Antiarrhythmic drugs

OBJECTIVES:

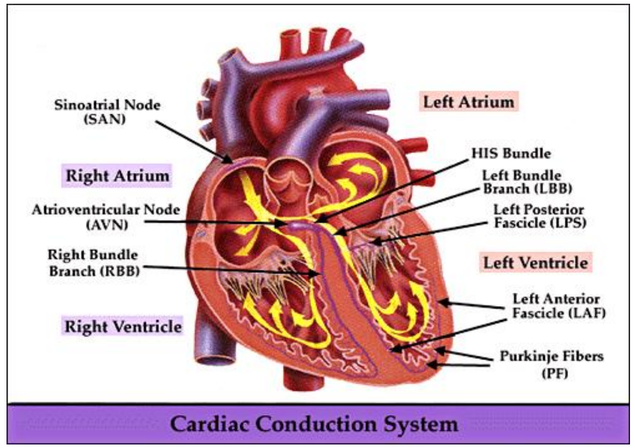
- Understand definition of arrhythmias and their different types
- describe different classes of Antiarrhythmic drugs and their mechanism of action
- understand their pharmacological actions, clinical uses, adverse effects and their interactions with other drugs.

- Titles
- Very important
- Extra information
- Doctor's notes

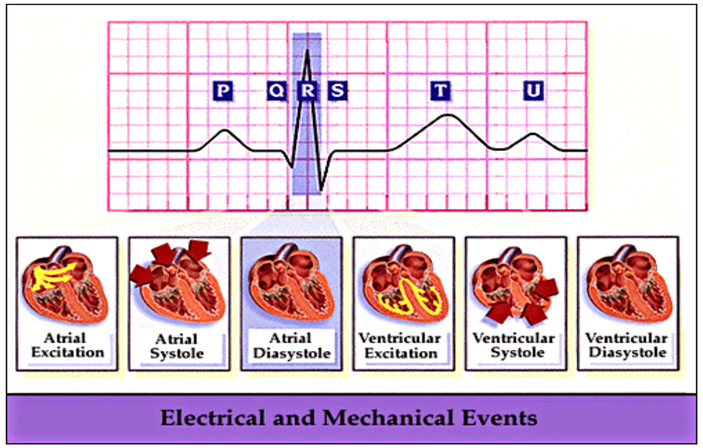
Physiology(For more understanding revise the Physiology lectures).

1- CARDIAC CONDUCTION SYSTEM:

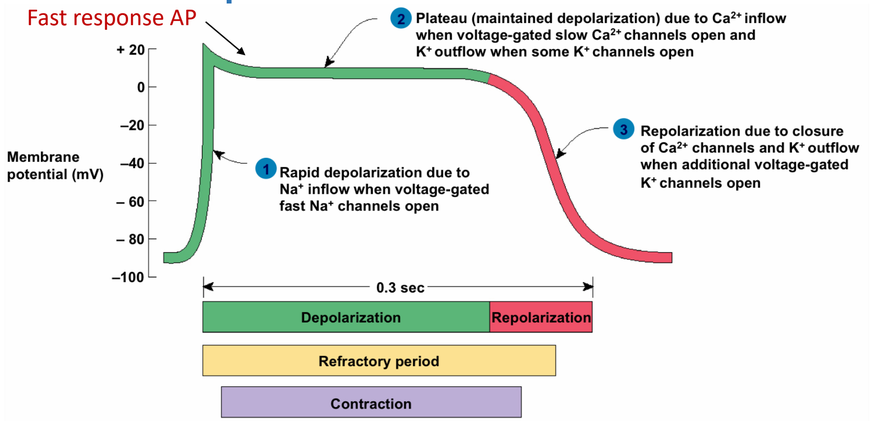
- **S.A. node.**
- **Inter-nodal pathways.**
- **A.V. node.**
- **Bundle of His and branches.**
- **Purkinje fibers.**

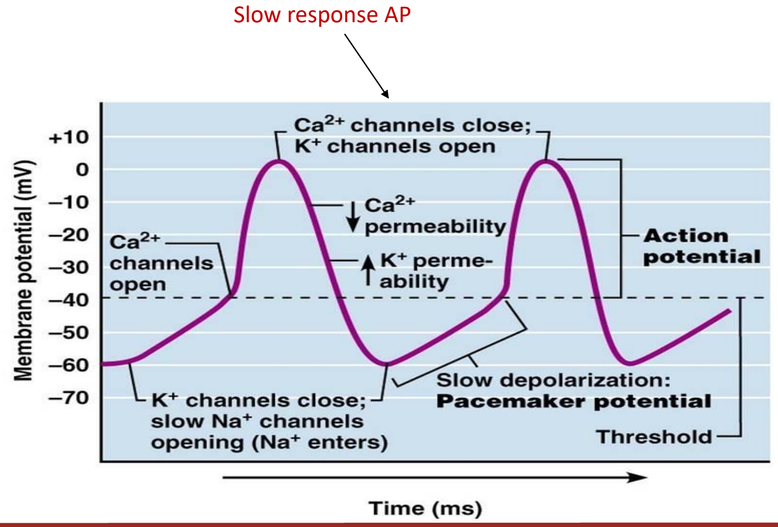


2- Electrocardiogram(ECG):



3- Fast response vs slow response:





What is arrhythmias ?

An abnormality in the :

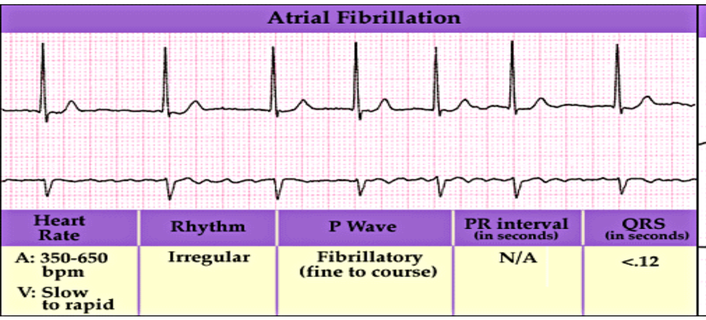
Rate:

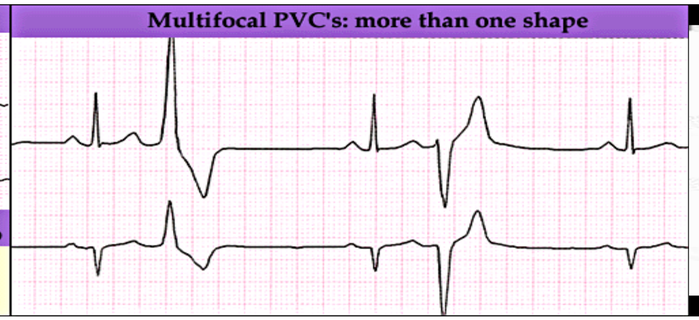
- high= tachycardia (more than 100 beats/min).
- low = bradycardia (less than 60 beats/min).

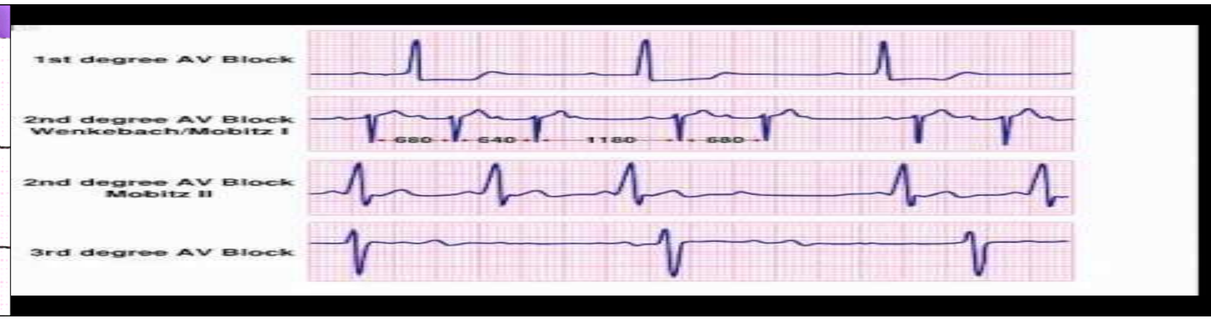
Regularity: extrasystoles (PAC,PVC). (Premature atrial contraction, Premature ventricle contraction)

Site of origin: ectopic pacemakers or disturbance in conduction.

Examples:







The ultimate goal of therapy

↓

Restore normal rhythm & conduction

↓ ↓

Maintenance of normal rhythm

Prevention of more serious arrhythmias

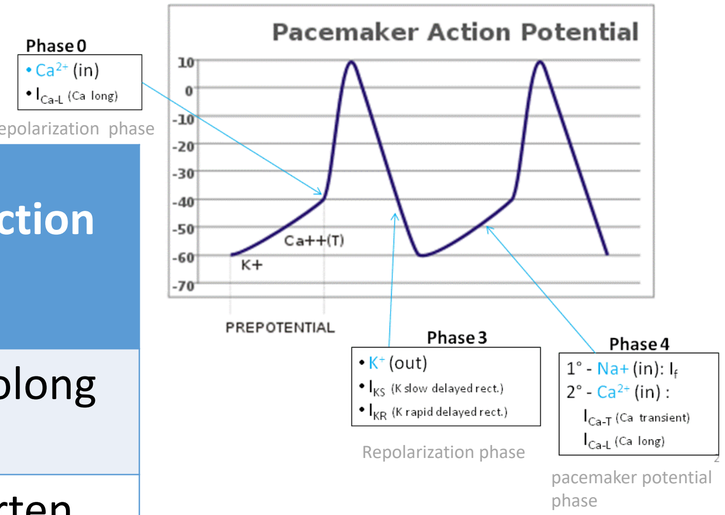
How antiarrhythmic drugs produce these effects?

- **Slow conduction velocity.**
- **Altering the excitability of cardiac cells by prolonging the effective refractory period.**
- **Suppressing ectopic pacemaker activity by inhibiting phase 4 slow depolarization.**

Classification of the antiarrhythmic drug:

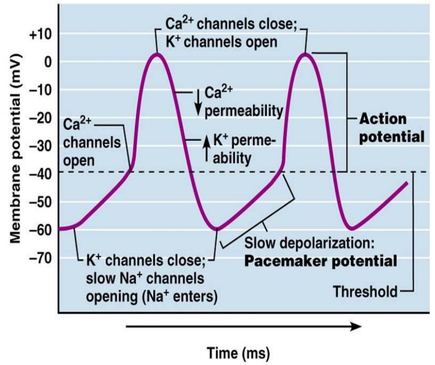
Vaughn-Williams CLASSIFICATION The most accepted classification	MECHANISM OF ACTION	Effect on pacemaker action potential
IA	Na+ channel blocker (Membrane stabilizing drugs)	Slow phase 0,4 in & prolong phase 3
IB		Slow phase 0,4 & shorten phase 3
IC		Markedly Slow phase 0
II	β- adrenoceptor blockers	Slow phase 4 depolarization
III	Drugs that prolong action potential duration K+ channel blocker	Prolongs Phase 3
IV	Calcium channel blocker	Slow Phase 4 spontaneous depolarization and conduction

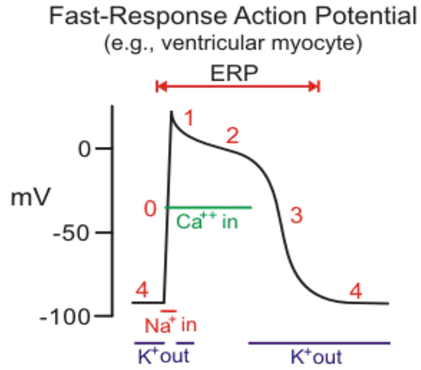
No bad boy keeps clean.=
Na – beta– K – Ca



Class I:

Drugs that block the influx of Na ions through Na channels (membrane stabilizing effect).
Either partial or complete block, as a result decrease of rise of phase 0



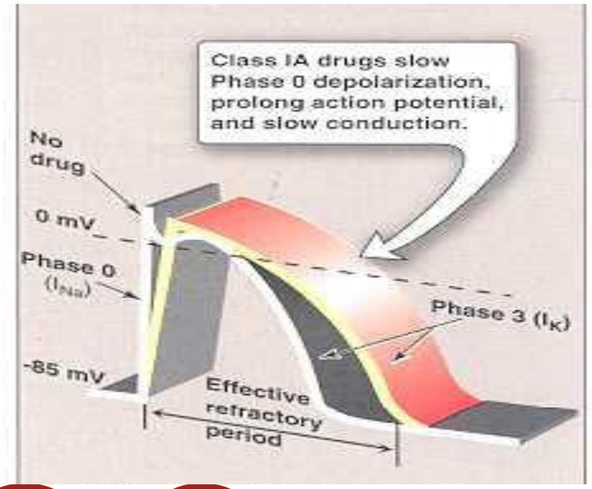


- have the following effects on the pacemaker action potential :

1. decrease the rate of rise of rapid depolarization (Phase 0).
2. decrease phase 4 slow depolarization (suppress pacemaker activity).

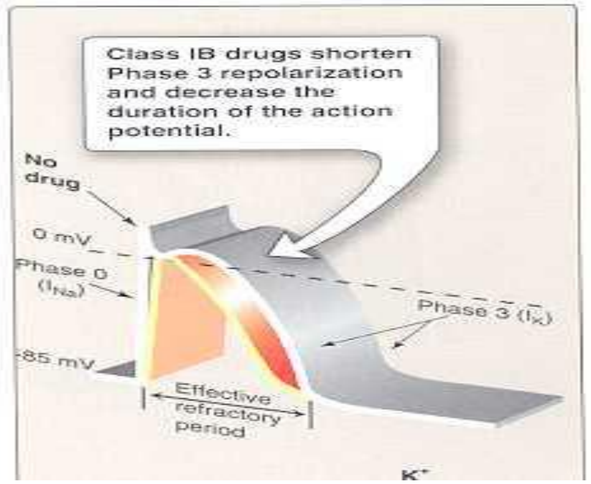
- Sub classified according to their effect on action potential duration (phase 3):

IA : prolongs action potential duration:



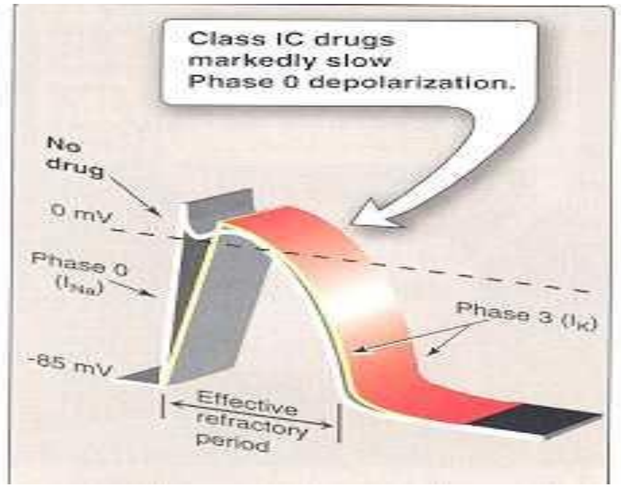
A for Active people who have potential for more duration

IB : shorten action potential duration:



B for Bored, not active people; have less or shortened potential.

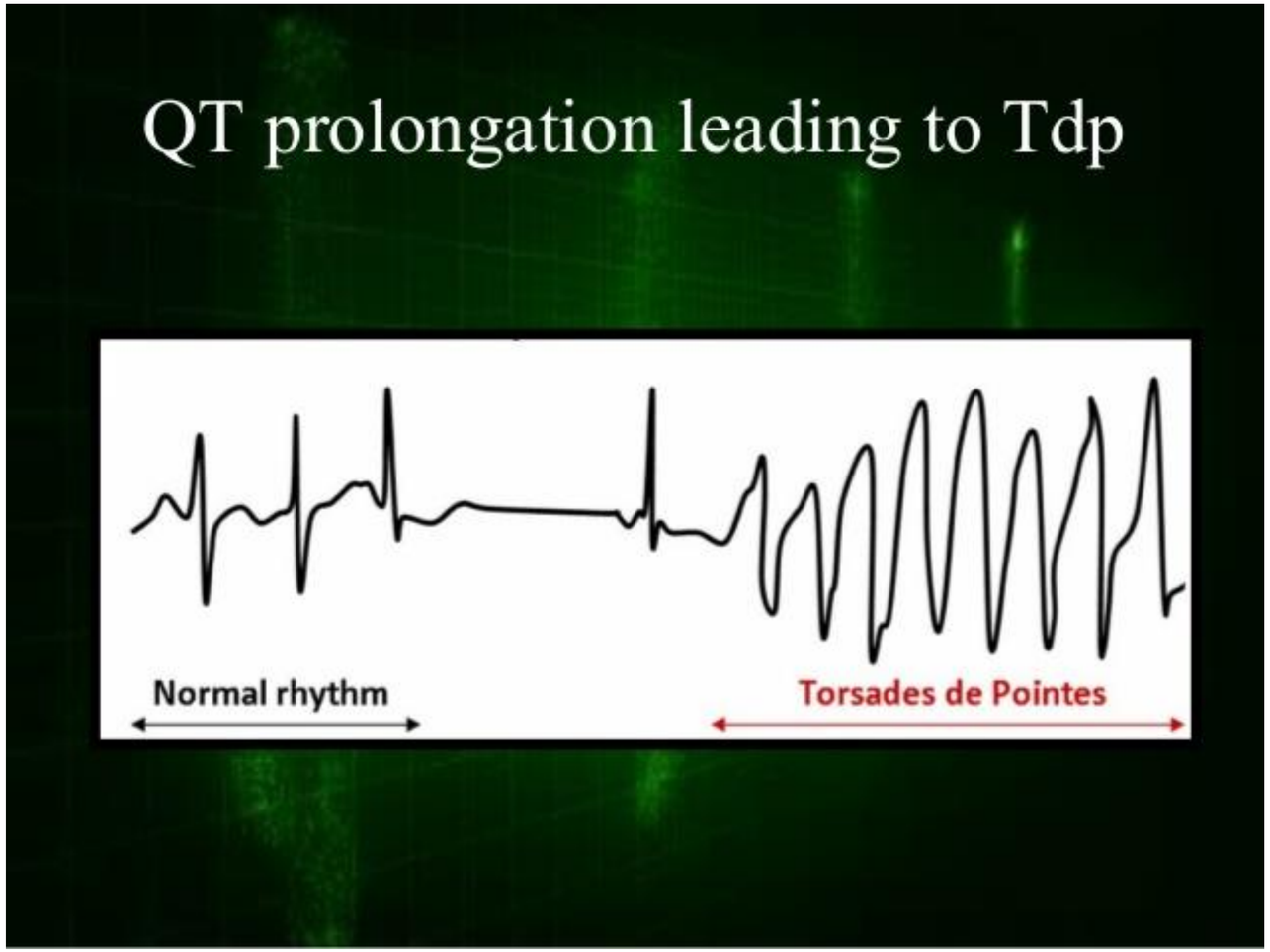
IC : no effect on action potential duration:



CLASS IA

Drug	Quinidine		Procainamide
Pharmacological action	**Cardiac effects (direct)** 1. Membrane stabilizing effect. 2. ECG changes: ❖ prolongs P-R and Q-T interval. ❖ widens QRS complex.	**Actions on ANS (indirect)** 1. Anticholinergic effect: atropine like effect ❖ Increase conduction through the A.V. node (risk of ventricular tachycardia) 2. α-adrenergic blocking effect: ❖ cause vasodilatation & reflex sinus tachycardia (seen more after I.V dose)	Similar to Quinidine except : 1. less toxic on the heart. 2. there is No anticholinergic or α-blocking actions. Pro =Professional ; cause its less toxic, No anticholinergic or α-blocking actions.
Therapeutic uses:	1. Atrial flutter & fibrillation. عطر = Atrial | So the queen like العطر 2. Maintaining sinus rhythm after cardioversion (conversion from arrhythmia to a normal rhythm using electricity or drugs)		More effective in ventricular than in atrial arrhythmias.
ADRs	1. quinidine syncope: episodes of fainting due to **Torsades de pointes** arrhythmia. Unlike other drugs, this side effect can occur even in therapeutic dose 2. Anticholinergic adverse effects: can be tolerated • Dry mouth - Blurred vision - Urinary retention – Constipation. 3. Hypotension - due to depressing contractility & vasodilatation.		1. In long term therapy causes reversible lupus erythematosus-like syndrome (SLE). SLE= سلي نفسك ب الروك Prokainamide ميوزك 2. Hypotension. 3. Torsades de pointes arrhythmia. 4. Hallucination & psychosis.
Administration	GIVEN ORALLY (Rarely given I.V.). في الأغلب Caine = IV الا الQuinidine لانه unique		I.V.

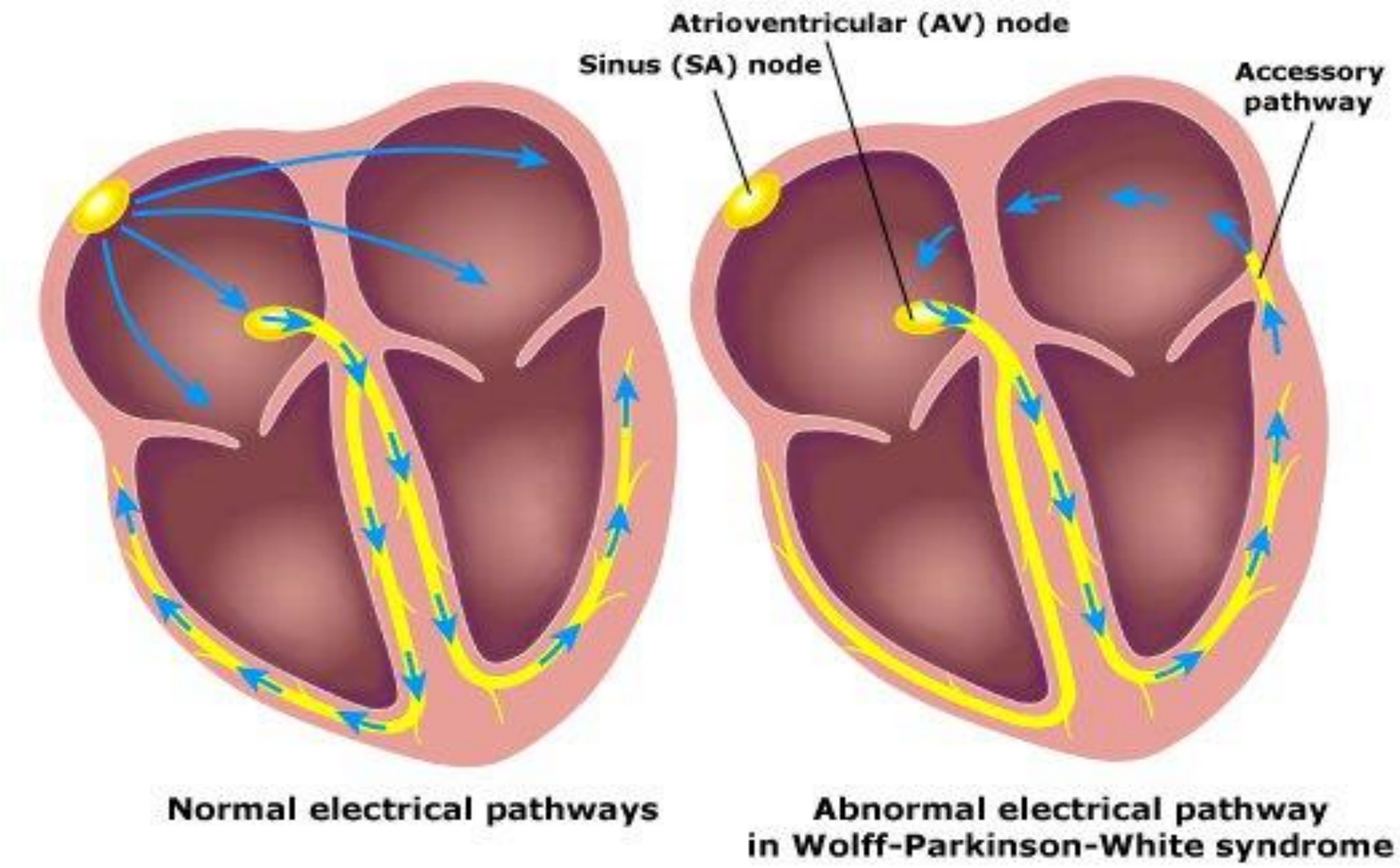
torsades de pointes arrhythmia (twisting of the spikes):



- It is the cause of quinidine syncope which is episodes of *fainting* develop at therapeutic plasma levels.
- May terminate spontaneously or lead to fatal ventricular fibrillation. Its lethal

CLASS	CLASS IB		CLASS IC
Drug	Lidocaine	Mexiletine	Flecainide
Therapeutic uses:	Treatment of emergency ventricular arrhythmias e.g.: • During surgery • Following acute myocardial infarction. Should be available in ER & ICU NOT effective in atrial arrhythmias. Lidocaine = (Lee do what u can) (to save people in ER)	1. Ventricular arrhythmia. 2. Digitalis-induced arrhythmias. (Digitalis are drugs used for congestive heart failure and atrial arrhythmias, yet cause ventricular and other types of arrhythmia as side effect) ابطال الديجيتال was excellent (Mexiletine) (Digitalis)	The most potent membrane stabilizer available 1. Supraventricular arrhythmias. 2. Wolff-Parkinson-White syndrome (WPW). (explained next slide) 3. Very effective in ventricular arrhythmias, but very high risk of pro-arrhythmia. 4. Should be reserved for resistant arrhythmias. WPW = iNi Flecainide
ADRs	1. Hypotension. depresses contractility 2. CNS ADRs (similar to other local anesthetics): • Paresthesia. تنميل بالاصابع • Tremor.رعشة • Dysarthria (slurred speech). ثقل باللسان • Tinnitus.طنين بالاذن • Confusion. • Convulsions.تشنجات	1. GIT: • Nausea , Vomiting. 2. CNS: since it's similar in action to Lidocaine • Tremor, Drowsiness, Diplopia (Double-vision). 3. CVS: • Arrhythmias & Hypotension.	1. Pro-arrhythmia. 2. CNS : • dizziness, tremor, blurred vision, abnormal taste sensations (Dysgeusia), paraesthesia. 3. heart failure due to -ve inotropic effect.
Administration	Given I.V. bolus (small amount given by syringe in mins) or slow infusion (mixing drug with saline and attaching it to a pump that infuse it drop by drop within hrs) (NOT effective orally due to only 3% bioavailability).	Effective ORALLY. Effective orally, Mexiletine = tongue	-
$t_{1/2}$	2 Hours.	10 Hours.	-

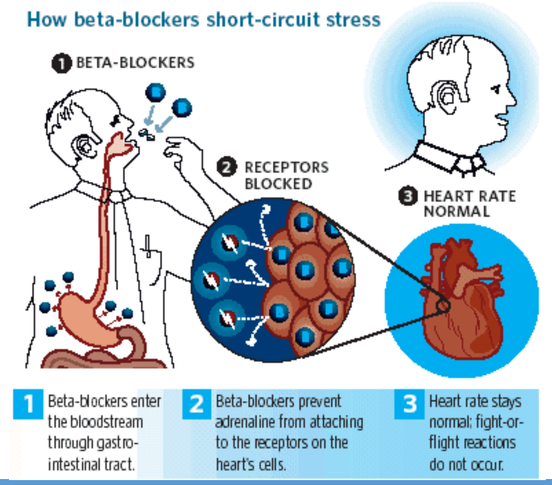
Wolff-Parkinson-White syndrome:

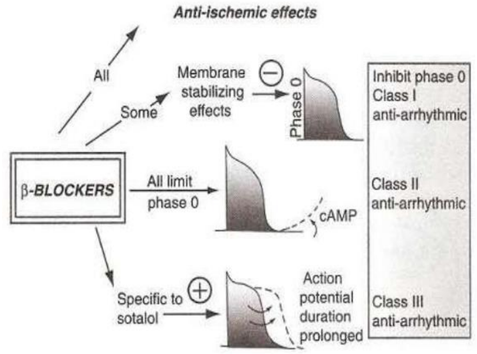


Pre-excitation of the ventricles due to an accessory pathway known as the Bundle of Kent.(the electrical signal re-enters the AV node)

In normal heart the only connection between atria and ventricles is the AV node, some people have congenital abnormality that there's an accessory piece of pathway called bundle of kent. In this case, the impulses will re-enter and there will be a circle.

Class II Drugs
β- Adrenoceptors Blockers





Pharmacological actions:

(protect the heart from the arrhythmogenic effect of the sympathetic N.S.)

Block β1- receptors in the heart

↓

Reduce the sympathetic effect on the heart

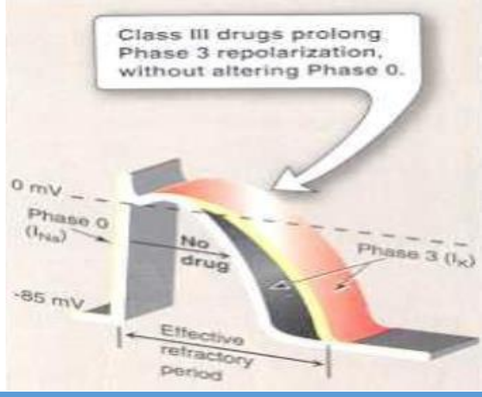
↓

1. Decrease automaticity of S.A. node and ectopic pacemakers.
2. Prolong refractory period (slow conduction) of the A.V node.

Drugs	Esmolol	Propranolol, Atenolol, Metoprolol
Therapeutic Uses (general)	1. Atrial arrhythmias associated with emotion: • After exercise. • Thyrotoxicosis (↑ thyroxine). 2. Wolff-Parkinson-White syndrome (WPW). 3. Digitalis-induced (digoxin) arrhythmias. بيتك (beta blockers) مليان الكترونيات (digitalis)	
Therapeutic Uses (specific)	• Very short acting (half-life = 9 min). لما نعطي الانجيكشن (IV) نسمي ونقول اسم الله (Esmolol)عليك وكل شيء يتيسر و يصير بسرعة(rapid action9 min) • Given I.V. for rapid control of ventricular rate in patients with atrial flutter or fibrillation. half-life = 10 min in beta blockers lecture	• Used in patients who had myocardial infarction to reduce incidence of sudden death due to ventricular arrhythmias.

Class III Drugs →

- Prolong the action potential duration and refractory period.
- Prolong phase 3 repolarization.



Pharmacological effect:

- Prolongs action potential duration and therefore prolongs refractory period. (Main effect).
- Additional class IA, II & IV effects. (special feature of Amiodarone).
- Vasodilating effects: (due to its α & β-adrenoceptor blocking effects and its calcium channel blocking effects).

Drug	أمي تدير كل شي **Amiodarone (prototype)**
Therapeutic Uses	1. Main use: serious resistant ventricular arrhythmias آمي حالتها خطيرة 2. Maintenance of sinus rhythm after cardioversion 3. Resistant supraventricular arrhythmias (e.g. W.P.W.)
Pharmacokinetics	• Extremely long $t_{1/2}$ = 13 - 103 days (causes difficulty in controlling the dose) أمي الله يطول بعمرها long half life • Metabolized by CYP3A4 and CYP2C8 to its major active metabolite: N-desethylamiodarone (stronger than Amiodarone itself) • Eliminated primarily by hepatic metabolism • Cross placenta and appear in breast milk (must be careful with pregnant and lactating patients) أمي حملتنا وارضعتنا
ADRs	• Exacerbation of ventricular arrhythmias (with high dose) (proarrhythmic) • Bradycardia and heart failure • Hyper- or hypothyroidism (due to Iodine found in the drug's structure) • Photodermatitis & skin deposits (patients should avoid exposure to the sun) آمي عندها بلاوي كثيرة cause of many ADRs • Neurological: e.g. Tremors and Peripheral neuropathy • Nausea, Vomiting and Constipation • Corneal micro deposits. • Hepatocellular necrosis. • Pulmonary fibrosis. (very common, 15% incidence)
Drug Interactions	1. Co-administration of amiodarone with drugs that prolong the QT interval increases the risk of Torsades de Points arrhythmia. • e.g.: - Macrolide antibiotics (Clarithromycin, Erythromycin) - azole antifungals (Ketoconazole). آمي صاحبة مشاكل cause of many drug interactions (pharmacodynamic interaction) 2. Drugs (or substances) that inhibit these enzymes (CYP3A4 and CYP2C8) Cause increase in serum concentration of amiodarone e.g. : Loratadine, Ritonavir , Trazodone, Cimetidine, Grapefruit juice 3. Drugs that induce these enzymes (CYP3A4 and CYP2C8) Cause decrease in serum concentration of amiodarone e.g. : Rifampin (pharmacokinetic interaction)

Pure class III: (no additional effects, unlike amiodarone)

- Ibutilide:
  - Given by rapid I.V. infusion.
  - Used for the acute conversion of atrial flutter or fibrillation to normal sinus rhythm.
  - Causes QT interval prolongation (may cause torsades de pointes).

اي بطلت احط عطر و
Atrium = عطر

فيه raper اسمها أمل

New Antiarrhythmic Drugs

Dronedarone

- A non-iodinated congener (similar structure) of amiodarone.
- Has antiarrhythmic properties belonging to all four classes.
- Used for maintenance of sinus rhythm following cardioversion in patients with atrial fibrillation.

WARNINGS: (contraindications)

- Should not be used in patients with severe (class IV) heart failure. Risk of death may be increased in these patients.
- Should not be used in patients with permanent atrial fibrillation. Risk of death and stroke, may be increased in these patients.

Class IV:

- Calcium channel blockers
- Verapamil, Diltiazem.

دليتي عازم ؟

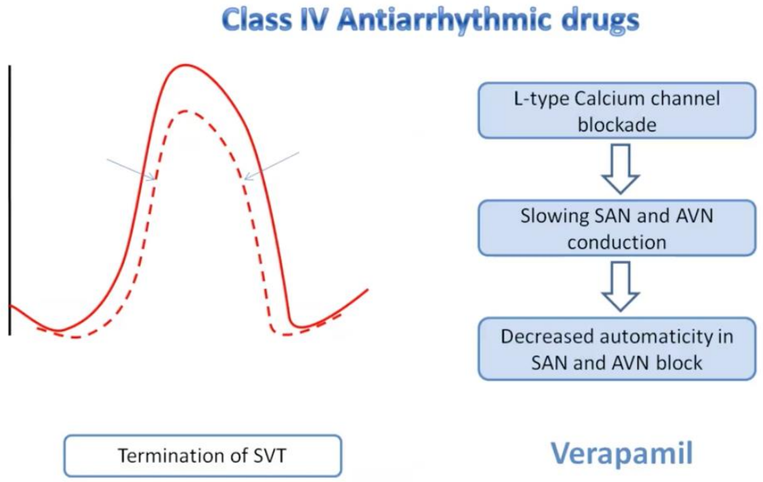
  - Main site of action on the A.V. node & S.A. node cause:
    → Slowing of conduction
    → Prolongation of effective refractory period

Therapeutic uses:

1. Atrial arrhythmias.
2. Re-entry supraventricular arrhythmias e.g. WPW.

Used only for atrial
عازم وامل يحبون العطر

❖ NOT effective in ventricular arrhythmias. (contraindicated).



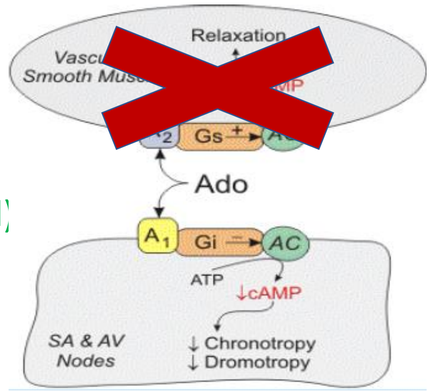
VT – Ventricular tachycardia **SVT** – Supraventricular tachycardia **AVN** – Atrio –ventricular node **SAN** – sino-atrial node

Adenosine

Mechanism of Action:

- Inhibits cAMP by binding to adenosine A1 receptors causing the following actions:

1. Opening of potassium channels (hyperpolarization) (-110 instead of -90 → more difficult to produce action potential)
2. Decreasing conduction velocity mainly at AV node (negative dromotropic* effect).
3. Inhibiting phase 4 pacemaker action potential at SA node (negative chronotropic* effect).



Therapeutic Uses	• Drug of choice for acute management of paroxysmal (متقطعة) supraventricular tachycardia. • Preferred over verapamil (calcium channel blockers have a very strong Inotropic effect) adenosine → safer and does not depress contractility.
Half-life	Less than 10 sec (ideal in emergency).
ADRs	• Flushing (dilatation of superficial blood vessels) in about 20% of patients. • Shortness of breath and chest burning in 10% of patients (due to bronchospasm). • Brief AV block → contraindicated in heart block (because it slows conduction velocity in A.V. node).

Inotropic: effect on contractility.
Dromotropic: effect on conduction velocity.
Chronotropic: effect on heart rate.

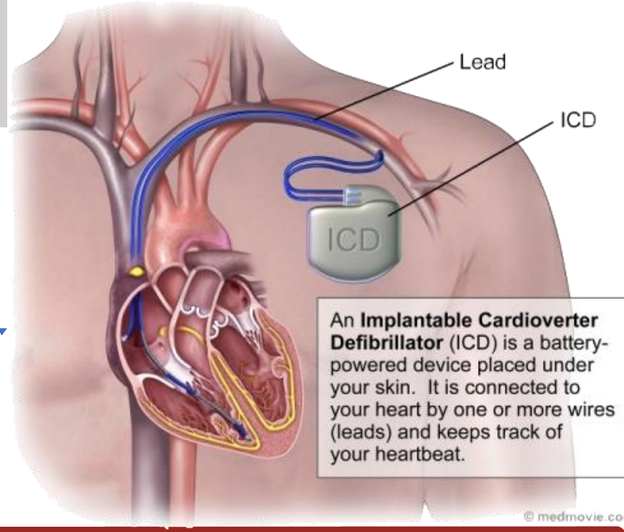
Bradyarrhythmias

❖ Atropine

- Used in sinus bradycardia after myocardial infarction and in heart block.
- In emergency heart block Isoprenaline may be combined with atropine (CAUTION) (could cause serious tachycardia)

Nonpharmacologic therapy of arrhythmias:

- **Implantable Cardiac Defibrillator (ICD):**
  - Can automatically detect and treat fatal arrhythmias such as ventricular fibrillation.



Antiarrhythmic Drugs

Class Ia

1 Double Quarter Pounder

Disopyramide
Quinidine
Procainamide

Class Ib

with Lettuce, Mayo & Tomato

Lidocaine
Mexeletine
Tocainide

Class Ic

and More Fries Please!

Moricizine
Flecainide
Propefanone

Class II

Beta blockers? Lol

Propanolol
Atenolol
Metoprolol

Class III

This is SAD

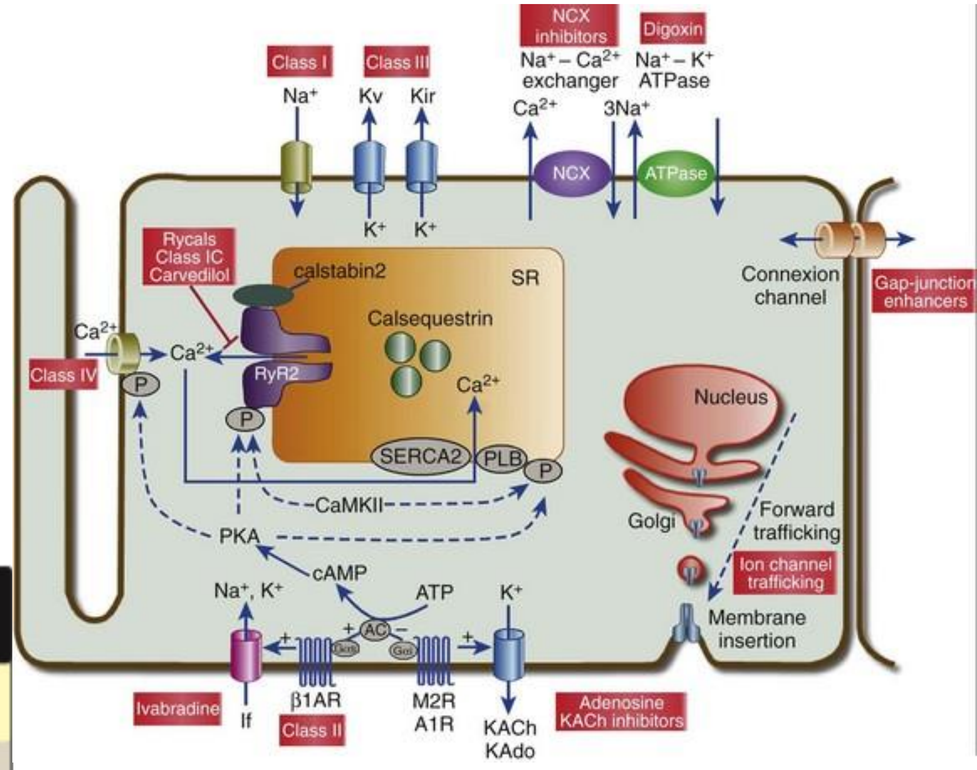
Sotalol
Amiodarone
Dofelitide

Class IV

I and V in Class IV?

Diltiazem
Verapamil

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes



Pharmacology
team 436

MEDICINE
KING SAUD UNIVERSITY

Editing file

Team leaders :

Abdulrahman Thekry
Ghadah Almuhana

Team members:

Abdulaziz Redwan
Khalid Aleisa
Omar Turkistani
Faris Nafisah
Mohammed Khoja
Abdulrahman Alarifi
Abdulrahman Aljurayyan
Moayed Ahmad
Faisal Alabbad
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Maha Alissa
Najd Altheeb
Rana Barasain
Reem Alshathri
Sama Alharbi
Shoag Alahmari
Shrooq Alsomali

Contact us :

@Pharma436

Pharma436@outlook.com