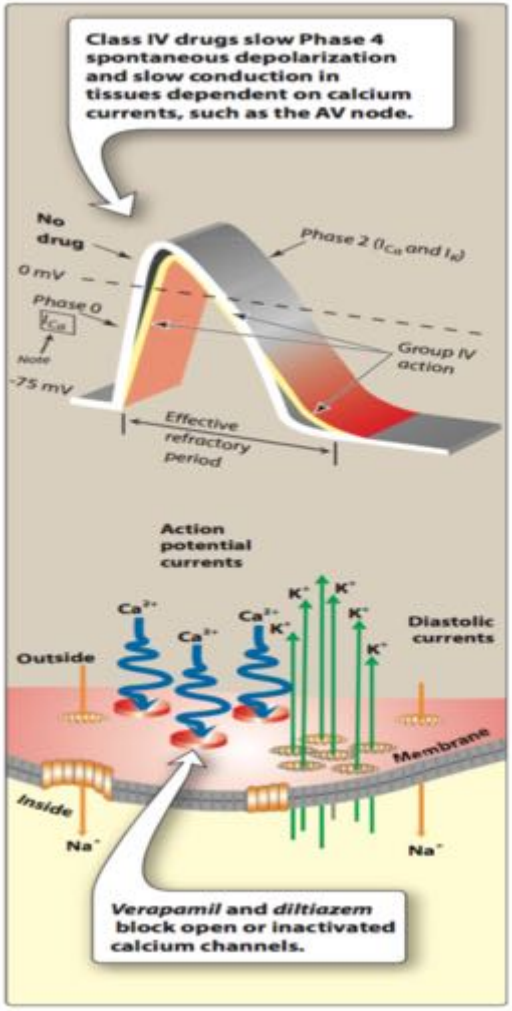
- *Sotalol* , although a class III antiarrhythmic agent, also has **potent nonselective β-blocker activity.**
- ***Sotalol* blocks a rapid outward potassium current, known as the delayed rectifier. This blockade prolongs both repolarization and duration of the action potential, thus lengthening the effective refractory period.**
- *Sotalol* is used for maintenance of normal sinus rhythm in patients with **atrial fibrillation, atrial flutter**, or refractory paroxysmal **supraventricular tachycardia and in the treatment of ventricular arrhythmias**.
- Since *sotalol* has β-blocking properties, it is commonly used for these indications in patients with **left ventricular hypertrophy or atherosclerotic heart disease.**
- This drug can cause the typical adverse effects associated with β-blockers but has a low rate of adverse effects when compared to other antiarrhythmic agents.

D. Dofetilide

- ***Dofetilide* is a pure potassium channel blocker.** It can be used as a first-line antiarrhythmic agent in patients with persistent **atrial fibrillation** and **heart failure or in those with coronary artery disease**.
- Because of the risk of **pro-arrhythmia, *dofetilide* initiation is limited to the inpatient setting.**
- The drug is mainly excreted unchanged in the urine. Drugs that inhibit active tubular secretion are contraindicated.

CLASS IV ANTIARRHYTHMIC DRUGS

- Class IV drugs are the **calcium channel blockers *verapamil* and *diltiazem*** . ***Verapamil* shows greater action on the heart than on vascular smooth muscle, and *diltiazem* is intermediate in its actions**.
- In the heart, ***verapamil* and *diltiazem* bind only to open depolarized voltage-sensitive calcium channels, thus decreasing the inward current carried by calcium.** They prevent repolarization until the drug dissociates from the channel, **resulting in a decreased rate of phase 4 spontaneous depolarization.** These drugs are therefore **use-dependent**.
- They also **slow conduction in tissues that are dependent on calcium currents, such as the AV and SA nodes.**
- These agents **are more effective against atrial** than against ventricular arrhythmias **(atrial flutter and fibrillation).**



VII. OTHER ANTIARRHYTHMIC DRUGS:

A. Digoxin

- ***Digoxin* inhibits the Na+/K+-ATPase pump, prolonging the effective refractory period and diminishing conduction velocity in the AV node.**
- ***Digoxin* is used to control ventricular response rate in atrial fibrillation and flutter**.
- At toxic concentrations, *digoxin* causes **ectopic ventricular beats** that may result in VT and fibrillation.
- [Note: Serum trough concentrations of **1.0 to 2.0 ng/mL are desirable for atrial fibrillation or flutter,** whereas lower concentrations of **0.5 to 0.8 ng/mL are targeted for systolic heart failure.]**

B. Adenosine

- *Adenosine* is a naturally occurring nucleoside, but **at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node.**
- Intravenous *adenosine* is the drug of choice for abolishing **acute supraventricular tachycardia.**
- It has low toxicity but causes **flushing, chest pain, and hypotension.**
- ***Adenosine* has an extremely short duration of action** (approximately 10 to 15 seconds) **due to rapid uptake by erythrocytes and endothelial cells.**

C. Magnesium sulfate

- ***Magnesium* is necessary for the transport of sodium, calcium, and potassium** across cell membranes.
- **It slows the rate of SA node impulse formation and prolongs conduction time along the myocardial tissue.**
- **Intravenous *magnesium sulfate*** is the **salt used to treat arrhythmias**, as oral *magnesium* is not effective in the setting of arrhythmia.
- Most notably, *magnesium* is the drug of choice for treating the potentially fatal arrhythmia **torsades de pointes** and ***digoxin*-induced arrhythmias.**


Thank
you!