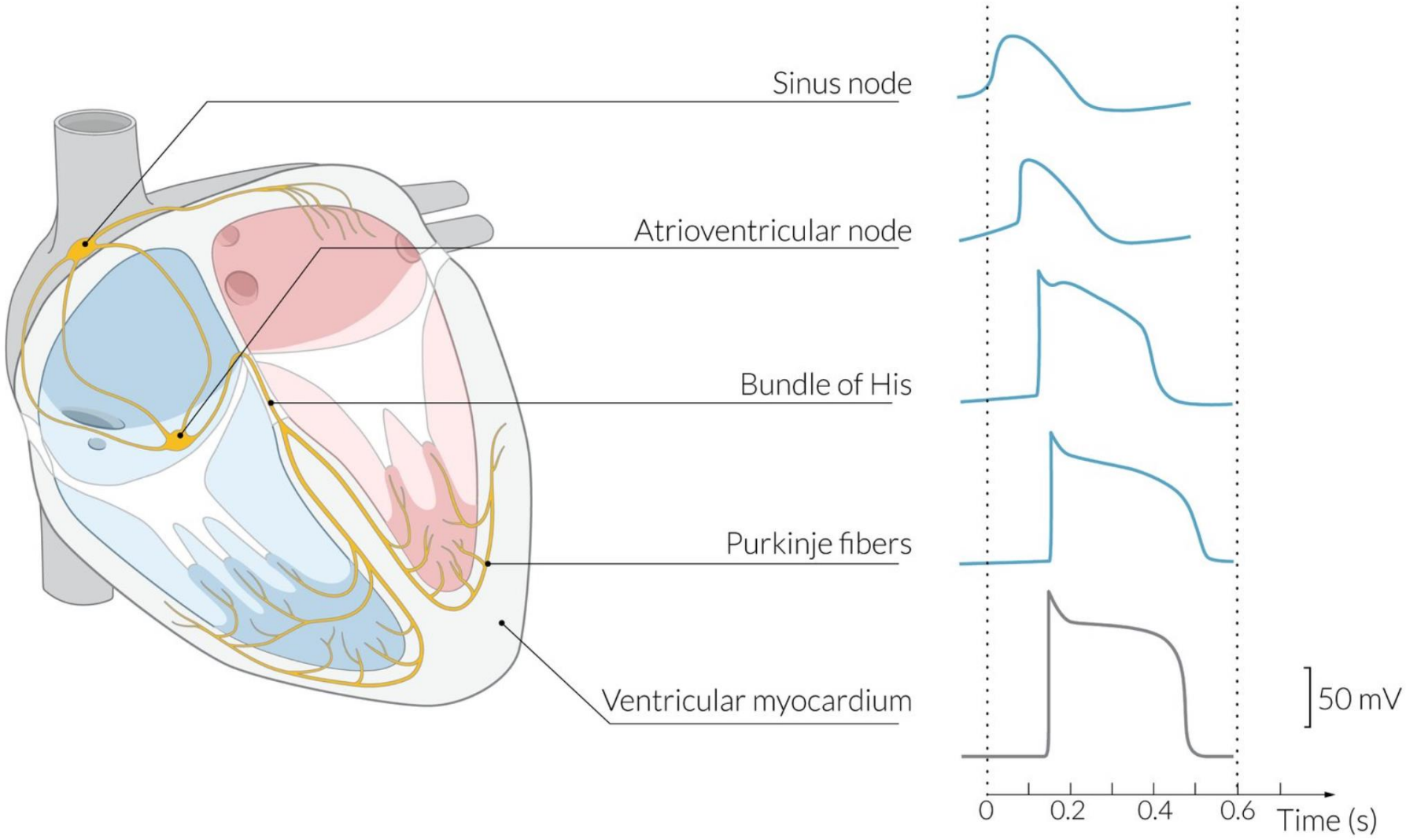
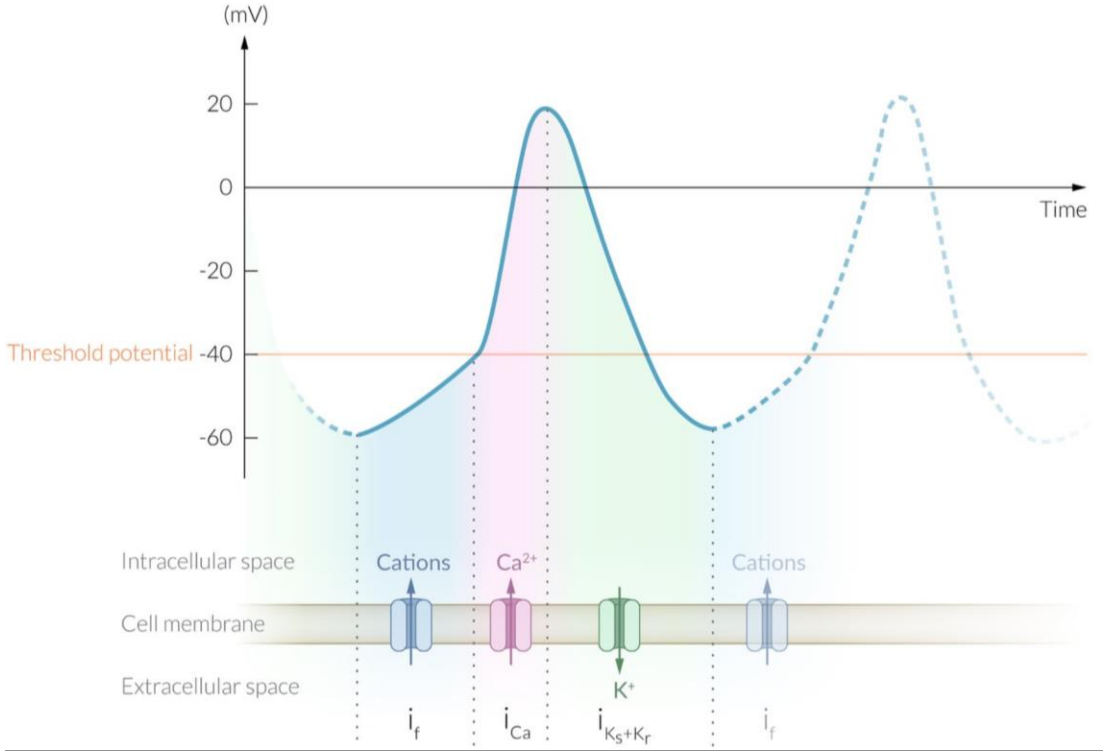
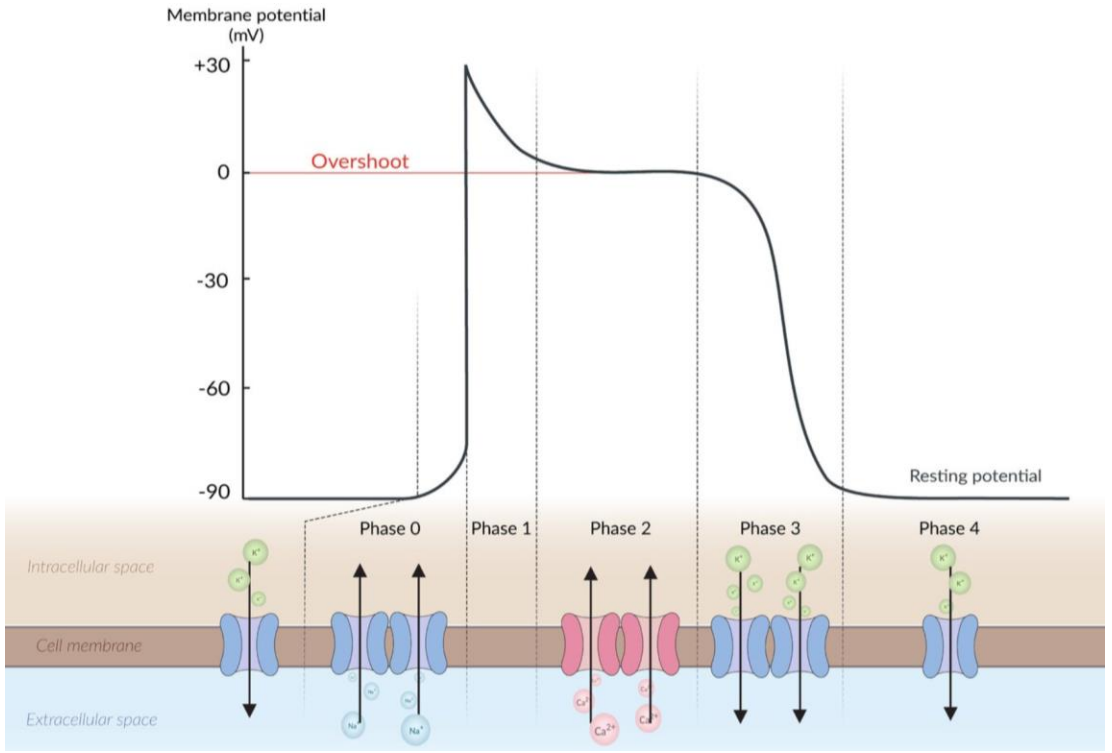
Anti-Arrhythmic Drugs

Abdalrhman Froukh


Sinus node
Atrioventricular node
Bundle of His
Purkinje fibers
Ventricular myocardium
50 mV
0
0.2
0.4
0.6
Time (s)





Action Potential of the Heart

Abbreviations

P = Plateau phase

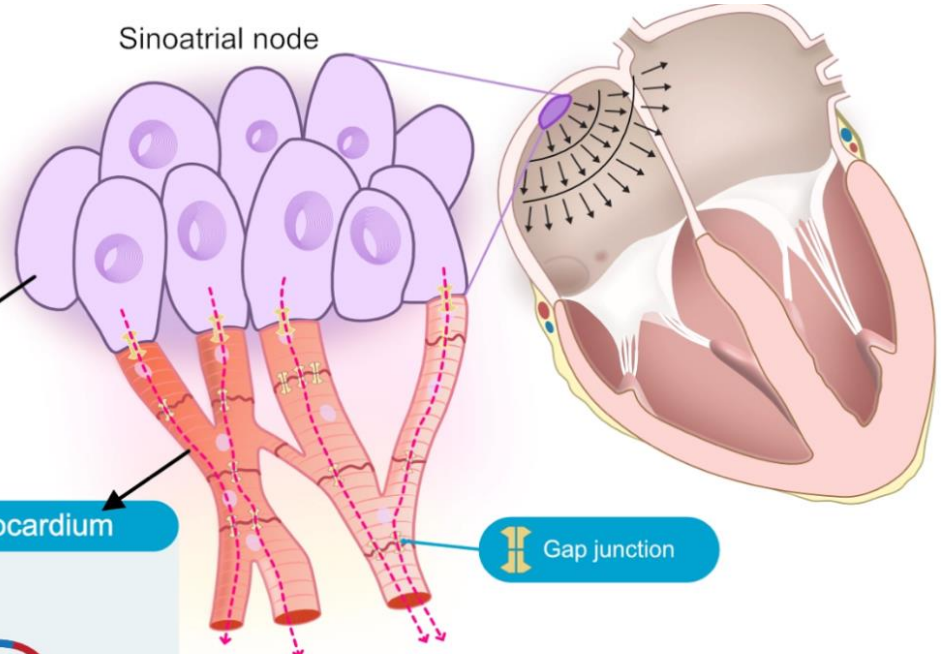
RE = Repolarization

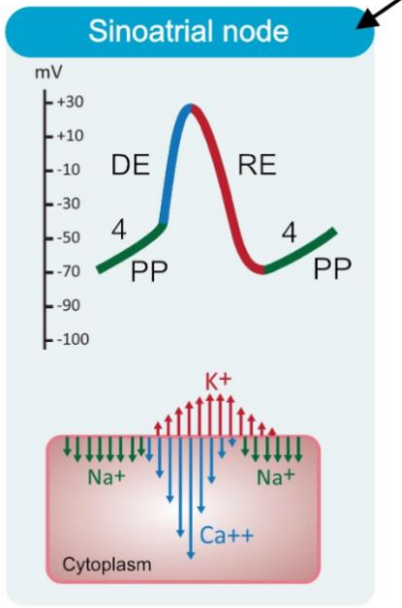
DE = Depolarization

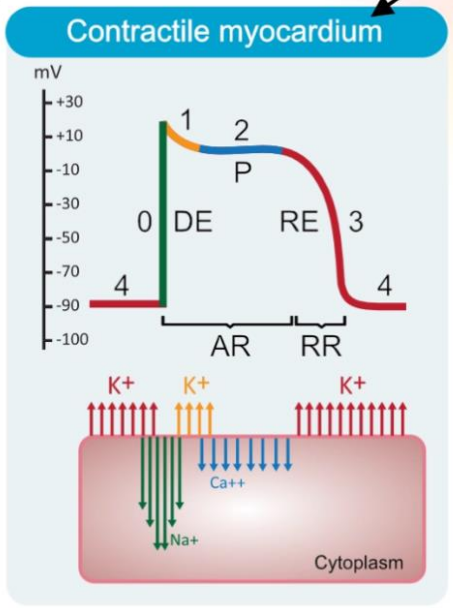
PP = Pacemaker potential

RR = Relative refractory period

AR = Absolute refractory period







Flow of ions across ion channels

Action Potential

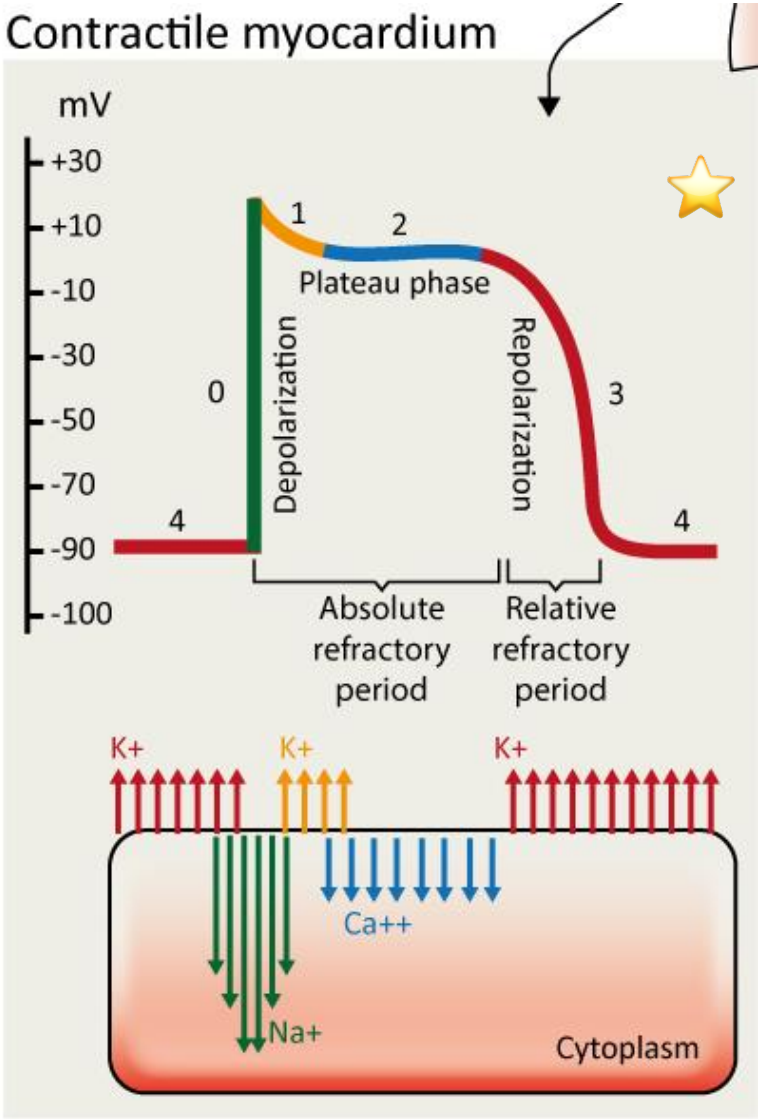
Phase 0: Rapid depolarization due to influx of Na+ via voltage dependent sodium channels [Happens in working muscle cells and conduction fibers].

Phase 1: Partial repolarization due to inactivation of Na+ channels.

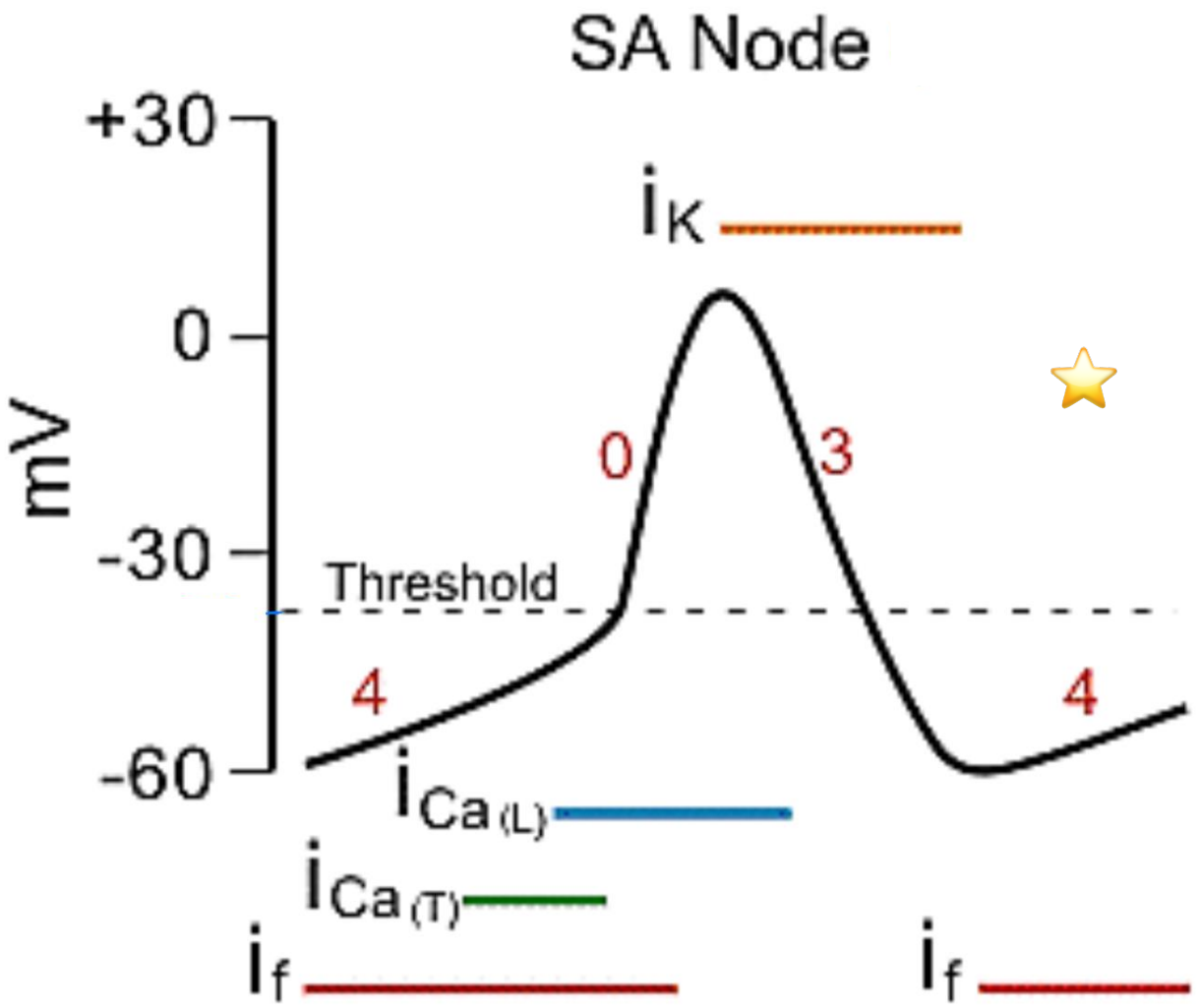
Phase 2: Plateau from slow Ca2+ influx via L-type voltage sensitive Ca2+ channels.

Phase 3: Replolaization due to inactivation of Ca2+ and efflux of K+ due to activation of K+ channels.

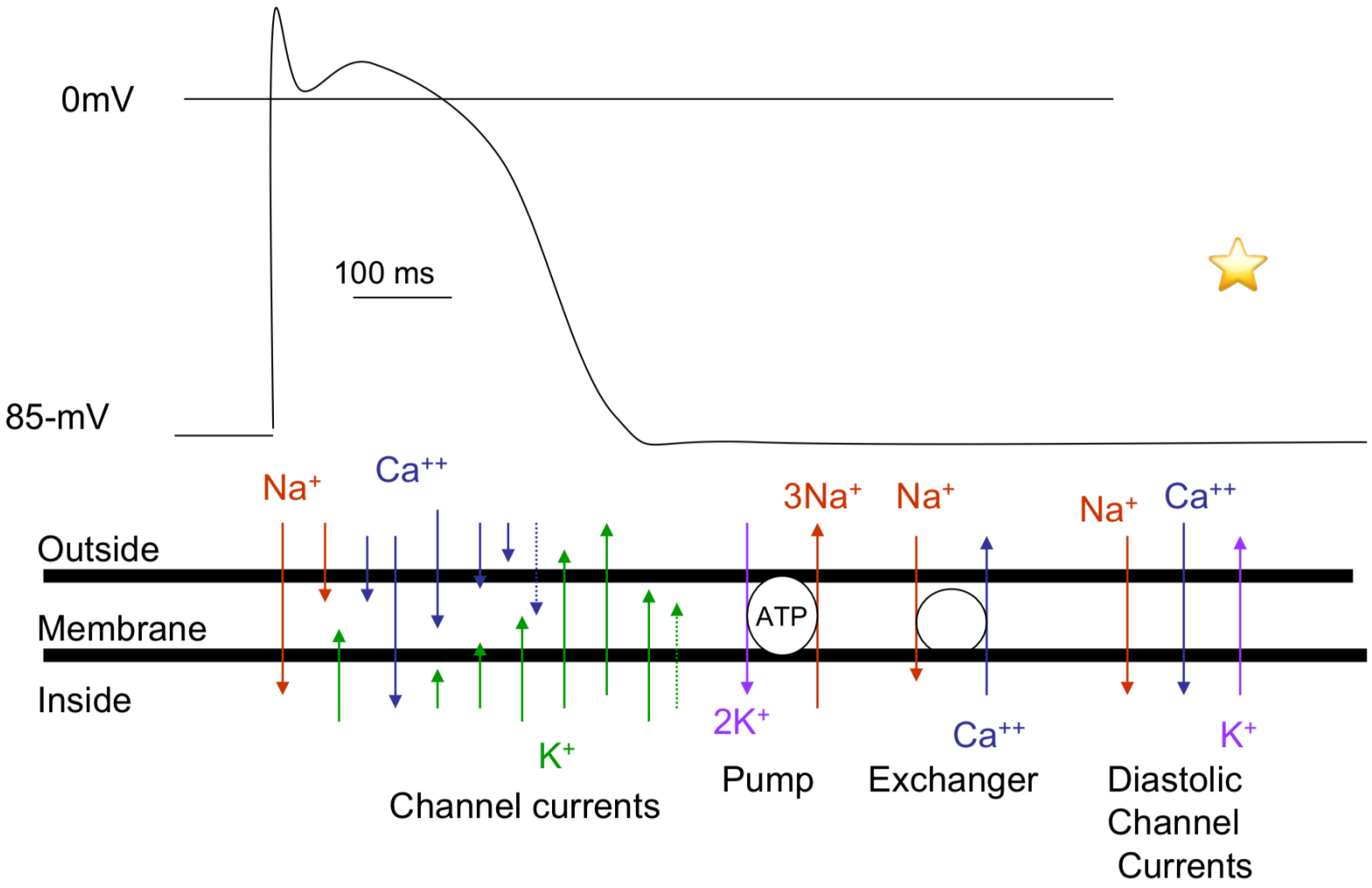
Phase 4: (the pacemaker potential) inward movement of Na+ and Ca +2.

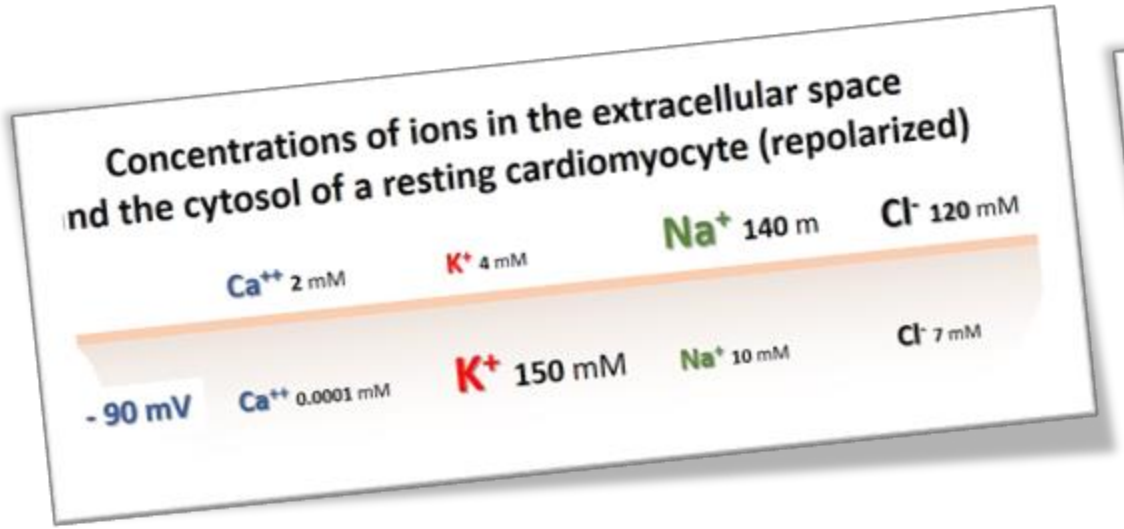


Action potential in non contractile myocardium (SA node)



Action Potential





Ion	Intracellular	Extracellular
Na^+	10	145
K^+	140	4
Cl^-	4	115
Ca^{++}	<0.001	2

Distribution of ions at rest [mM]

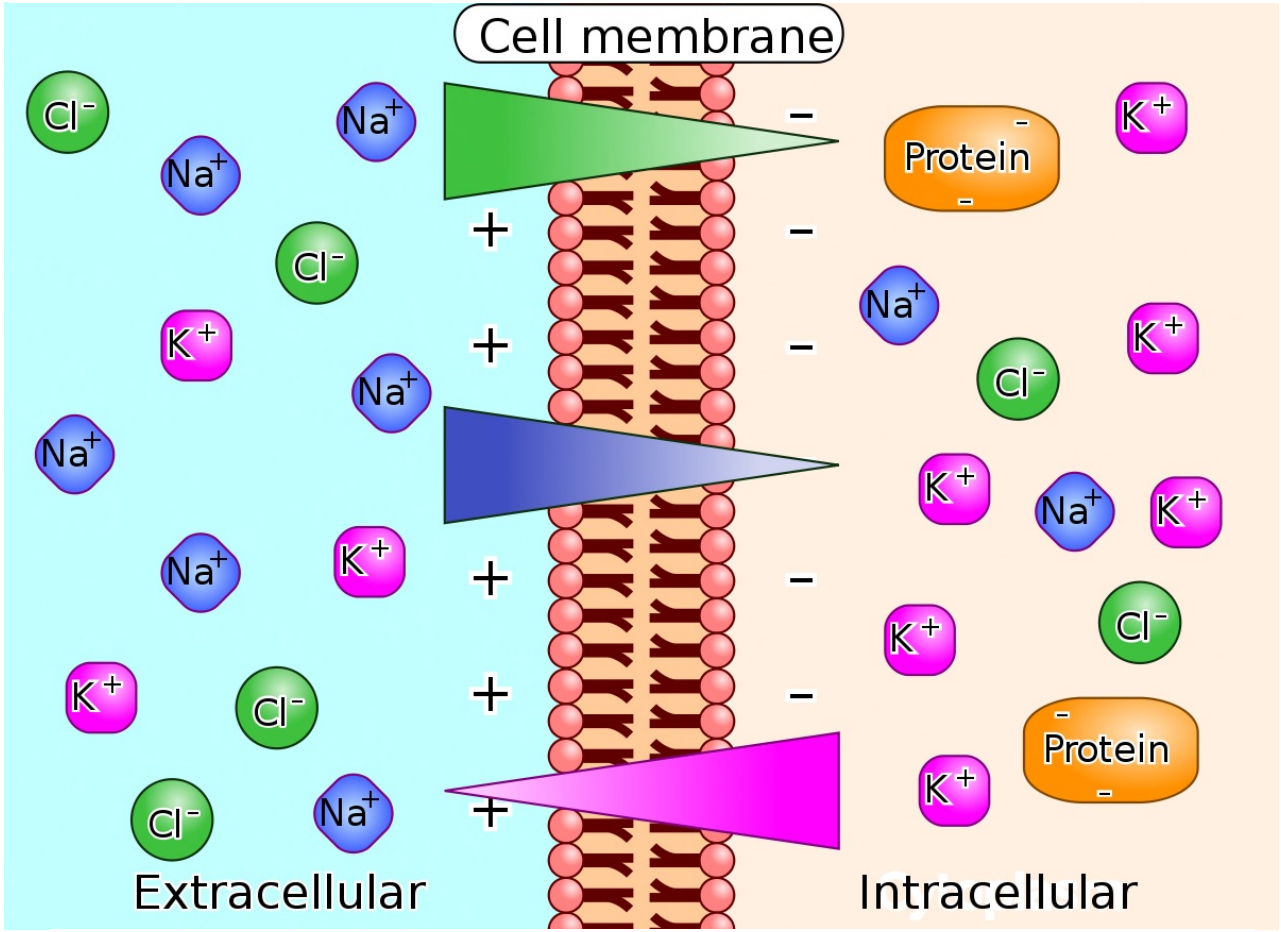
Cardiac Electrophsiology

Resting Membrane Potential (RMP) - A voltage difference (about -90 mV) exists across the surface membrane of all cardiac cells due to uneven distribution of ions.

This is created primarily by active cell membrane transport of Na+ (3 out) and K+ (2 in) by Na+/K+ ATPase.

Action Potential (AP) - When cardiac cells are electrically excited, a sequence of voltage changes (depolarization and repolarization) occur as a function of time.

These changes in voltage are due to changes in conductance of ions (mainly Na+, Ca++, and K+) across the cell membrane.

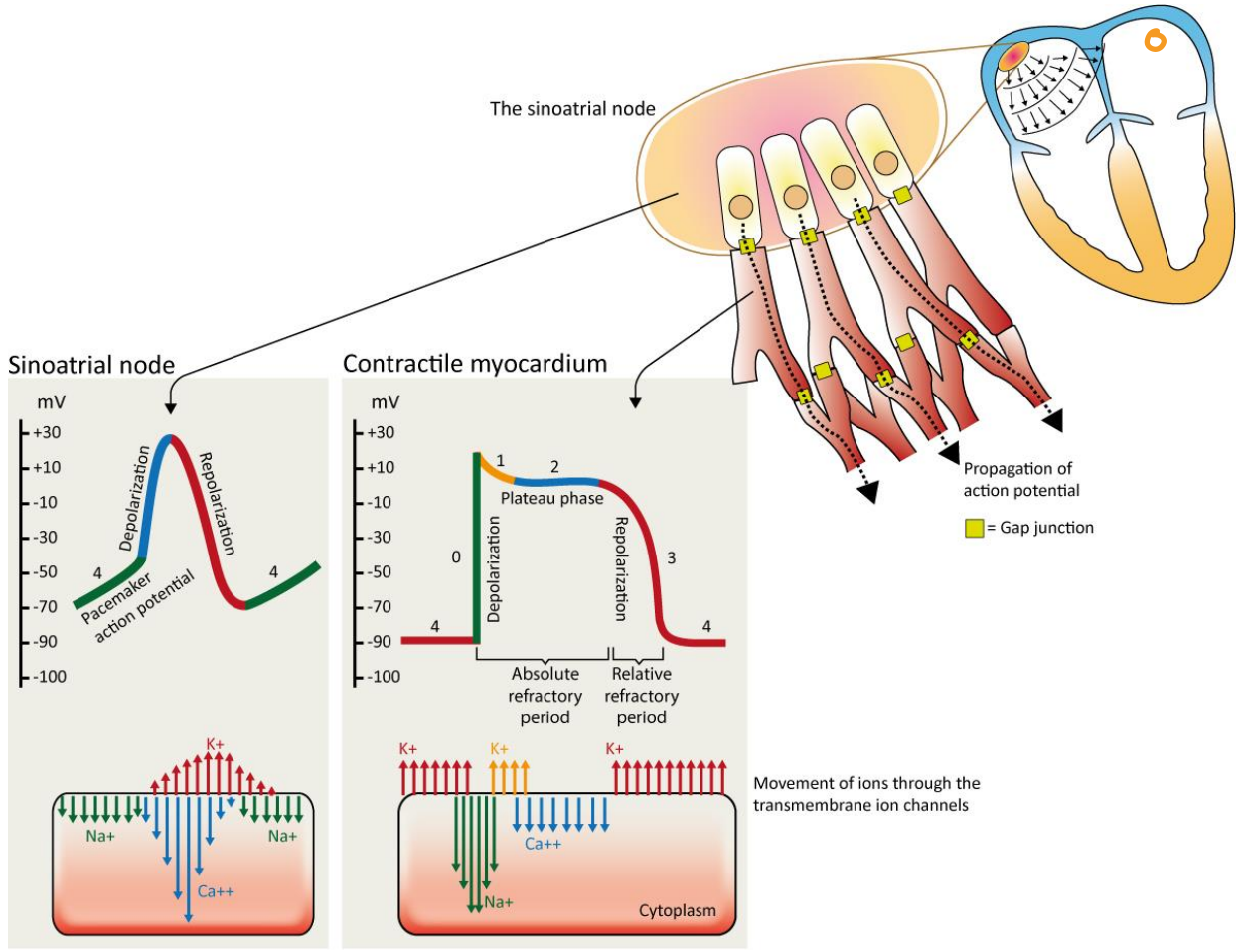


Electrical Activity of the Heart

Cardiac cells undergo depolarization and repolarization to initiate cardiac action potentials: 60 times/ minute.

The shape and duration of each action potential are determined by the activity of ion channel protein complexes in the membranes of individual cells.

Ion channel function can be disrupted by inherited mutation/polymorphism, acute ischemia, sympathetic stimulation, or myocardial scarring, to create arrhythmias.



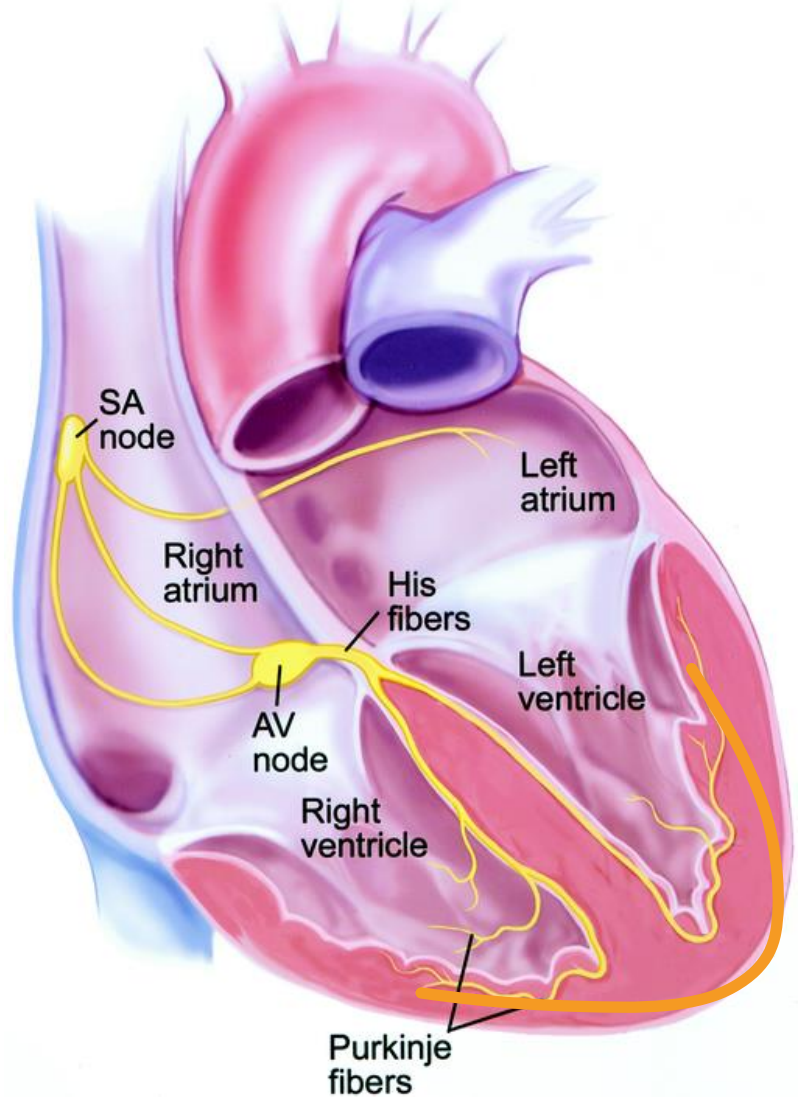
Cardiac Arrhythmias

These are disorders of rate, rhythm, electrical impulse generation or conduction in the heart.

Disorders can range from benign to life threatening.

Anti-arrhythmic drugs alter movement of ions in cardiac cells.

All these drugs can aggravate or generate arrhythmias.



Cardiac Arrhythmias

Arrhythmia it is a disfunction that occur leading to abnormalities in impulse formation and conduction in the myocardium.

It has a lot and different systemic symptoms (complex with variety of symptoms):

Sinus bradycardia.

Tachycardia:

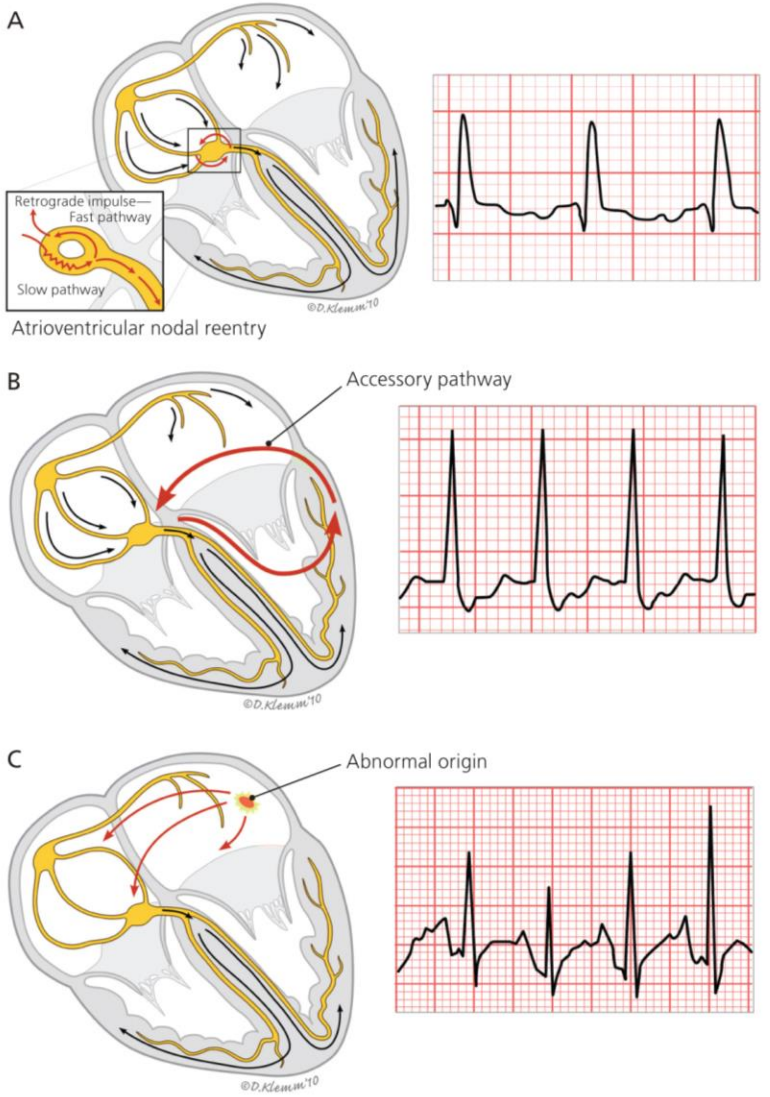
A. Sinus tachycardia. B. ventricular tachycardia.

C.Atrial or ventricular premature depolarization. D.Atrial flutter.

It can be due different causes:

1. Ectopic peacemaker (like AV node firing instead of SA).

2. Traveling impulses through extra pathways; leading to deviation in polarization (ex. AV reentry or Wolff-Parkinson's-white syndrome (WPWS)).



Types of Cardiac Arrhythmias

Abnormalities of Impulse Formation:

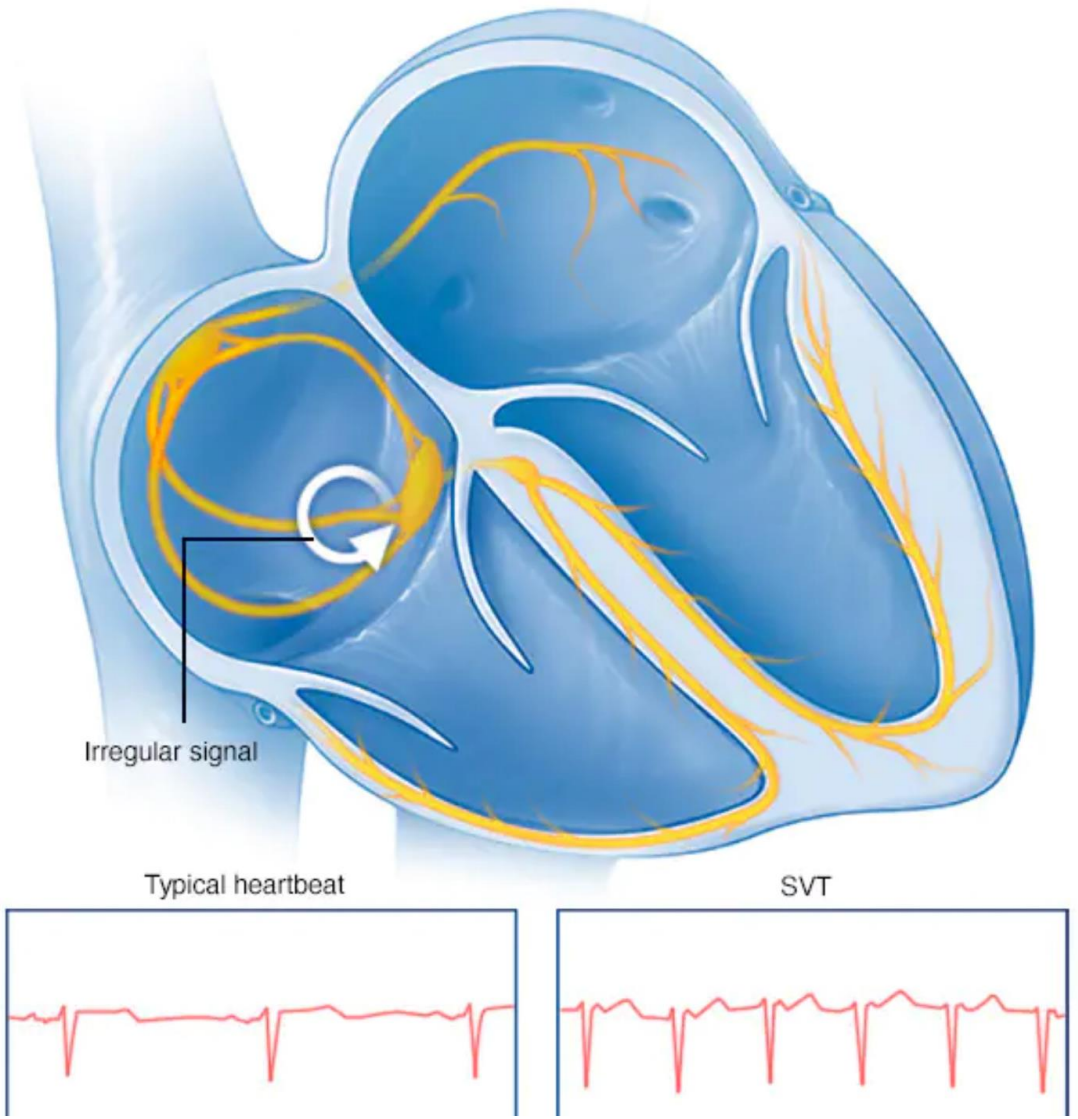
Rate disturbances [Tachycardia or bradycardias].

Triggered automaticity [Automaticity is the property of cardiac cells to generate spontaneous action potentials].

Abnormalities of Impulse Conduction:

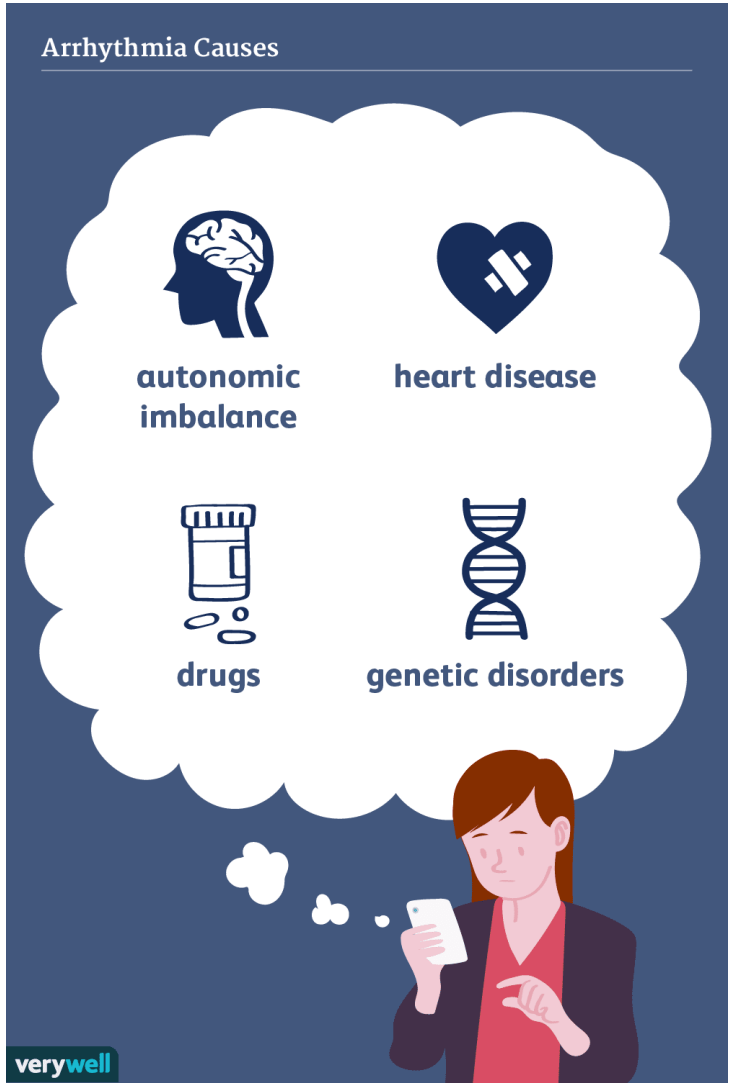
Blocks.

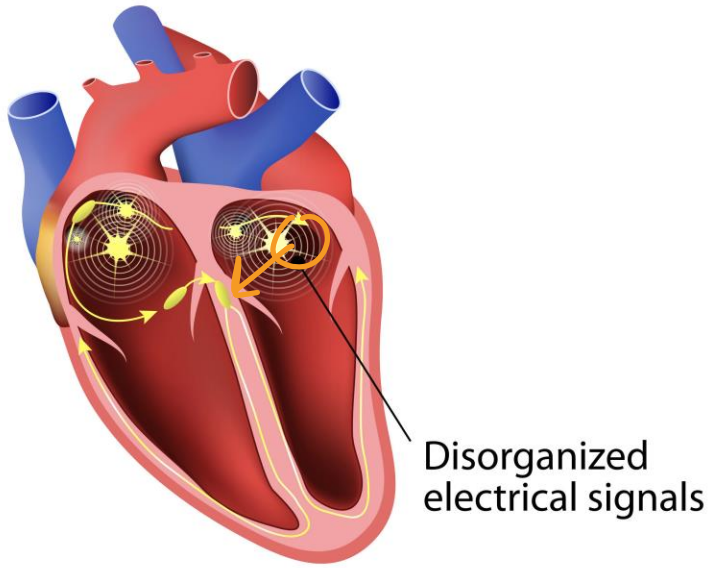
Reentry.



Cardiac Causes of Arrhythmias

- Ischemic heart disease.
- Inflammation.
- Trauma e.g. heart surgery.
- Congestive heart failure.
- Hypotension.





Non-Cardiac Causes of Arrhythmias

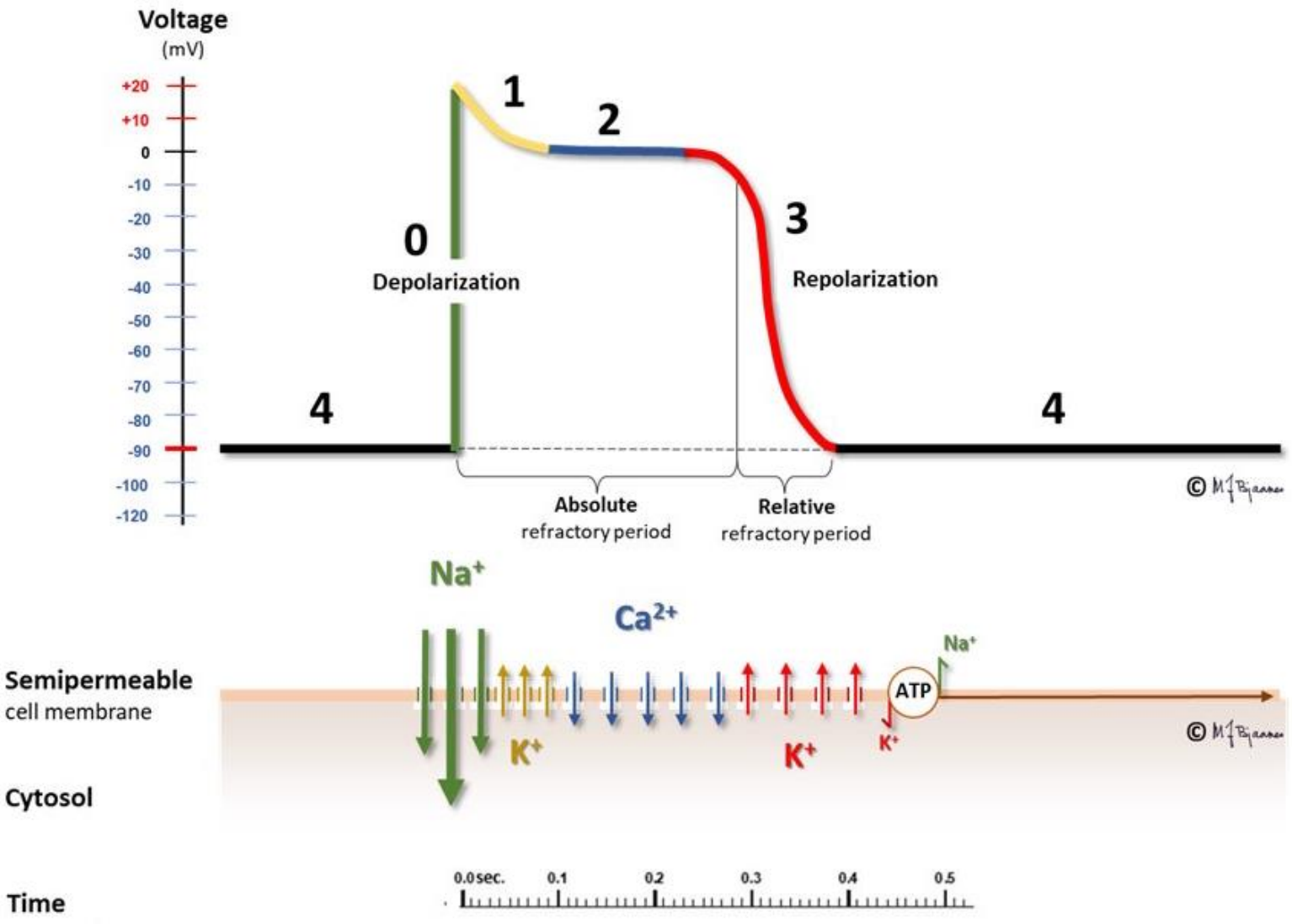
Electrolyte imbalance.

Acid base imbalance.

Hypoxia.

Drugs: Digitalis, Anesthetics, Tricyclic, Diuretics, Bronchodilators.

GI and Neural Reflexes.



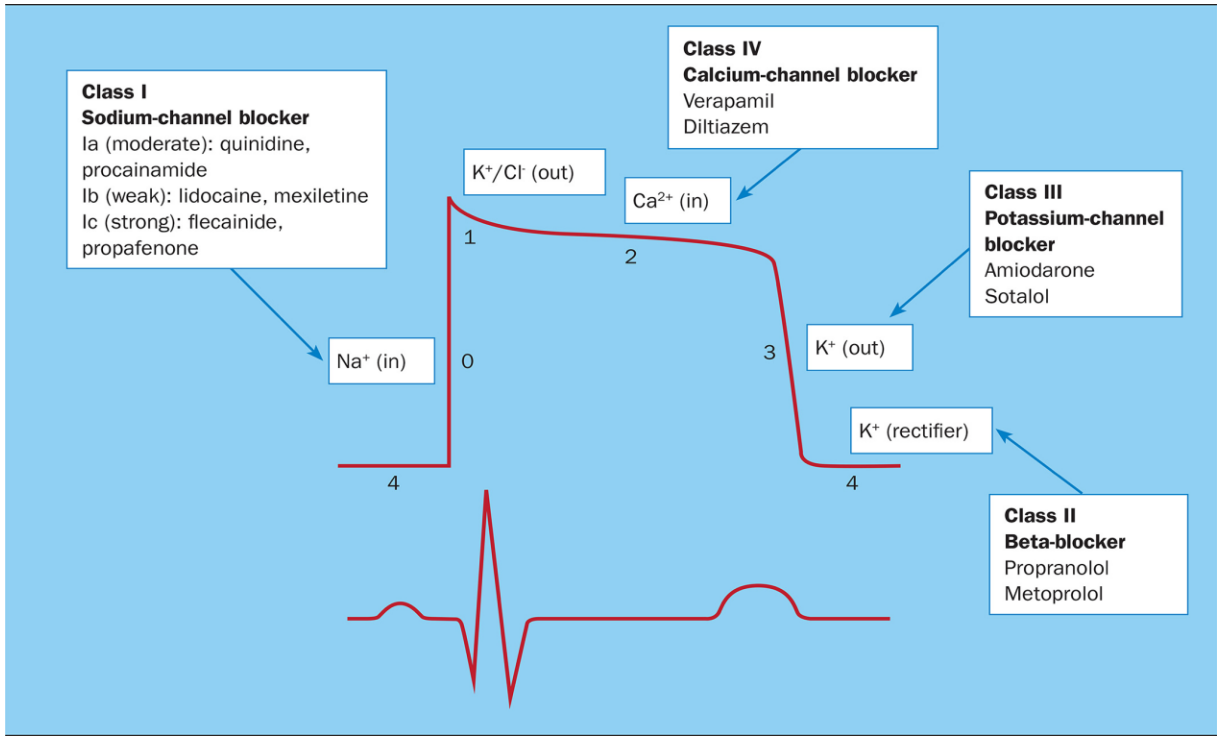
Anti-arrhythmic Drugs

Effect of drugs on automaticity:

Most of the arrhythmic agents suppress automaticity by blocking either sodium or calcium channels to reduce the ratio of these ions to potassium, thus result in a reduction in the depolarization or diastolic and raises the threshold of discharge to a less negative voltage.

Effect of drugs on conduction abnormalities:

Prevent reentry by slowing conduction and/or increasing the refractory period,



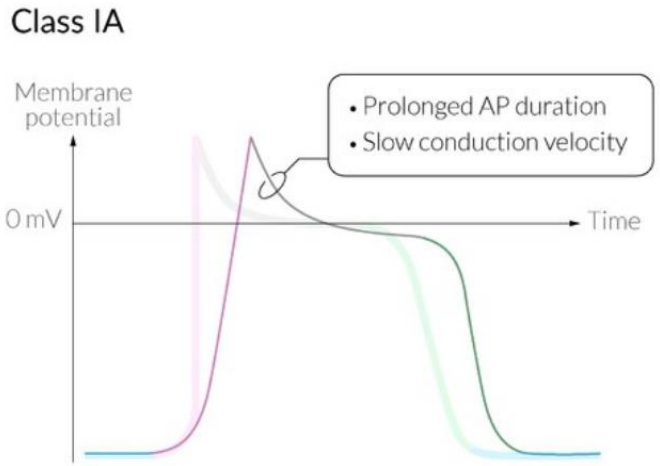
Class I

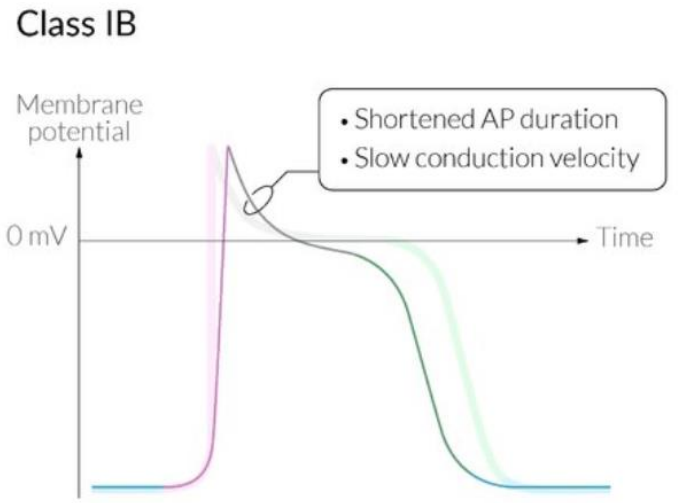
Agents with local anesthetic properties; blockade of Na channels:

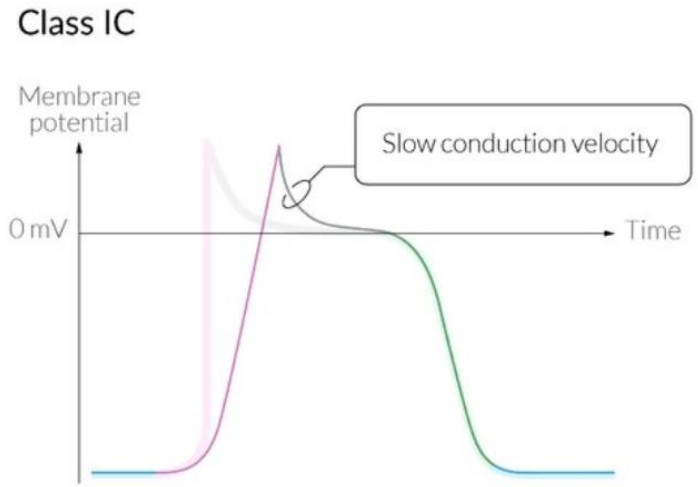
A. Procainamide, Quinidine (lengthen action potential duration).

B. Lidocaine, Phenytoin (abbreviate action potential duration).

C. Flecainide (produces no change in action potential duration, but marked depression of conduction velocity).







Class IA : Procainamide

Uses: Atrial and ventricular arrhythmias (acute MI).

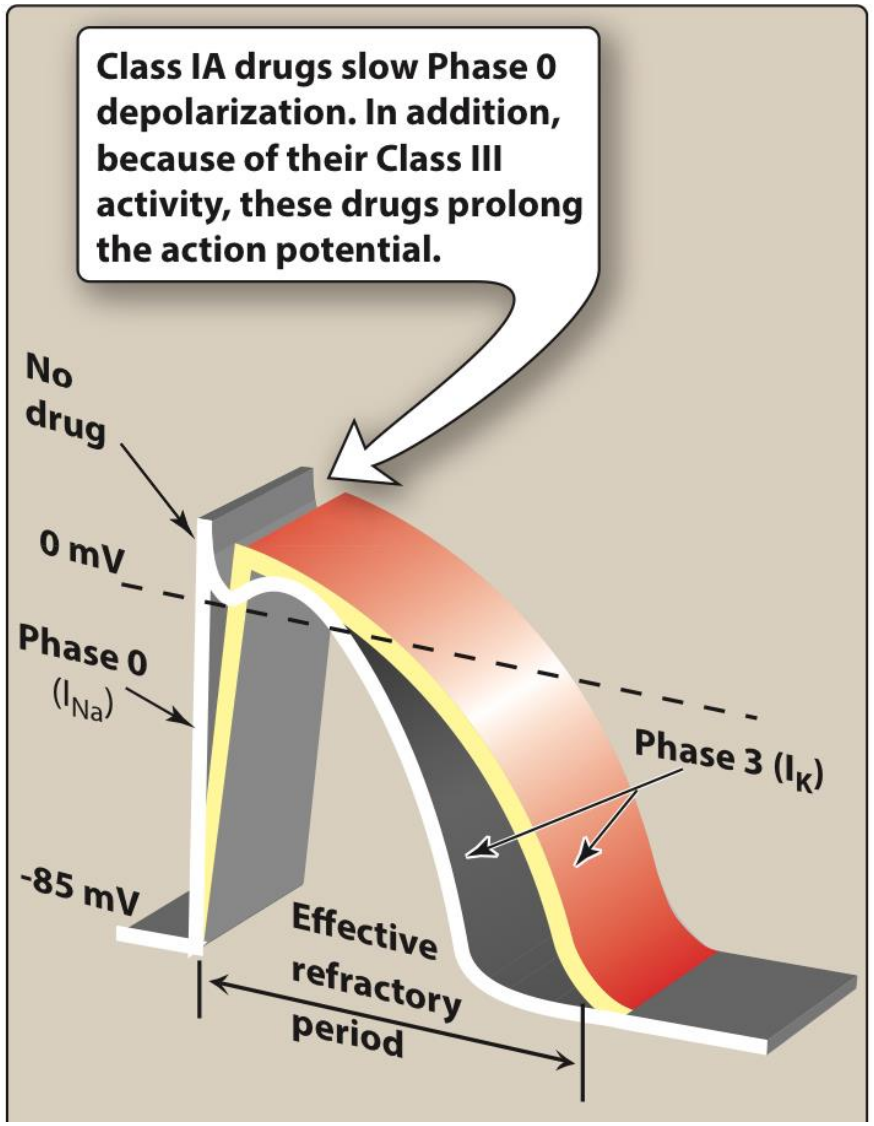
Procainamide structurally related to the local anesthetic procaine.

Major electrophysiological effects in heart:

A. Decrease automaticity – decrease phase 4 spontaneous depolarization and increase threshold.

B. Decrease conduction velocity throughout heart due to decrease in membrane responsiveness (Vmax) by decreasing the sodium leakage.

C. Increase in action potential duration and refractory period in atrial and ventricular cells – blocks K+ efflux.



Class IA : Procainamide

Other Cardiac Effects:

A. ECG may be greatly altered; P-R, QRS and QT Intervals are prolonged.

B. Possible excessive slowing of conduction.

Adverse Effects:

A. Hypotension with large i.v. doses.

B. Lupus erythematosis-like (auto-immune) syndrome mayoccur.

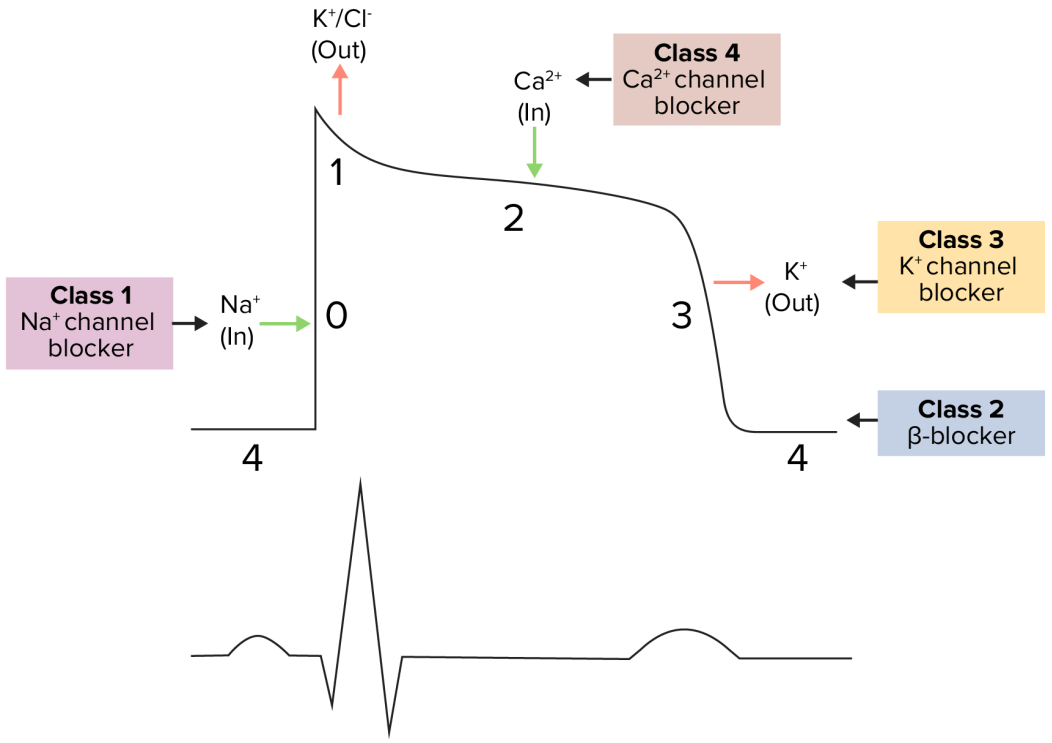
C. Prolongs QT interval, possible "torsades de pointe"

Pharmacokinetics:

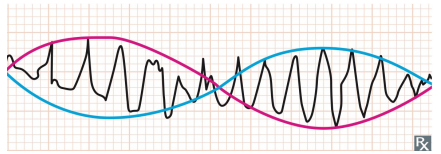
A. Can be given orally, I.V., or I.M.

B. Has short T1/2 (3-4 hrs); frequent administration or use sustained release formulation.

C. Some individuals rapidly acetylate procainamide (NAPA - cardioactive metabolite).



Torsades de pointe

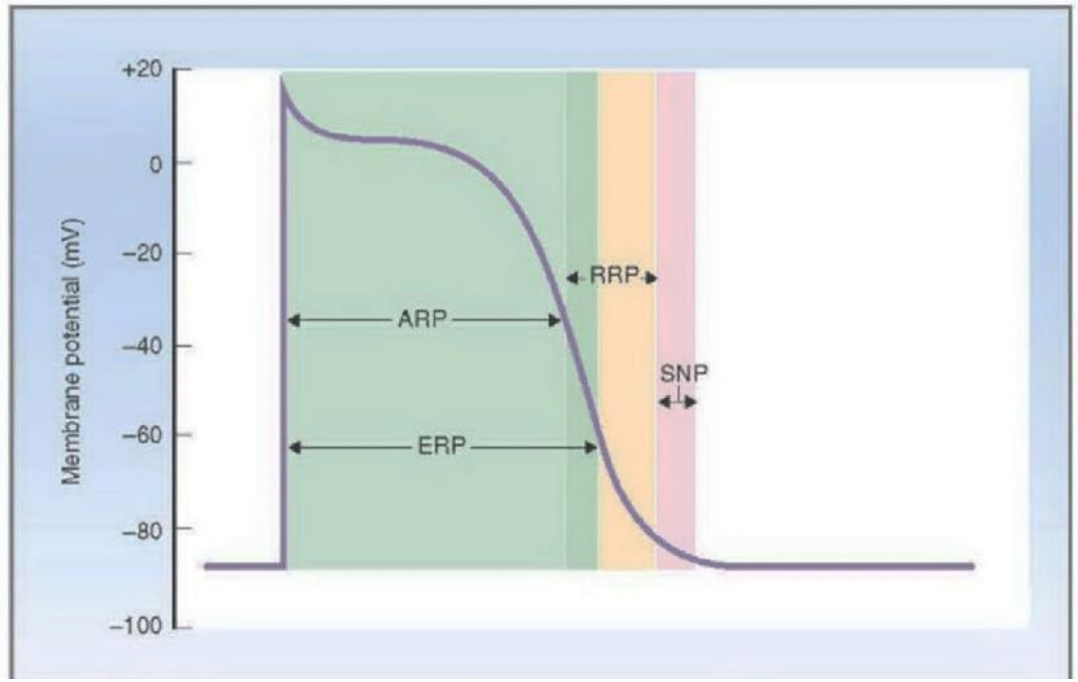


Refractory Period

Refractory period is the time interval between two impulses until the second impulse propagate.

It is a target for certain drug such as acetylcholine which lengthens the period on the other hand the norepinephrine which shortens the time.

In case of a refractory period propagate after an effective refractory period but still the heart did not recover the full function this will cause decrease in conduction velocity.

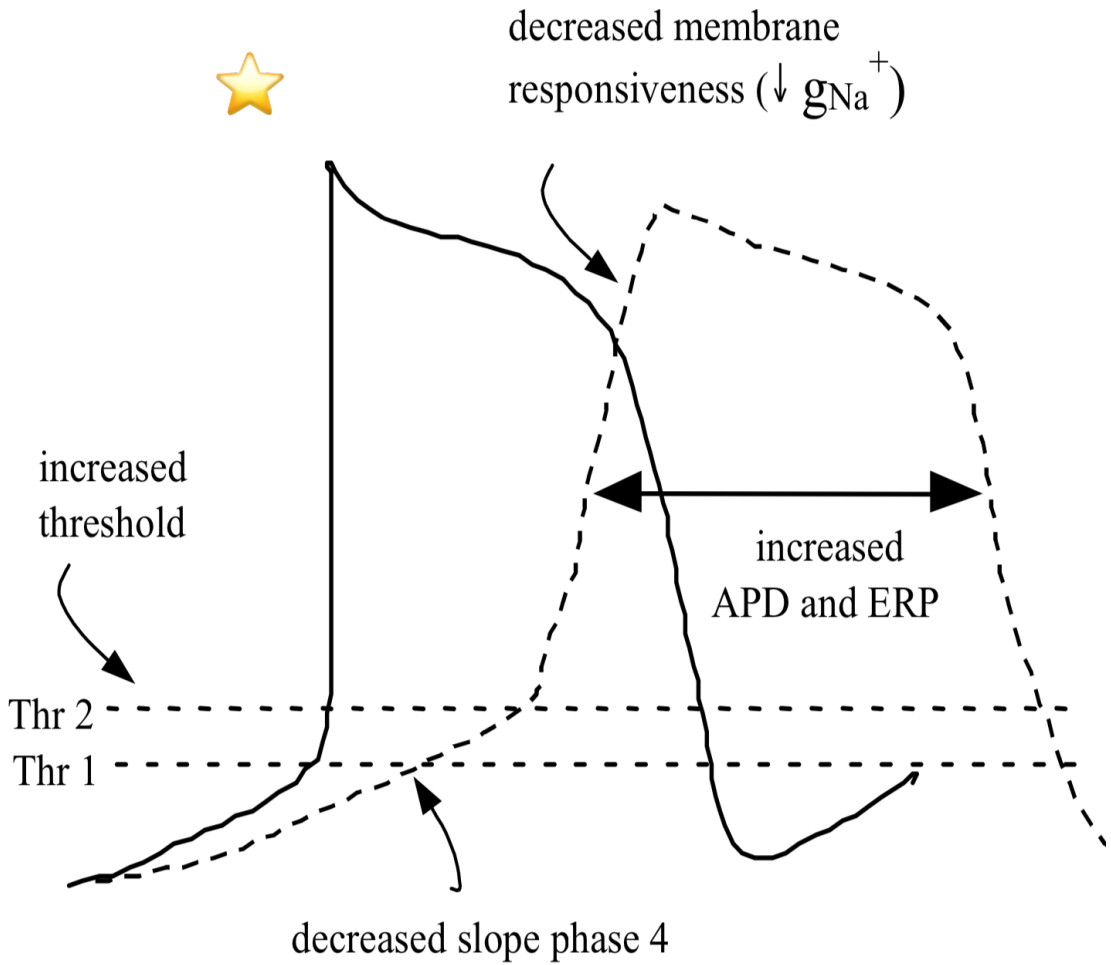


Class IA : Quinidine

Quinidine is also a class 1A with similar effects as procainamide, but it can precipitate fatal ventricular fibrillation.

It has drug toxic potential when interacting with calcium channels blockers such as Verapamil.

It has been replaced by other drugs.



Class IB : Lidocaine

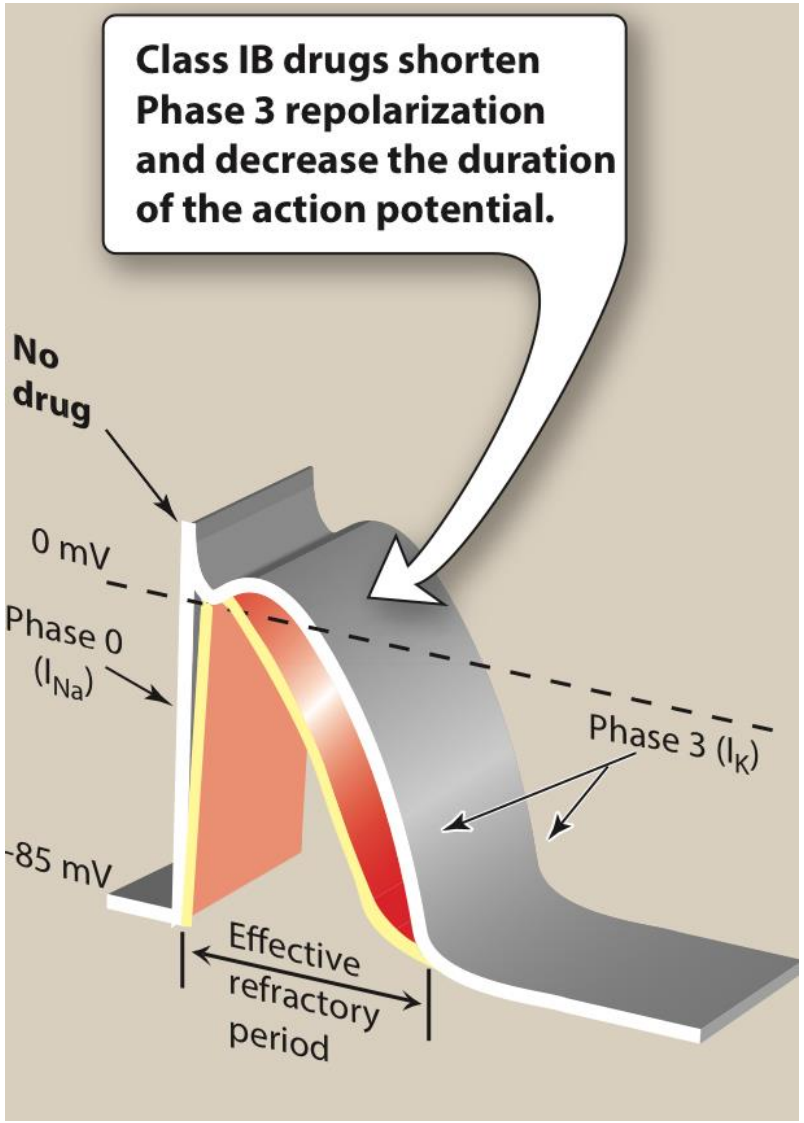
Lidocaine (Xylocaine®) is used to teat ventricular arrhythmias caused by myocardial infarction.Prominent use in emergency treatment of venticular arrhythmias.

Major Electrophysiological Effects:

A. Depresses automaticity (phase 4 slope).

B. Shortens ventricular action potential (AP) duration and effective refractory period (RP).

C. Usually no effect upon conduction velocity.



Class IB : Lidocaine

Toxic or Adverse Effects:

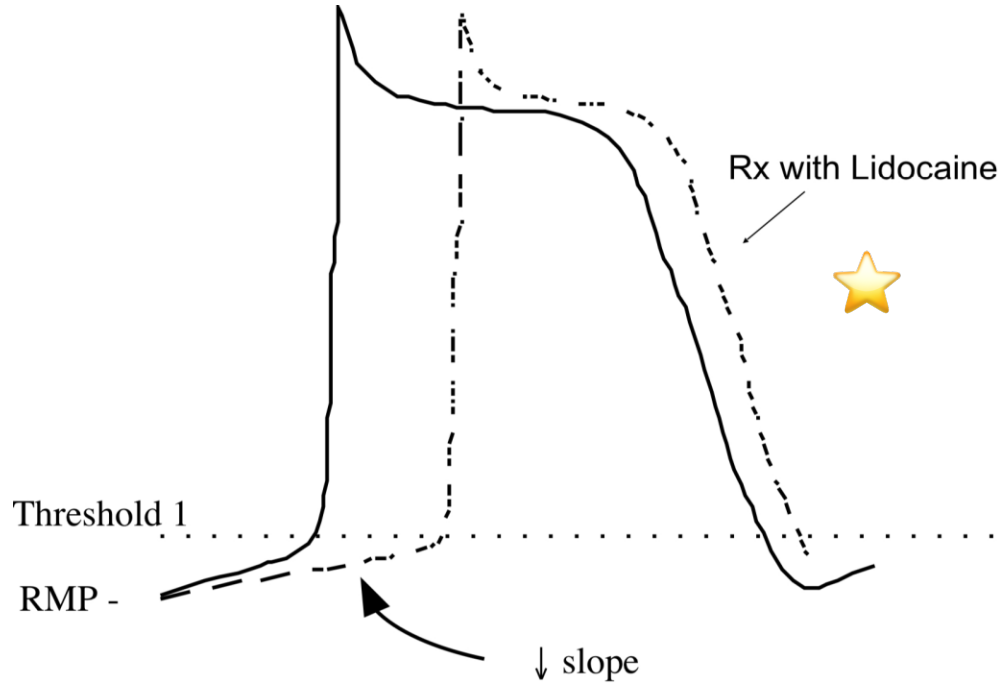
Involving central nervous system: disorientation, convulsions, drowsiness, coma.

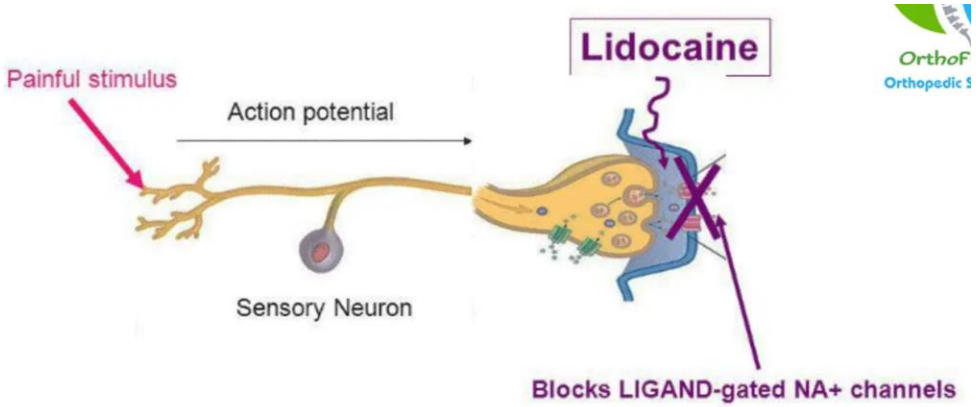
Pharmacokinetics:

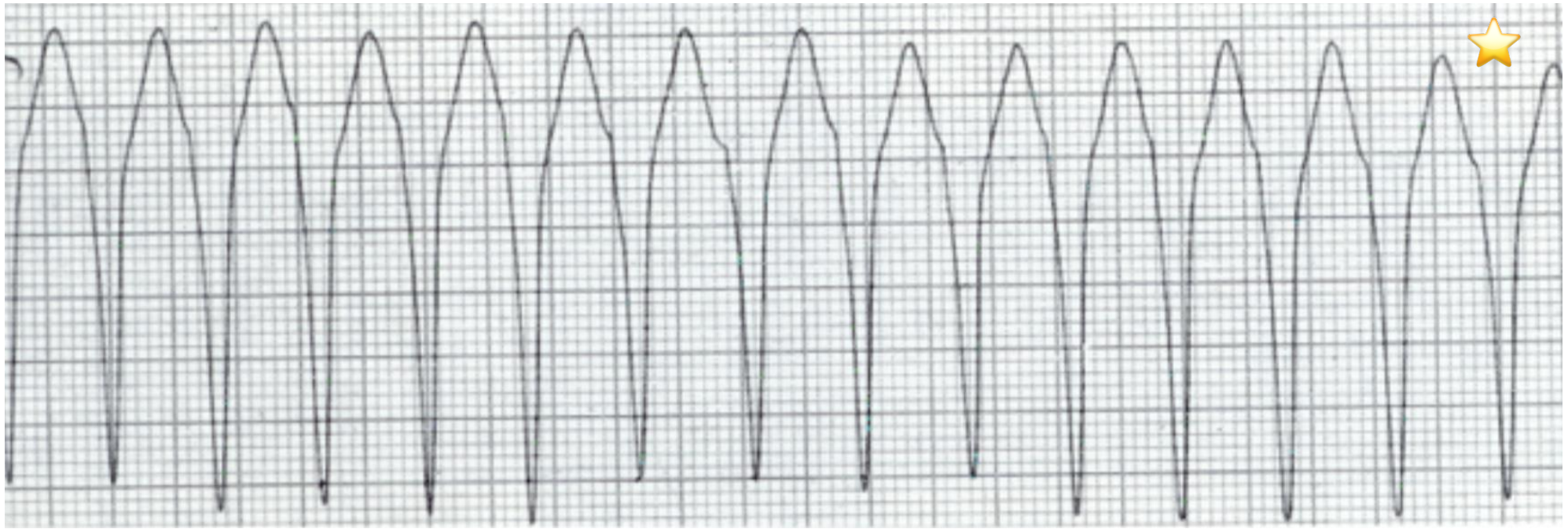
Given I.V. or I.M. only-Rapidly inactivated by liver; plasma T1/2 of 0.5 – 1 hour

Due to high first pass effect on liver it must be given IV or IM other types from same family can be given orally such (mexiletine and tocainide).

Used as an local anaesthetic (be careful for patient with arrhythmias since it can blocks sodium channels).







Class IB : Lidocaine

Used mainly with : Ventricular Tachycardia.

Lidocaine - Rx of VT / prevent Vfib after cardioversion.

Class IC : Flecainide

General Properties:

A. Marked affinity for and blockade of Na+ channels.

B. Marked slowing of conduction velocity (shallow phase oslope).

C. Little change in AP duration.

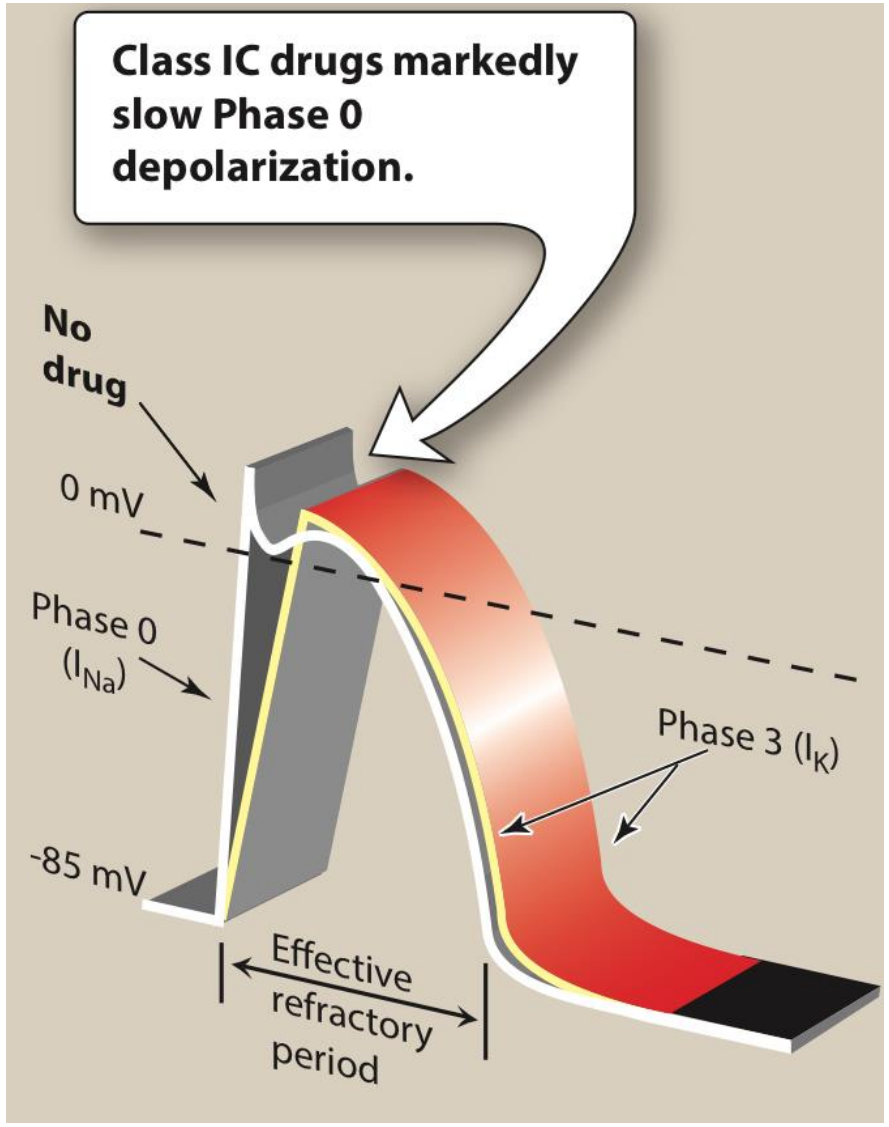
D. Useful in resistant, life-threatening ventricular arrhythmias.

Propafenone is a drug with same affect (wide spectrum antiarrhmatic)

Toxicity:

Proarrhythmic, particularly in MI patients.

Blurred vision.



CLASS II : β Blockers

Propranolol (Inderal®), Metoprolol (Lopressor®), Esmolol (Brevibloc®), Carvedilol – β and α adrenergic blocking agent.

Cardiac actions: blocks effects of catecholamines on:

A. Automaticity (S-A node and elsewhere; heart rate)

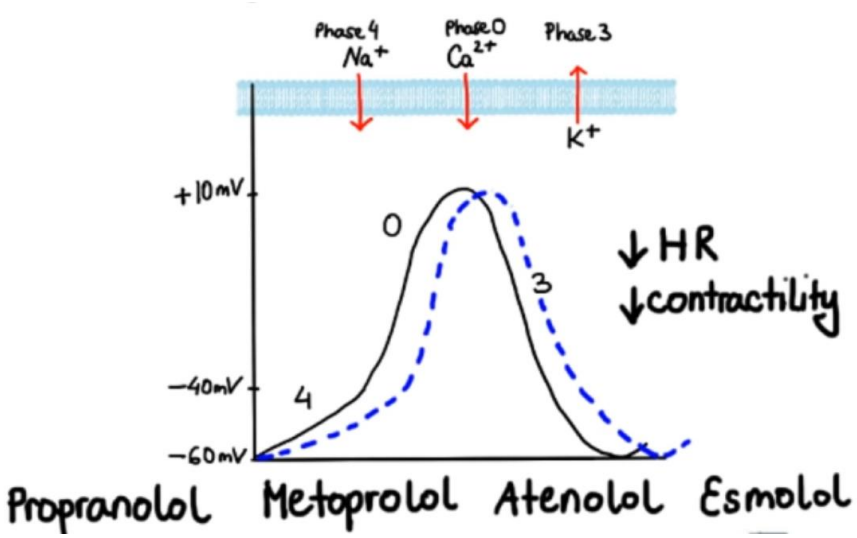
B. A-V conduction.

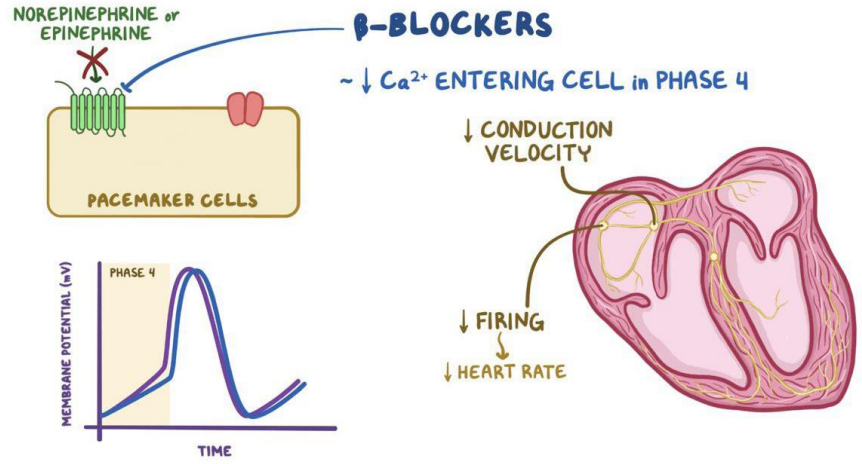
C. Refractory period

Electrophysiological effects:

Quinidine-like effects on membranes.

Depression of conduction velocity.





CLASS II : β Blockers

Uses:

A. Paroxysmal atrial tachycardia.

B. Arrhythmias associated with hydrocarbon anesthetics.

C. Arrhythmias resulting from tricyclic antidepressants or L-dopa.

D. Pheochromocytoma.

Adverse effects:

A. Negative inotropic action on heart.

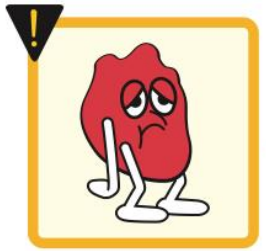
B. Bronchospasm.

C. Depression and nightmares (lipid-soluble agent).

D. Rebound increase in sensitivity to β-adrenergic agonists onwithdrawal.

E. A-V block.

Hypotension



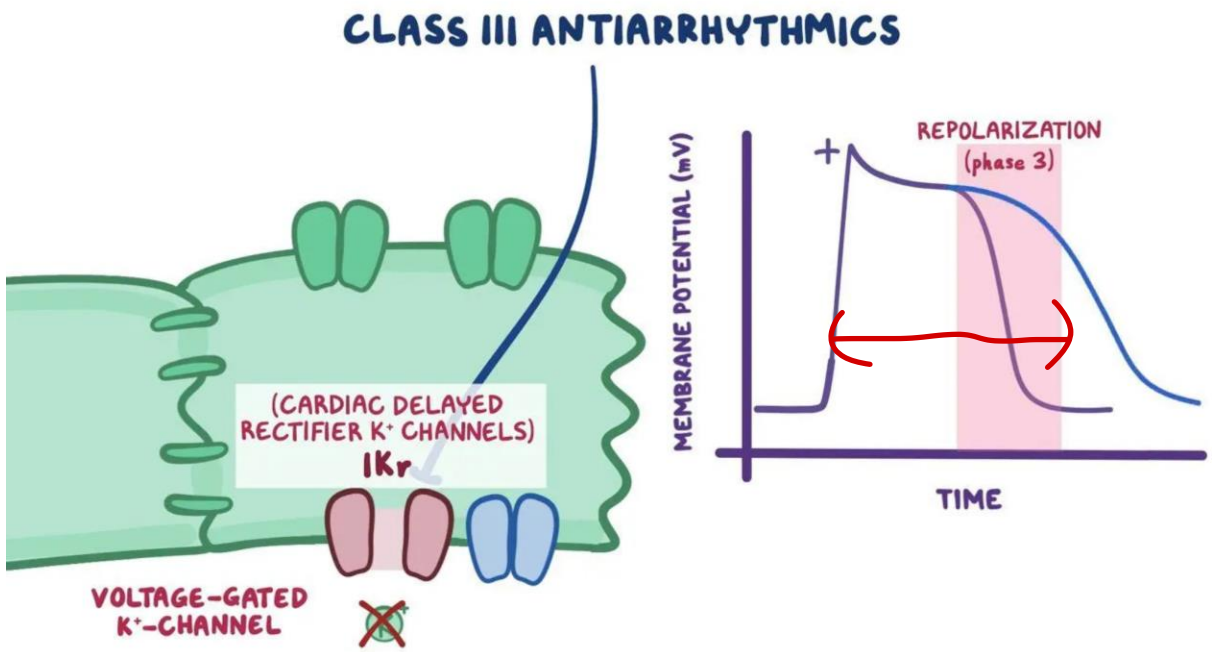
Bradycardia

Fatigue

Insomnia

Class III

Agents which prolong refractory period;
Amiodarone, Sotalol, Dofetilide



Class III : Amiodarone

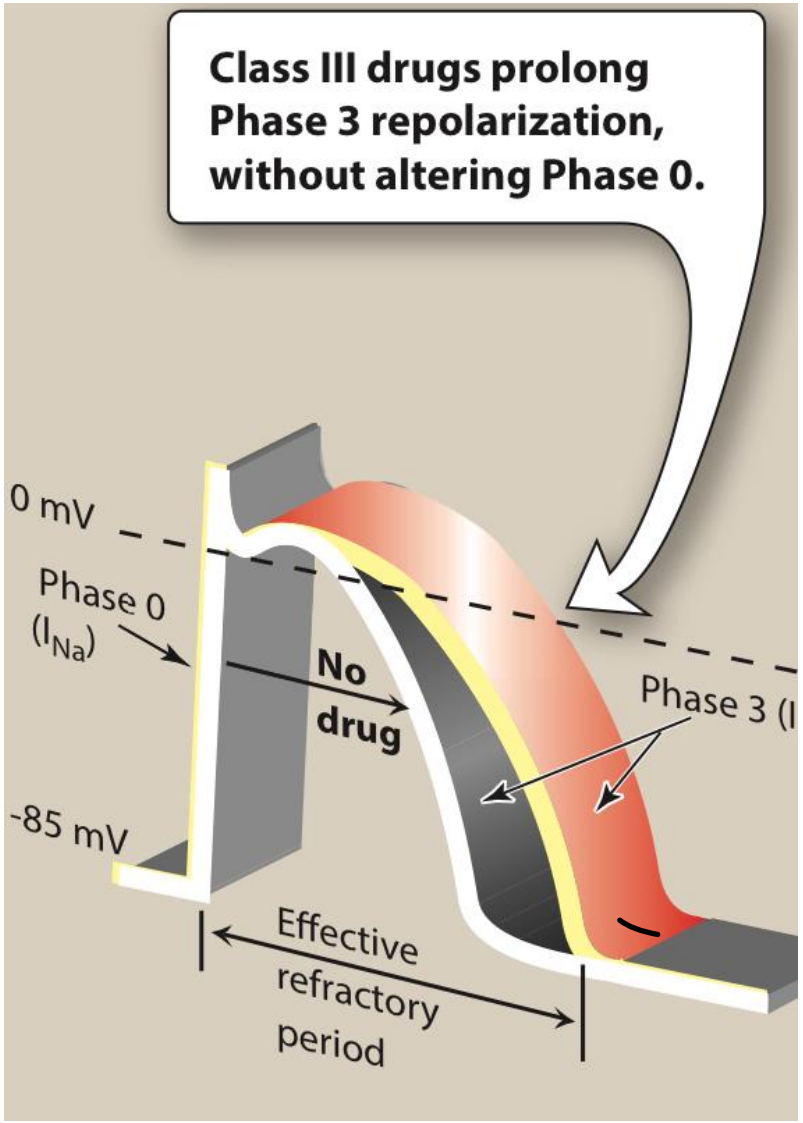
AMIODARONE (Cordarone ®): Originally a coronary vasodilator; very effective in resistant ventricular arrhythmias but dangerous.

Electrophysiologic actions:

A. Blocks outward K+ current.

B. Marked prolongation of refractory period all over the heart (including the accessory A-V pathway associated with WPW syndrome). Without affecting the phase o or resting membrane potential.

C. Efficacy for life-threatening arrhythmias.



Class III : Amiodarone

Adverse effects:

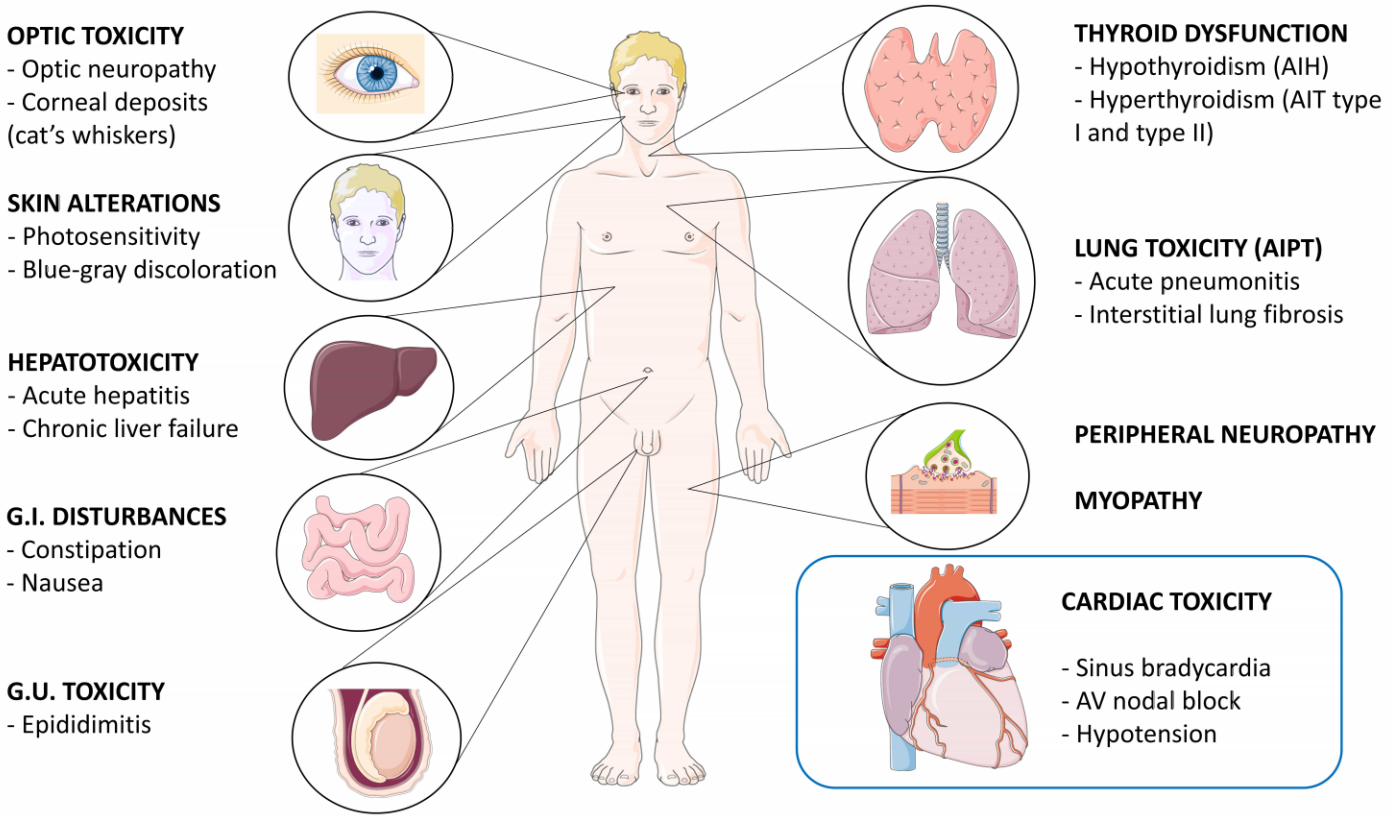
A. Yellowish brown corneal deposits.

B. Slate blue color to skin with long use.

C. Pulmonary fibrosis.

D.Thyroid dysfunction.

E. Risk of 'torsade' less than with other K+ current blockers.



Class III : Amiodarone

Also used as antianginal agent (coronary vasodilator).

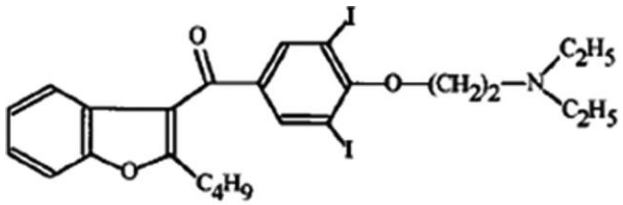
This drug contain iodine and related structurally to thyroxine.

It resembles classes 1, 2 and 4 in action.

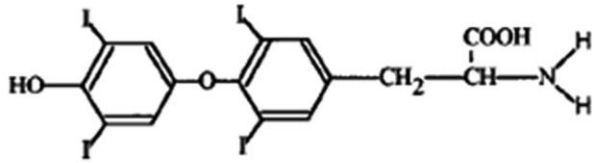
The dominant effect is to prolong the refractory period and action potential period.

Unlike class 1 drugs, it doesn't prolong the QT interval (used with moderate to sever heart failure patients).

Used to treat severe refractory supra-ventricular tachyarrhmias.



Amiodarone



Thyroxine (T_4)

Class III : Amiodarone

- Pharmacokinetics:
- A. Long half-life (~100 days) makes dosing difficult.
- B. i.v. form available for acute therapy
- Uses:
- A. Efficacy for resistant life-threatening arrhythmias (VT / VF).
- B. Efficacy in atrial fibrillation.
- C. A-V re-entry arrthythmias associated with WPW syndrome.

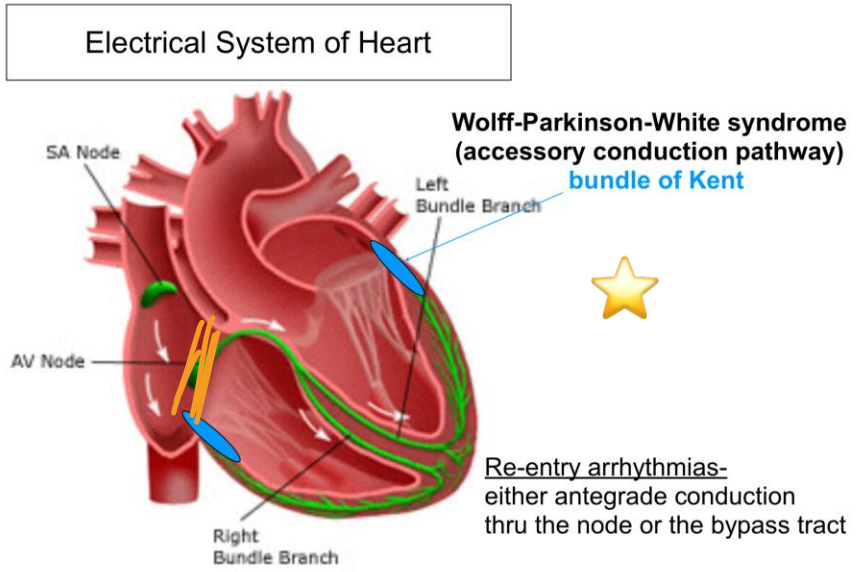
Wolff-Parkinson-White (WPW) and reentry arrhythmia

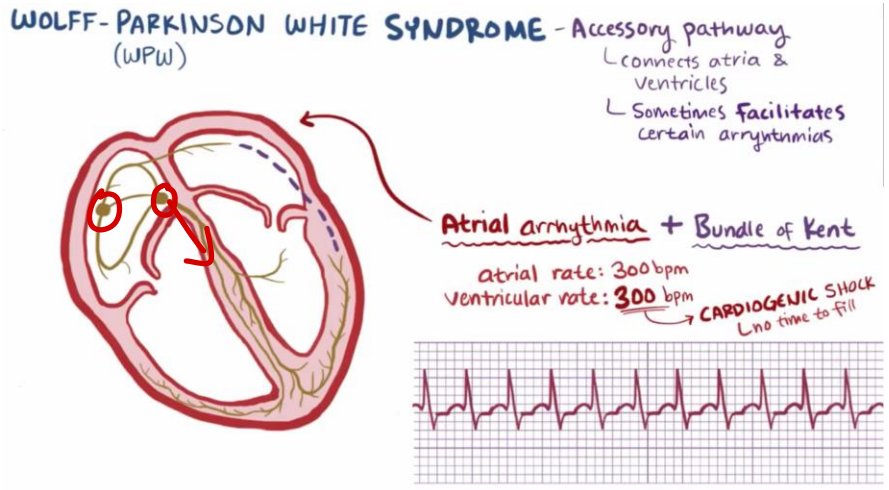
A reentry arrhythmia is a self-sustaining cardiac rhythm abnormality in which the action potential propagates in a manner analogous to a closed-loop circuit.

It is a disorder of impulse conduction and is discrete from disorders of impulse generation such as automaticity or triggered activity.

Wolff-Parkinson-White (WPW) syndrome is a relatively common heart condition that causes the heart to beat abnormally fast for periods of time.

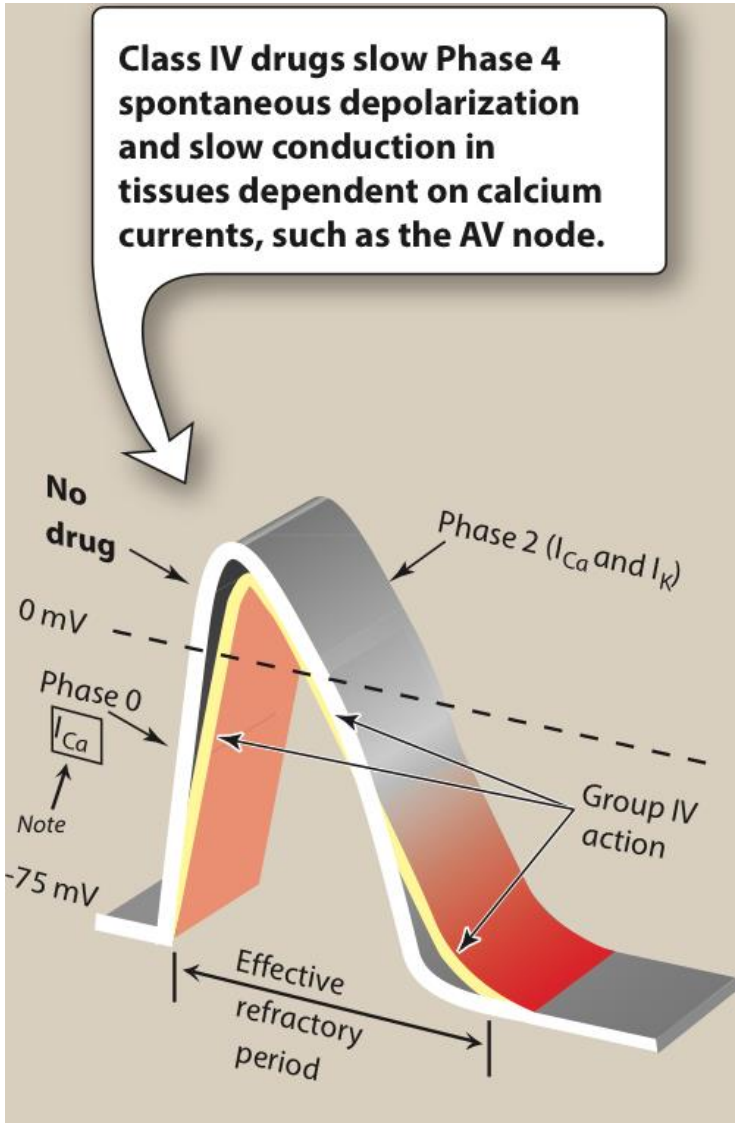
This causes an extra electrical connection in the heart (due to injury or congenital problem).





Class IV

Class IV - Ca++ channel antagonists; Verapamil, Diltiazem



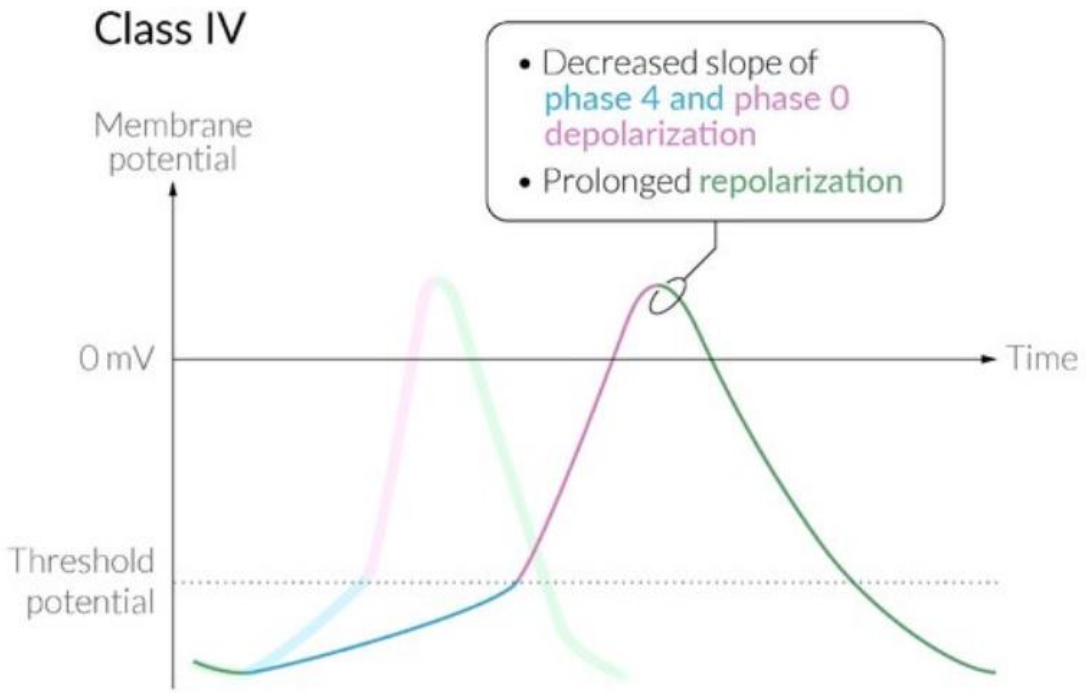
Class IV : Verapamil

Verapamil (Isoptin®)

Electrophysiological actions:

A. Inhibits transmembrane fluxes of Ca++ mediated slow response activity.

B. Suppresses Ca ++ fluxes in S-A and A-V nodes; prolongs A-V node refractory period.



Class IV : Verapamil

Adverse effects:

A. Bradycardia.

B. Complete A-V block.

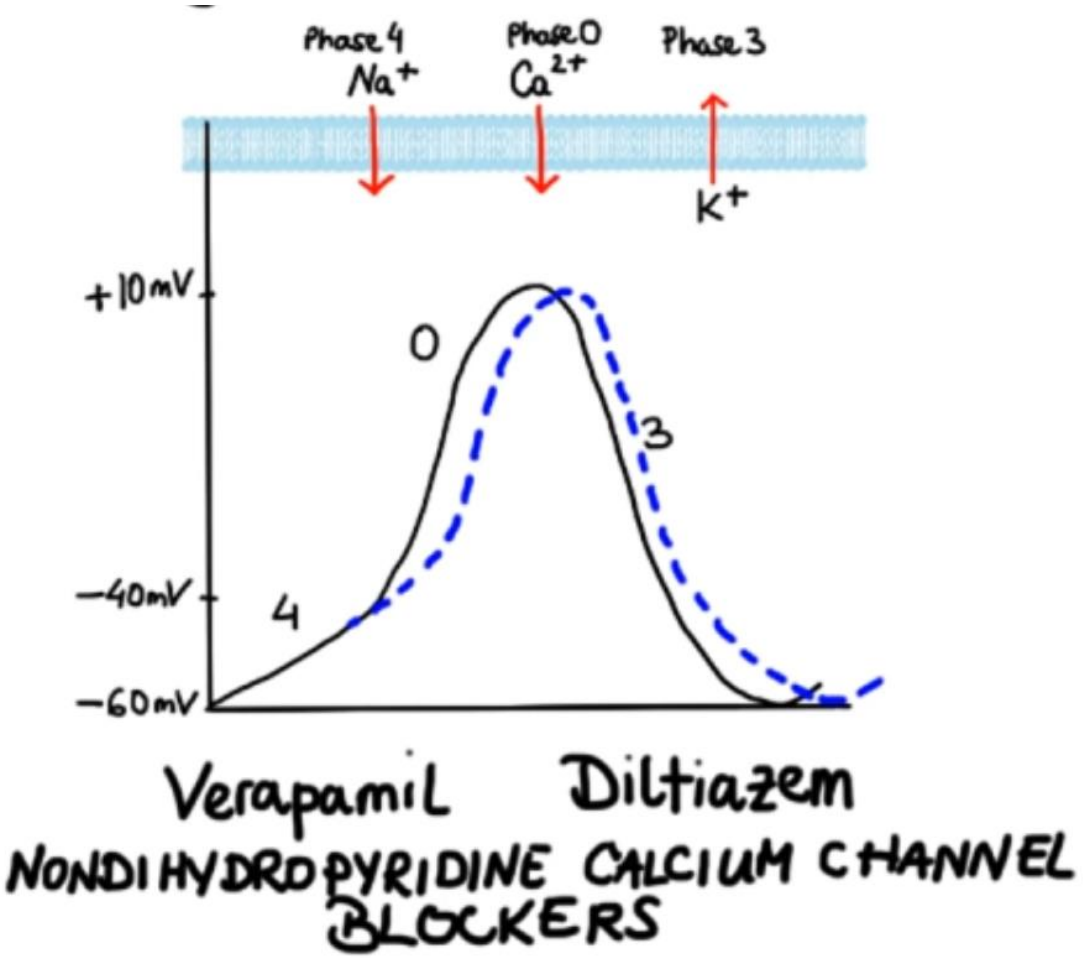
C. Depressed cardiac contraction and hypotension.

Uses:

A. Paroxymal atrial tachycardia.

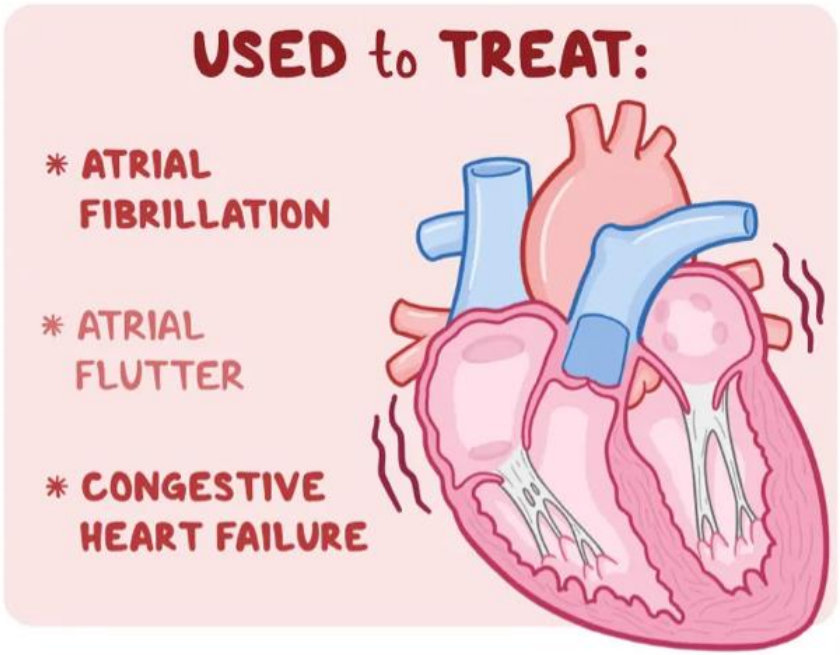
B. Atrial fibrillation and flutter.

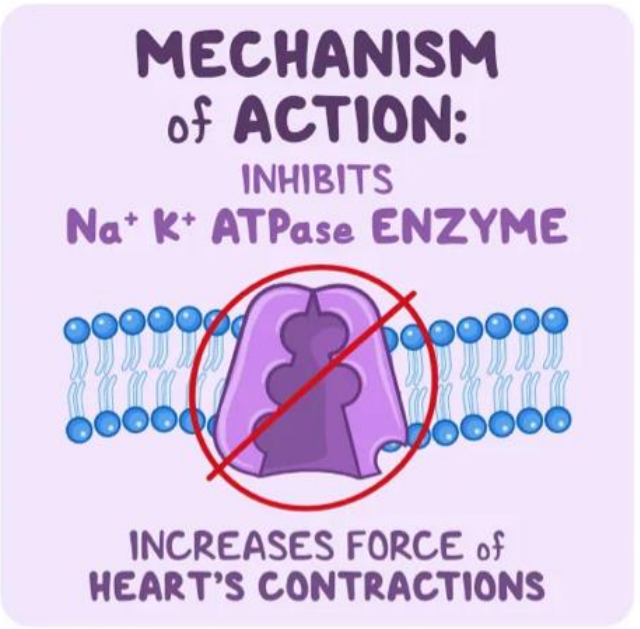
C. A-V nodal rhythms [used with re-entry arrhythmias also].



Miscellaneous Agents

- Digitalis - sensitizes baroreflexes to increase vagal tone and depress sympathetic activity to heart.
- Adenosine - brief slowing of AV conduction.





Digitalis Used For:

Congestive Heart Failure: Increases force of myocardial contraction, and Reduce reripheral vascular resistance (Afterload).

Atrial Fibrillation & Flutter: Increases A-V Refractory Period.

Digitalis

- Electrophysiological actions:
- A. Prolong A-V refractory period.
- B. Effect largely through sensitization of baroreflex receptors; Enhancement of vagal tone and withdrawal of sympathetic nerve activity.
- Therapeutic action:
- Reduces ventricular rate by making A-V node more refractory to the numerous atrial impulses.
- Adverse actions:
- Arrhythmias (PVCs, AV conduction block), nausea, and blurred vision – often with halos.

Adenosine

ADENOSINE (Adenocard®):

Concentration of adenosine rises with hypoxia as ATP production is reduced.

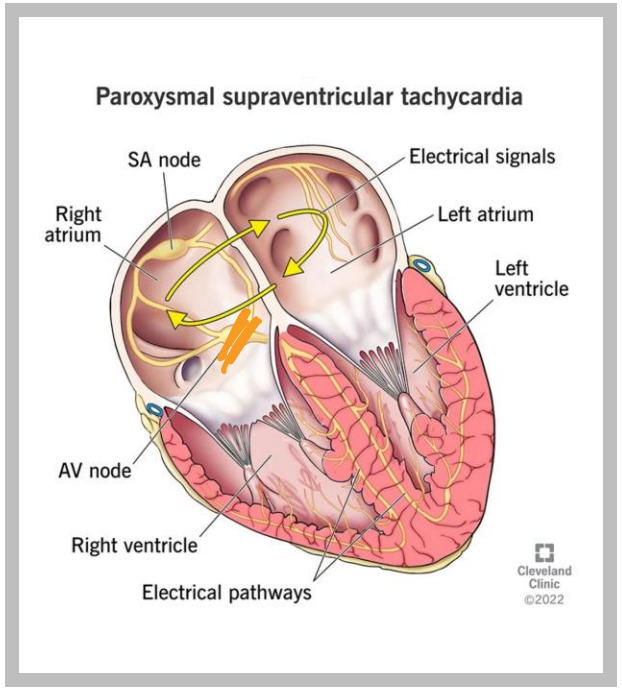
Use in paroxysmal supraventric tachycardias (PSVT).

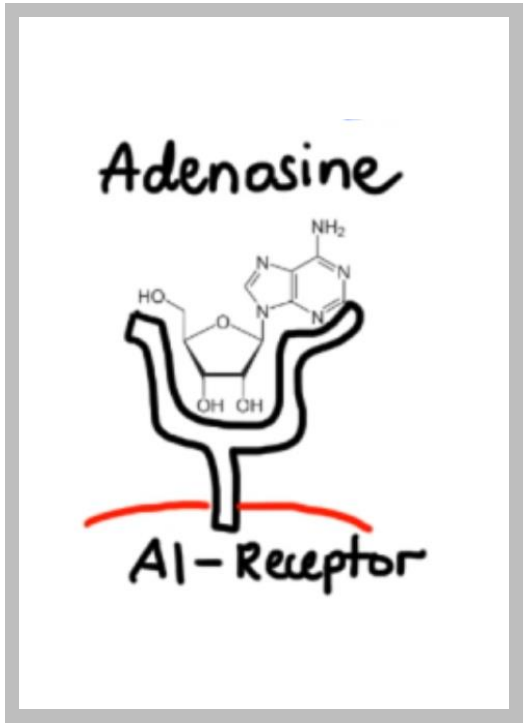
Major actions:

A. Acts on A1 receptors to inhibit adenylate cyclase (↓cAMP).

B. Activates K+ currents and hyperpolarizes nodes.

C. Slows conduction in AV node.





Adenosine

Pharmacokinetics:

A. rapid onset of action, i.v. – 10-20 seconds.

B. very short half life – 10 seconds.

Adverse Effects:

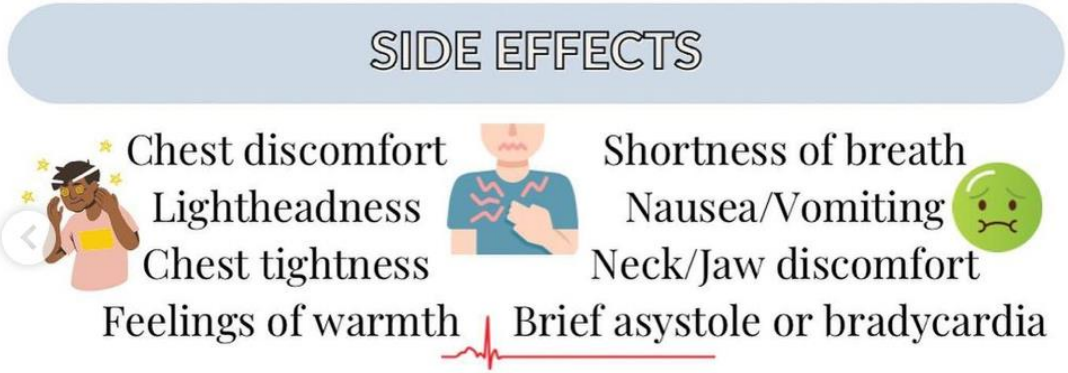
A. hypotension, facial flushing, headache.

B. Possible "symptoms" of angina.

C. bronchoconstriction, arrhythmias.

Uses:

Treatment of PSVT (nodal reentry) / diagnosis of supraventricular vs ventricular tachycardia.



class	mechanism	action	notes
I	Na^+ channel blocker	Change the slope of phase 0	Can abolish tachyarrhythmia caused by reentry circuit
II	β blocker	↓heart rate and conduction velocity	Can indirectly alter K and Ca conductance
III	K^+ channel blocker	1. ↑action potential duration (APD) or effective refractory period (ERP). 2. Delay repolarization.	Inhibit reentry tachycardia
IV	Ca^{++} channel blocker	Slowing the rate of rise in phase 4 of SA node(slide 12)	↓conduction velocity in SA and AV node