Antiarrhythmic drugs

LECTURE'S OUTLINE

Electrophysiology of the heart

Arrhythmia: definition, mechanisms, types

Drugs :class I, II, III, IV

Guide to treat some types of arrhythmia

Questions

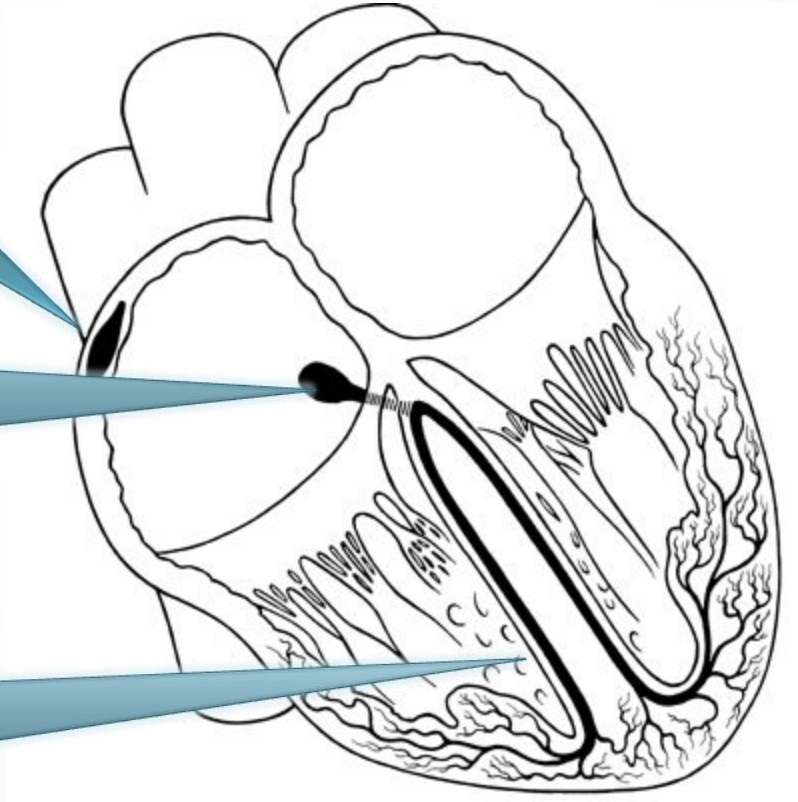
Physiology of the normal heart

Normal conduction pathway:

1- SA node generates action potential and delivers it to the atria and the AV node

2- The AV node delivers the impulse to purkinje fibers

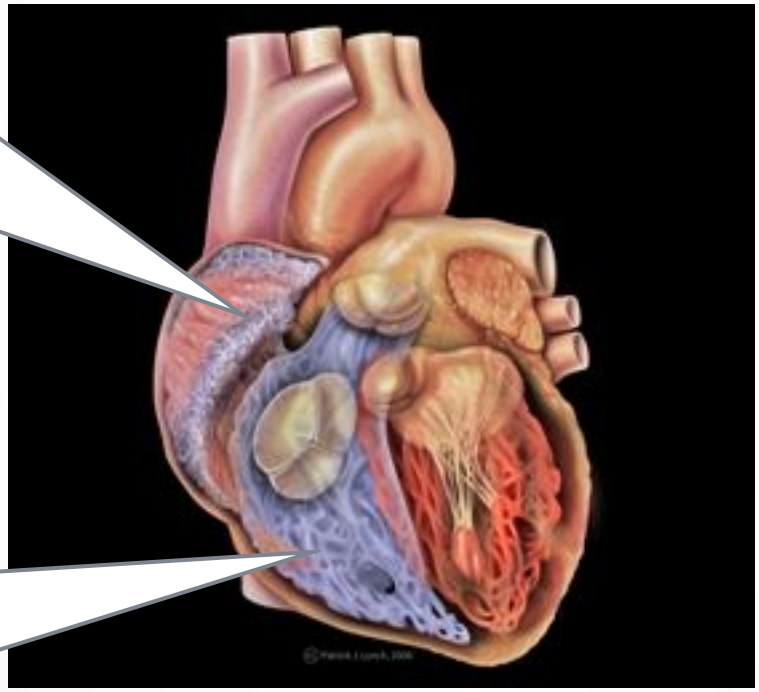
3- purkinje fibers conduct the impulse to the ventricles



Arrhythmia

Arrhythmia /dysrhythmia: abnormality in the site of origin of impulse, rate, or conduction

If the arrhythmia arises from atria, SA node, or AV node it is called supraventricular arrhythmia



If the arrhythmia arises from the ventricles it is called ventricular arrhythmia

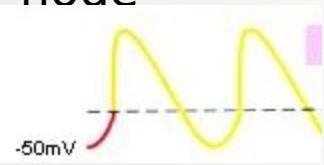
Causes of arrhythmia

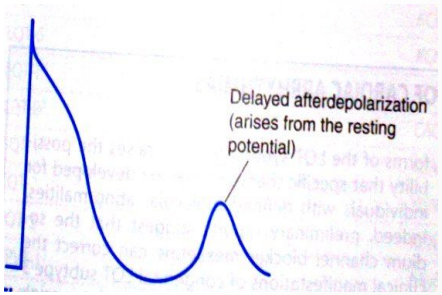
- arteriosclerosis
- Coronary artery spasm
- Heart block
- Myocardial ischemia

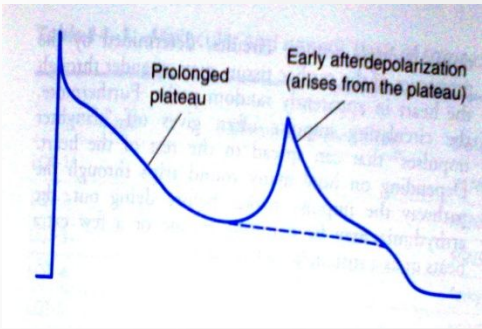
Mechnisms of Arrhythmogenesis

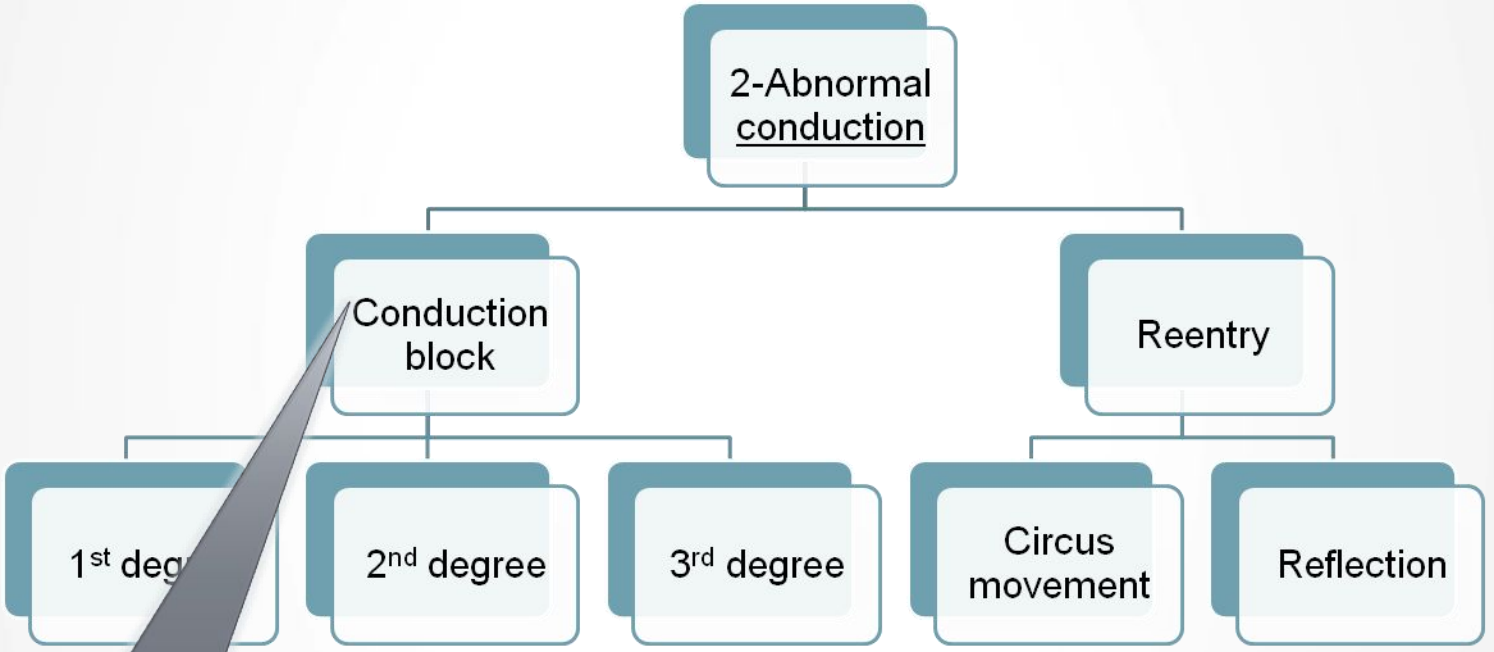
1- Abnormal impulse generation

- Automatic rhythms
  - Enhanced normal automaticity → ↑AP from SA node
  - Ectopic focus → AP arises from sites other than SA node
- Triggered rhythms
  - Delayed afterdepolarizati
  - Early afterdepolarizati on









This is when the impulse is not conducted from the atria to the ventricles

Types of Arrhythmia

Supraventricular Arrhythmia

- **Sinus Tachycardia**: high sinus rate of 100-180 beats/min, occurs during exercise or other conditions that lead to increased **SA nodal firing rate**

- **Atrial Tachycardia:** a series of 3 or more consecutive atrial premature beats occurring at a frequency >100/min

- **Paroxysmal Atrial Tachycardia (PAT):** tachycardia which begins and ends in acute manner

- **Atrial Flutter**: sinus rate of 250-350 beats/min.

- **Atrial Fibrillation**: uncoordinated atrial depolarizations.

AV blocks

A conduction block within the AV node

Impairs impulse conduction from the atria to the ventricles.

ventricular Arrhythmias

Ventricular Premature Beats (VPBs): caused by ectopic ventricular foci; characterized by widened QRS.

Ventricular Tachycardia (VT): high ventricular rate (100 to 200 beats/min) caused by abnormal ventricular automaticity or by intraventricular reentry; **characterized by** widened QRS; life-threatening.

Ventricular Flutter - ventricular depolarizations >200/min.

Ventricular Fibrillation - uncoordinated ventricular depolarizations

Pharmacological Rationale & Goals

The ultimate goal of antiarrhythmic drug therapy:

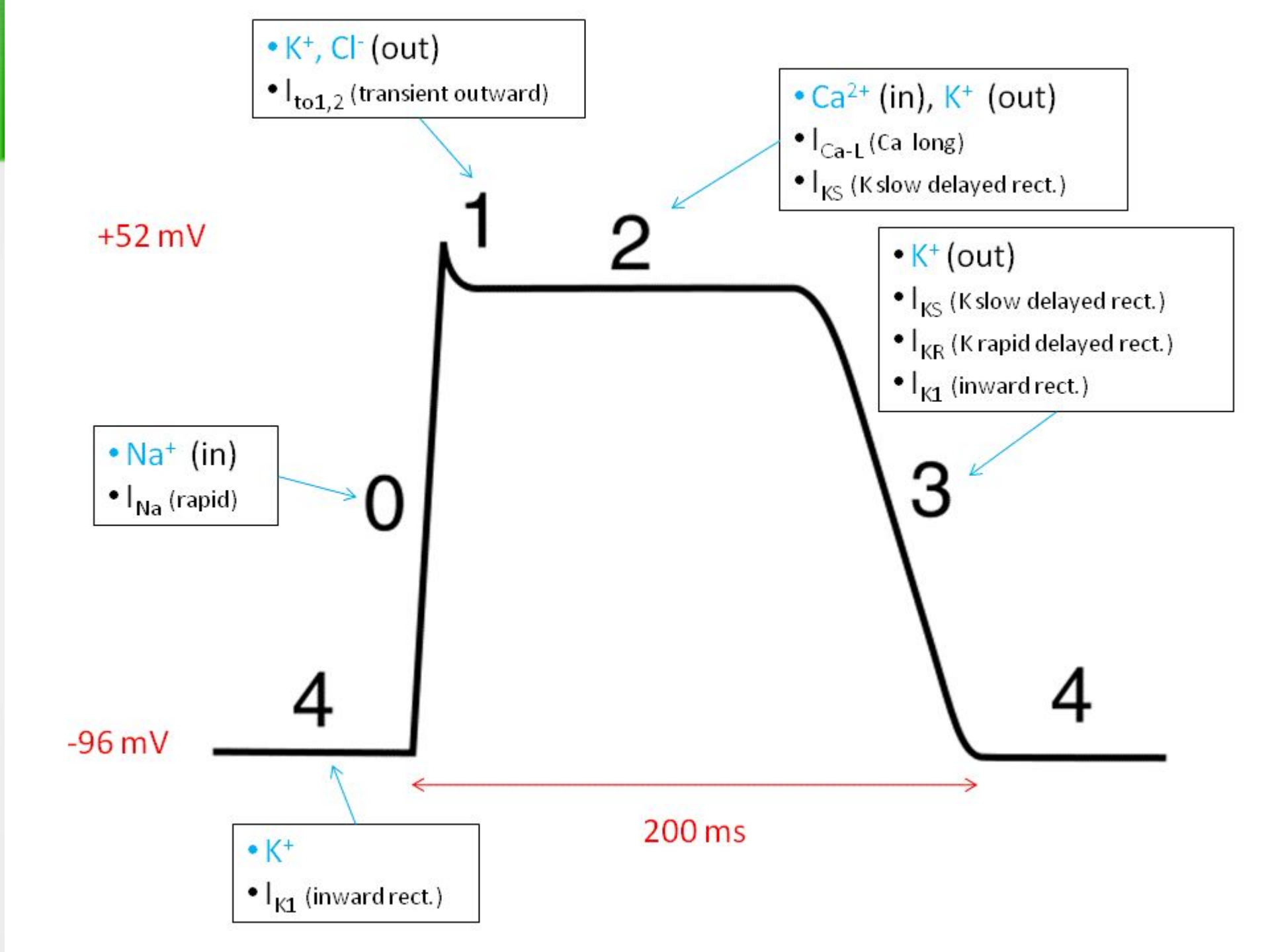
- **Restore** normal sinus rhythm and conduction
- **Prevent** more serious and possibly lethal arrhythmias

Antiarrhythmic drugs are used to:

decrease conduction velocity

change the duration of the Effective Refractory Period (ERP)

suppress abnormal automaticity


• 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.)

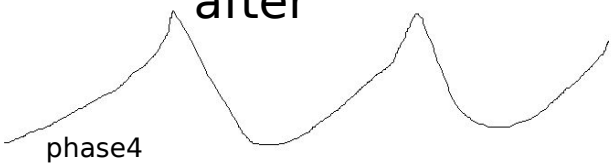
Action of drugs

In case of abnormal generation:

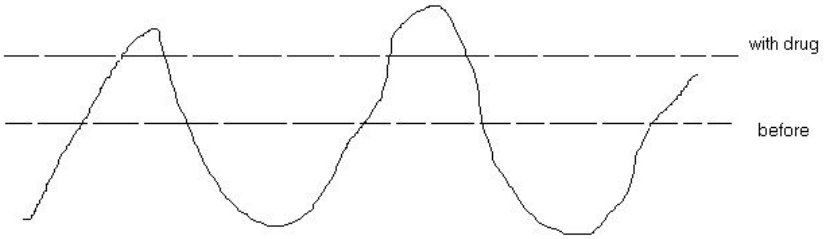
Decrease of phase 4 slope (in pacemaker cells)

Before drug

after



Raises the threshold



In case of abnormal conduction:

↓conduction velocity

↑ERP (so the cell won't be reexcited again)

Anti-arrhythmic drugs

- Most antiarrhythmic drugs are pro-arrhythmic (promote arrhythmia)
- They are classified according to ***Vaughan William*** into four classes according to their effects on the cardiac action potential

Class	Mechanism	Action	Notes
I	Na^+ channel blocker	Change the slope of phase 0	**Can abolish tachyarrhythmia**
II	β blocker	↓heart rate and conduction velocity	**Can indirectly alter K & Ca conductance**
III	K^+ channel blocker	↑**AP** duration (APD) or effective refractory period (ERP). 1. Delay repolarization.	**Inhibit reentry tachycardia**
IV	Ca^{++} channel blocker	Slowing the rate of rise in phase 4 of SA node	**↓conduction velocity in SA and AV node**

Clinical Classification I

class	mechanism	Examples
I	Na^+ channel blocker	**IA.** Quinidine, Procainamide **IB.** Lignocaine, Phenytoin **IC.** Flecainide
II	β blocker	Labetelol
III	K^+ channel blocker	Amiodarone, Sotalol
IV	Ca^{++} channel blocker	Verapamile

The choice of anti-arrhythmic drug is depend on:

- Correct diagnosis
- Urgency for treatment
- Route of administration
- Extend of cardiac damage
- Risk benefit ratio

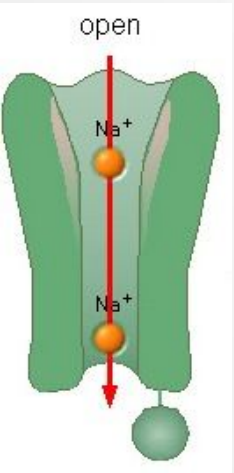
Class I drugs

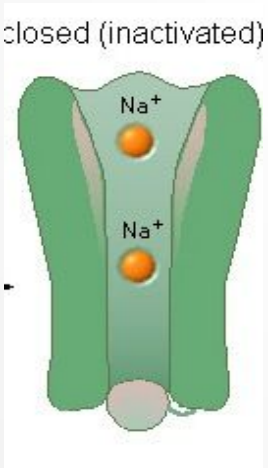
Have moderate K^+ channel blockade

- Class I
  - IA
  - IB
  - IC

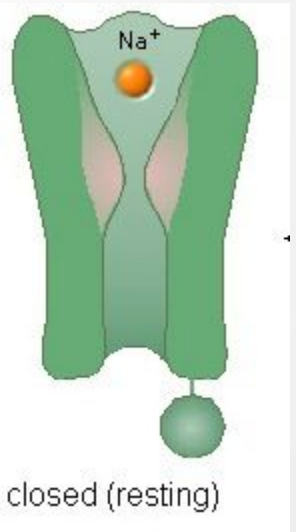
They act on open OR Inactivated Na^+ channels

They ↓ conduction velocity (in atria, ventricles, and purkinje fibers)





So they are used when many Na^+ channels are opened (in tachycardia only) because in normal rhythm the channels will be at rest state so the drugs won't work



FAST SODIUM CHANNEL BLOCKERS: CLASS I DRUGS

Class I Drugs are further subdivided into:

- **IA: Causes moderate Phase 0 depression**

Eg. Quinidine, Procainamide

- **IB: Causes weak Phase 0 depression**

Eg. Lignocaine, Phenytoin

- IC: Causes marked Phase 0 depression

Eg. Flecainide

Quinidine:

- 1st Anti-arrhythmic agent
- Isomer of antimalerial drug Quinine (Alkaloid from Cinchona Bark)

Pharmacological Action:

I. Cardiac

II. Extracardiac action

Pharmacological Action:

I. Cardiac:

A. <u>Automaticity, Excitability & Conduction velocity:</u>

- Depresses all tissues especially the ectopic pacemaker

- **Does not** suppress the **automaticity** of normal SA node

B. Refractory period:

- Depresses the potassium efflux during repolarization

↓

Prolong repolarization & RP

↓

Prevent premature & rapid stimulation of heart

C. **AV Conduction:**

- Depresses the conduction predominantly within the atria
- Enhances the AV Conduction, causing ventricular tachycardia

Contraindicated in ventricular conduction abnormalities

D. Contractility:

- Negative inotropic action on the heart-----
  Disadvantageous

II. Extra cardiac action:

1. Blood pressure:

-Significant lowering of BP

2. Miscellaneous action:

- Depresses the skeletal muscle

- Antimalerial, antipyretic and weak oxytocic activity

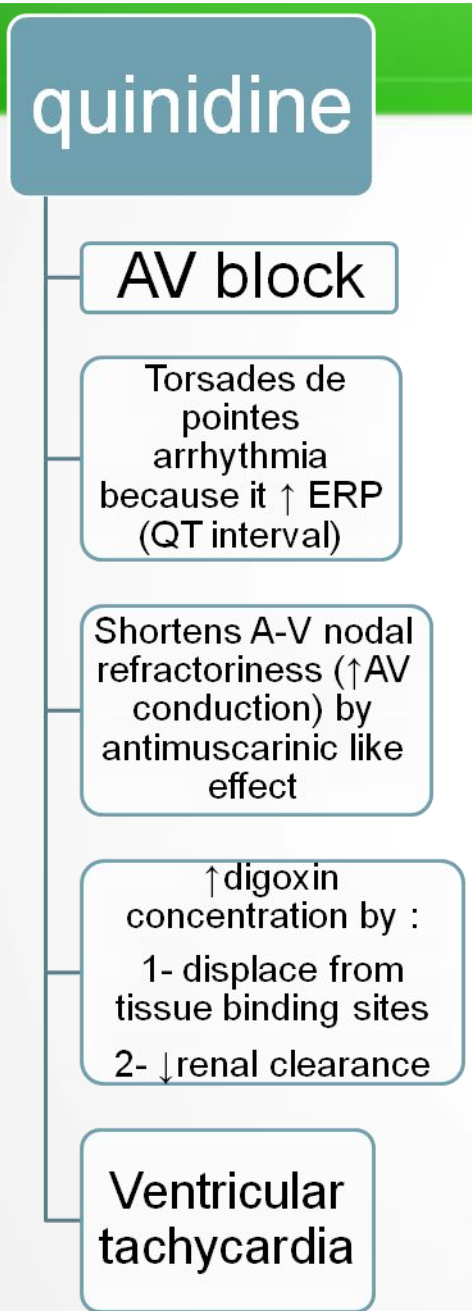
Pcokinetics:

- Completely absorbed from the gut.

- Metabolize in the liver---- 3- Hydroxyquinidine (One of the metabolite) as potent as quinidine.

- Electrophysiology and toxic effects correlate better with serum level of quinidine.

Quinidine Drugs Toxicity



Hypotension:
More common in older patient

Embolic phenomena:
Precipitate the embolic occlusion of vital organs

Miscellaneous:
Allergic reactions: Skin rashes, fever, thrombocytopanic purpura

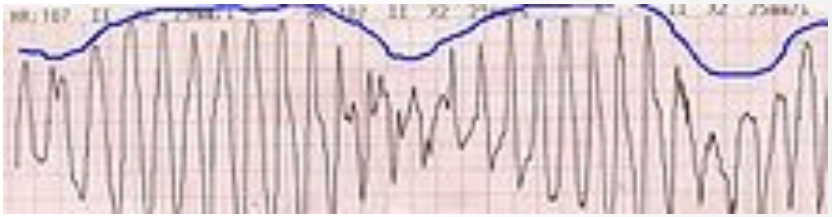
GIT: Nausea, vomiting and diarrhoea

Cerebral: Headache, dizziness, convulsion

Cinchonism: Impairment of hearing, ringing in ears, vertigo, blurred vision and tremor.

Notes:

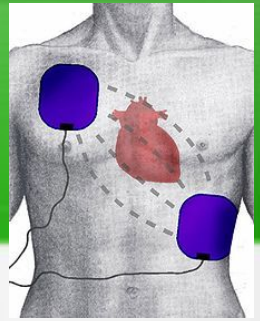
Torsades de pointes: twisting of the point .
Type of tachycardia that gives special characteristics on ECG



At large doses it lead to **cinchonism**

Digoxin is administered before quinidine to prevent the conversion of atrial fibrillation or flutter into ventricular tachycardia

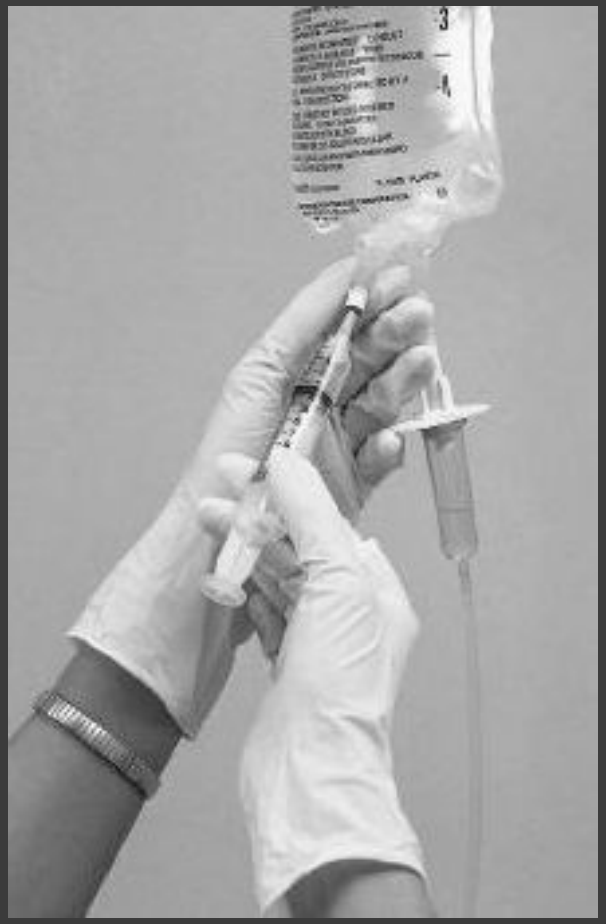
Therapeutic Use



Quinidine/procainamide are used with class III drugs in refractory ventricular tachycardia -- patients with **implantable defibrillator**

defibrillato

Lidocaine



- Class IB antiarrhythmic (Na^+ channel blocker)
- **Indication**: Ventricular tachycardia
- IV preferred (unpredictable first-pass metabolism) when administered orally)
- Systemic lidocaine administration- reduces incidence of premature action potentials originating in cardiac muscle
- Overdose can lead to drowsiness, seizures, twitching, possible cardiac arrest and death

Class II ANTIARRHYTHMIC DRUGS (β-adrenergic blockers)

Mechanism of action

Negative inotropic and chronotropic action.

Prolong AV conduction (delay)

Diminish phase 4 depolarization

Suppressing automaticity (of ectopic focus)

Uses

Treatment of increased sympathetic activity-induced arrhythmias such as stress and exercise-induced arrhythmias

Atrial flutter and fibrillation.

AV nodal tachycardia.

Reduce mortality in post-MI

Protection against sudden cardiac death

Class II ANTIARRHYTHMIC DRUGS

Propranolol (nonselective): was proved to reduce the incidence of sudden arrhythmatic death after myocardial infarction

Metoprolol

reduce the risk of bronchospasm

selectiv
e

Esmolol

Esmolol is a very short-acting β_1-adrenergic blocker that is used by IV in acute arrhythmias occurring during surgery or emergencies

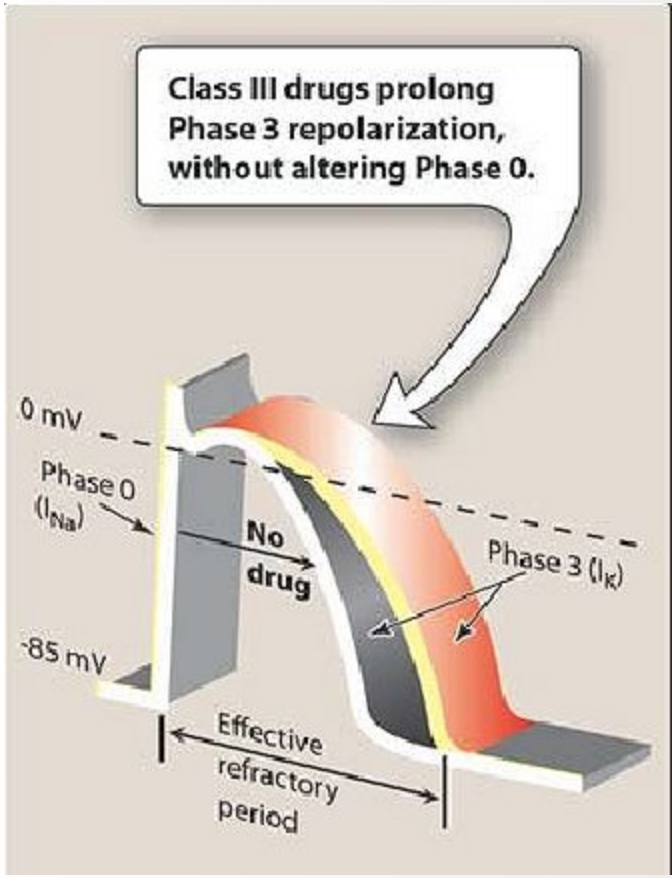
Class III ANTIARRHYTHMIC DRUGS
K^+ blockers

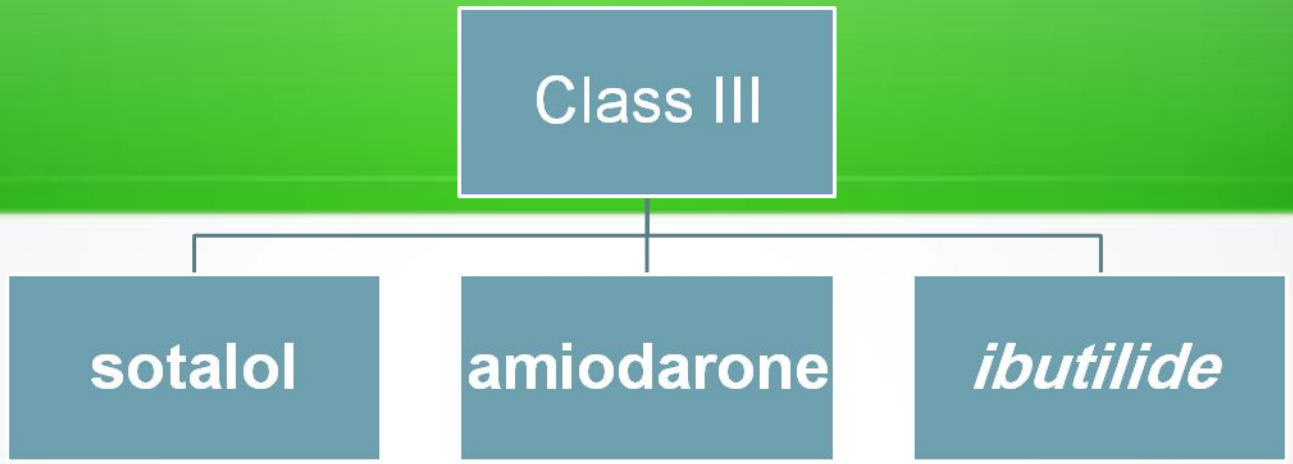
Prolongation of phase 3 repolarization without altering phase 0 upstroke or the resting membrane potential

They **prolong** both the duration of the AP and ERP

MOA: is not clear

but it is thought that they block potassium channels





Uses:

Ventricular arrhythmias, especially ventricular fibrillation or tachycardia

Supra-ventricular tachycardia

Amiodarone usage is limited due to its wide range of side effects

Amiodarone (Cordarone)

Amiodarone is a drug of multiple actions and is still not well understood

It is extensively taken up by tissues, especially fatty tissues (extensive distribution)

$t_{1/2}$ = 60 days

Potent P450 inhibitor

Amiodarane antiarrhythmic effect **is complex comprising of** class I, II, III, and IV actions

Dominant effect:

- Prolongation of action potential duration.

- It slows cardiac conduction,

- Works as Ca^{2+} channel blocker,

- and as a weak β-adrenergic blocker

Toxicity

- Most common include GI intolerance, tremors, ataxia, dizziness, and hyper or hypothyrodism

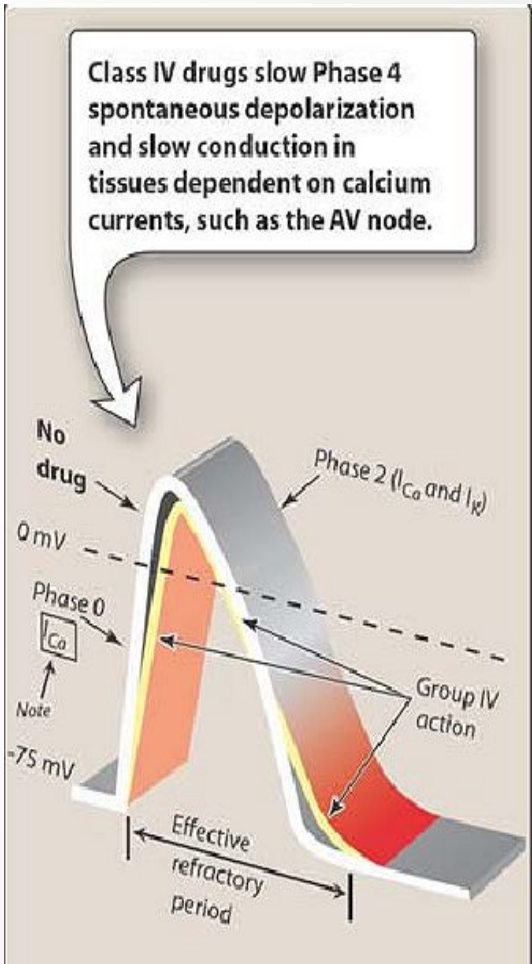
- **Corneal microdeposits** may be accompanied with disturbed night vision

- **Others**: liver toxicity, photosensitivity, gray facial discoloration, neuropathy, muscle weakness, and weight loss

- The most dangerous side effect is ***pulmonary fibrosis*** which occurs in 2-5% of the patients

Class IV ANTIARRHYTHMIC DRUGS (Calcium Channel Blockers)

- Calcium channel blockers decrease inward Ca^{2+} currents resulting in a decrease of phase 4 spontaneous depolarization (SA node)
- They slow conductance in Ca^{2+} current-dependent tissues like AV node.
- **Examples**: verapamil & diltiazem



Mechanism of action

They bind only to depolarized (open) channels prevention of repolarization

So they act only in cases of arrhythmia because many Ca^{2+} channels are depolarized while in normal rhythm many of them are at rest

They prolong ERP of AV node ↓conduction of impulses from the atria to the ventricles

Uses

Treatment of supra-ventricular tachycardia

Treatment of atrial flutter and fibrillation

Contraindication

Contraindicated in patients with pre-existing depressed heart function because of their negative inotropic activity

Adverse effects

Cause bradycardia and asystole especially when given in combination with β-adrenergic blockers