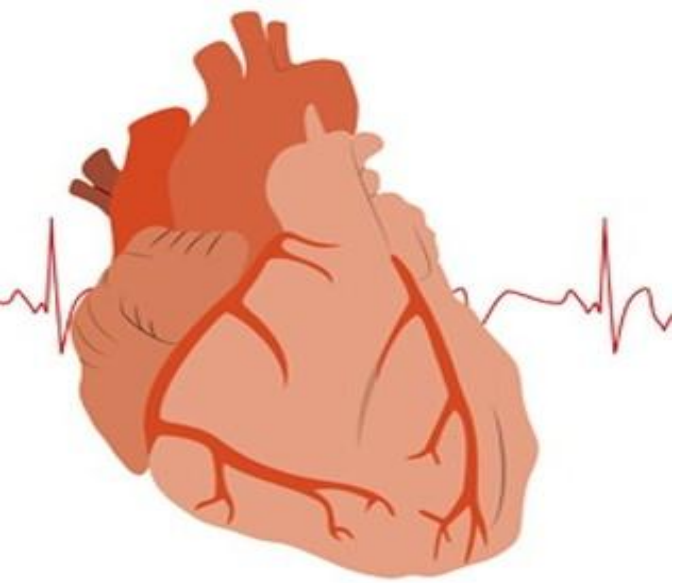
Anti-arrhythmic drugs

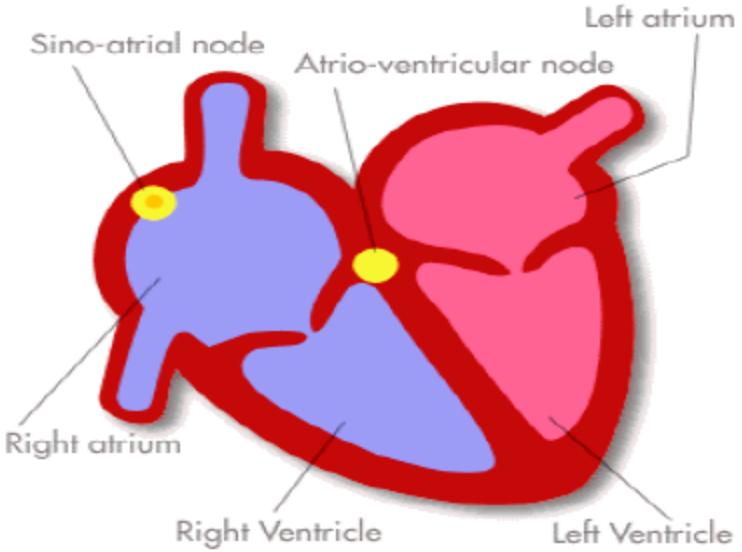


Mr. Bairagi S M

Department of Pharmacology

MES'S College of Pharmacy, Sonai

- # A-RHYTHM –IA
- *Defn-* Arrhythmia is deviation of heart from normal RHYTHM.



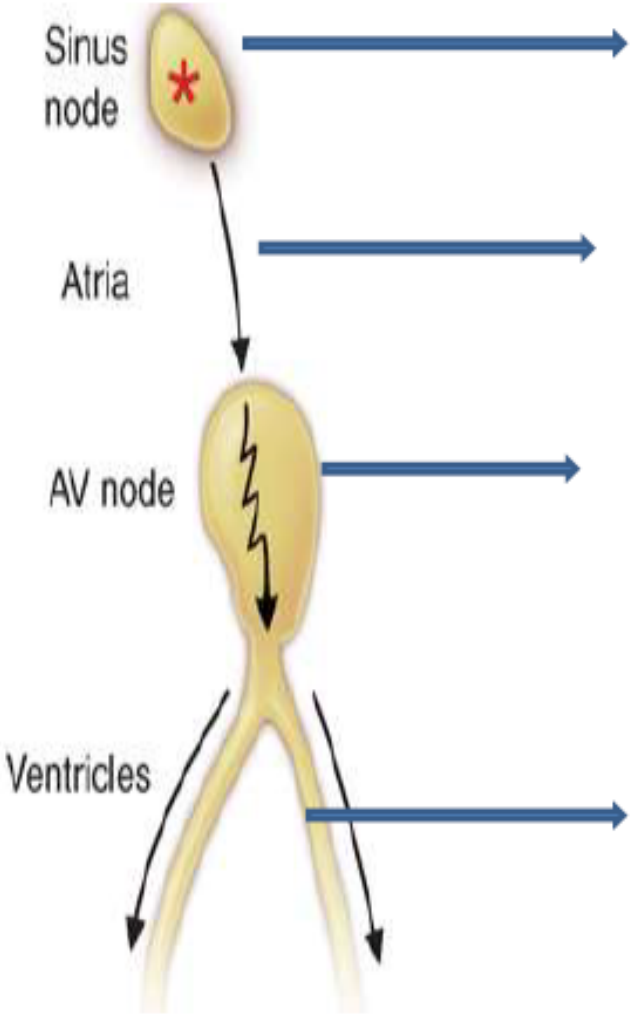
- *RHYTHM*

1) HR- 60-100
2) Should origin from SAN
3) Cardiac impulse should propagate through normal conduction pathway with normal velocity.

• CLASSIFICATION OF ARRHYTHMIAS

500	Atrial fibrillation
350	Atrial flutter
200	Paroxysmal TA
150	Simple tachyarrythmia
100 60	Normal range
40	Mild bradyarrhythmias
20	moderate BA
	Severe BA

ARRHYTHMIAS



Sinus arrythmia

Atrial arrhythmia

Nodal arrhythmia (junctional)

SVT

Ventricular arrhytmia

Electrophysiology of cardiac tissue

- Impulse generation and transmission
- Myocardial action potential
- Depolarization and repolarization waves as seen in ECG

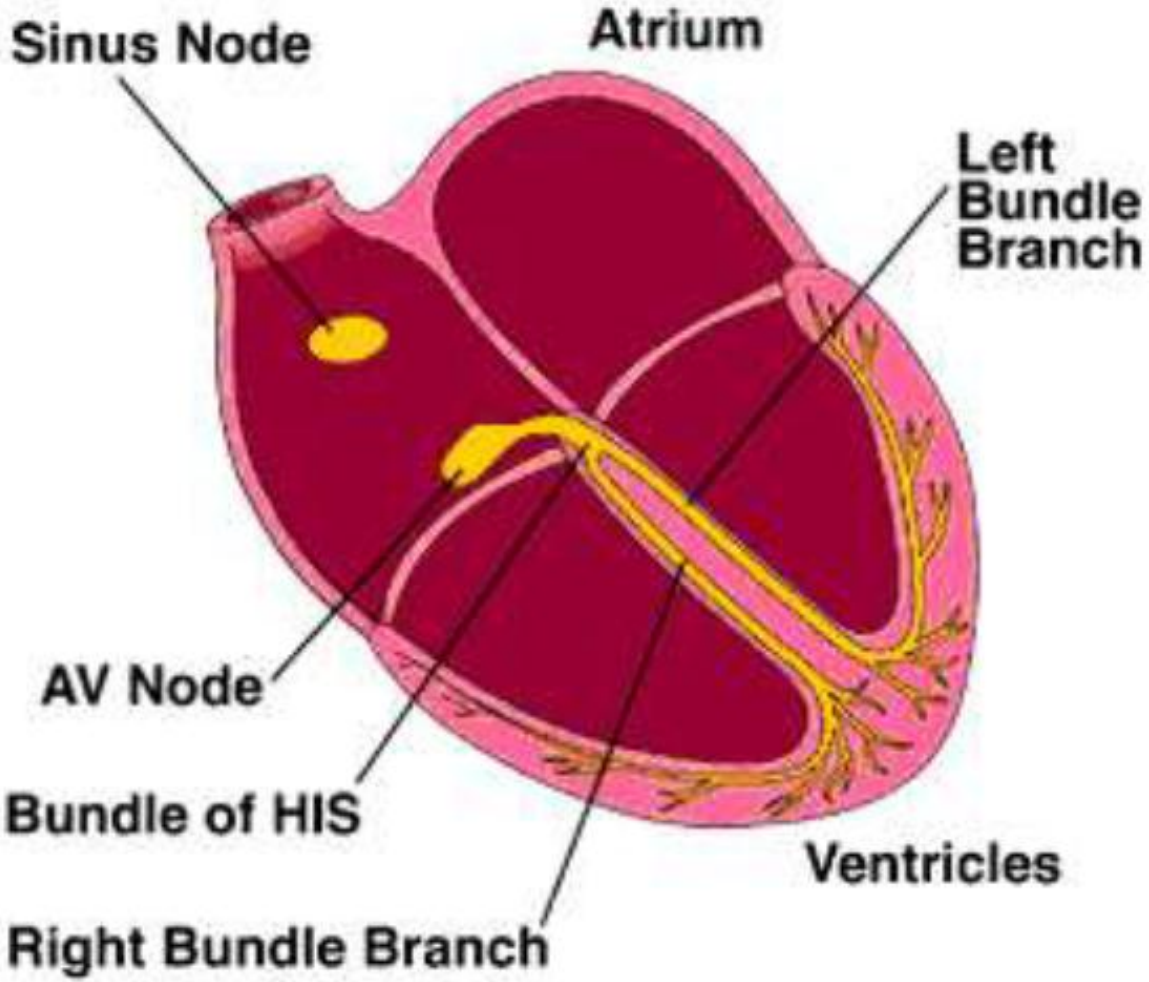
Types of cardiac tissue (on the basis of impulse generation)

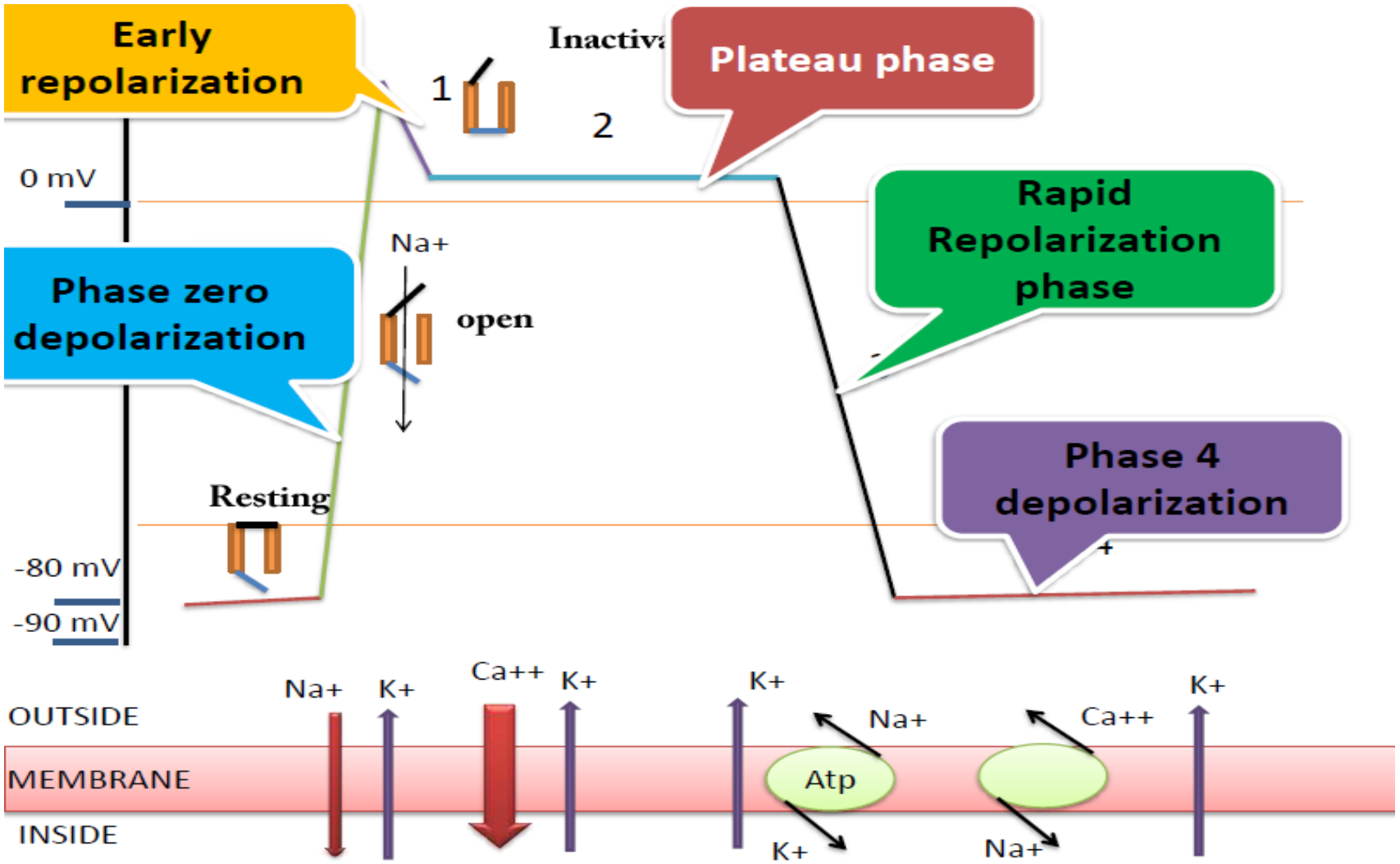
- **AUTOMATIC/ PACEMAKER/ CONDUCTING FIBRES**

  (Ca++ driven tissues)

  - Includes SA node, AV node, bundle of His, Purkinje fibres
  - Capable of generating their own impulse
  - Normally SA node acts as Pacemaker of heart
- **NON-AUTOMATIC MYOCARDIAL CONTRACTILE FIBRES** (Na+ driven tissues)
  - Cannot generate own impulse
  - Includes atria and ventricles

Impulse generation and transmission




Early repolarization
Inactiva
1
2
Plateau phase
0 mV
Rapid Repolarization phase
Na+
Phase zero depolarization
open
Resting
Phase 4 depolarization
-80 mV
-90 mV
Na+
K+
Ca++
K+
K+
Na+
Ca++
K+
OUTSIDE
MEMBRANE
INSIDE
Atp
K+
Na+

Fast channel Vs slow channel AP

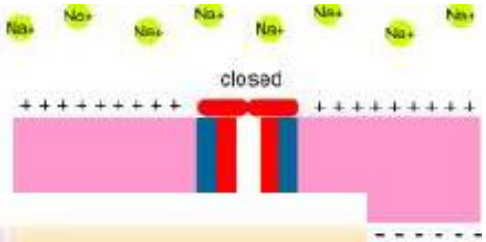
Fast channel AP

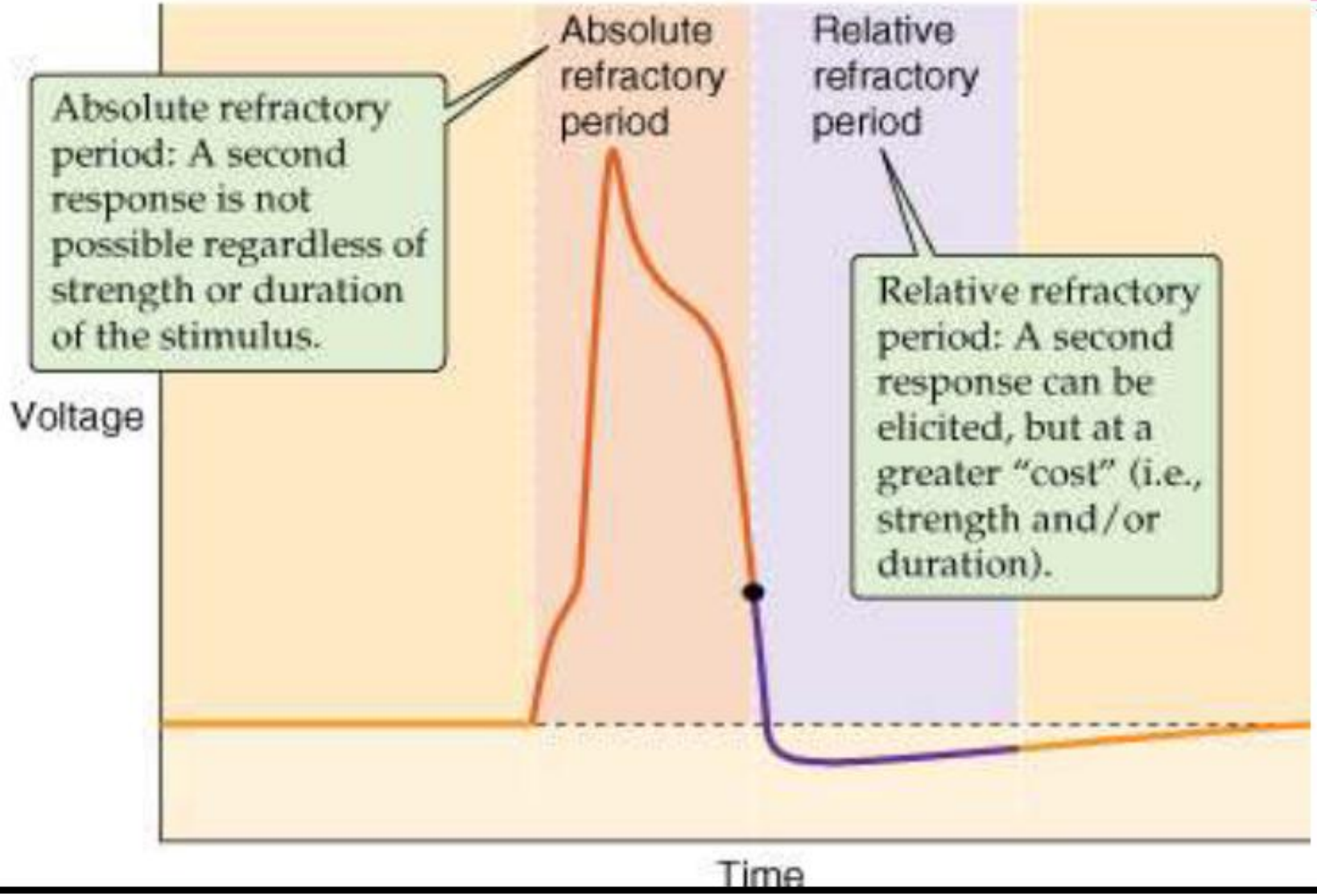
- Occurs in atria, ventricles, PF
- Predominant ion in phase-0 is Na+
- Conduction velocity more
- Selective channel blocker is tetradotoxin , LA

Slow channel AP

- Occurs in SA node, A-V node
- Predominant ion in phase-0 is Ca^{2+}
- Less
- Selective channel blockers are calcium channel blockers

Refractory period





ECG is used as a rough guide to some cellular properties of cardiac tissue

- P wave: atrial depolarization
- PR-Interval reflects AV nodal conduction time
- QRS DURATION reflects conduction time in ventricles
- T-wave: ventricular repolarization
- QT interval is a measure of ventricular APD

Mechanisms of cardiac arrythmia

- Abnormal impulse generation:
  - Depressed automaticity
  - Enhanced automaticity
- Triggered activity (after depolarization):
  - Delayed after depolarization
  - Early after depolarization
- Abnormal impulse conduction:
  - Conduction block
  - Re-entry phenomenon
  - Accessory tract pathways

a) Enhanced automaticity

Automatic behavior in sites ordinarily lacking pacemaker activity

CAUSES: Ischaemia/digitalis/catecholamines/acidosis/ hypokalemia/stretching of cardiac cells

↓

Nonpacemaker nodal tissues: membrane potential comes to -60mv

↓

Increased slope of phase 4 depolarisation

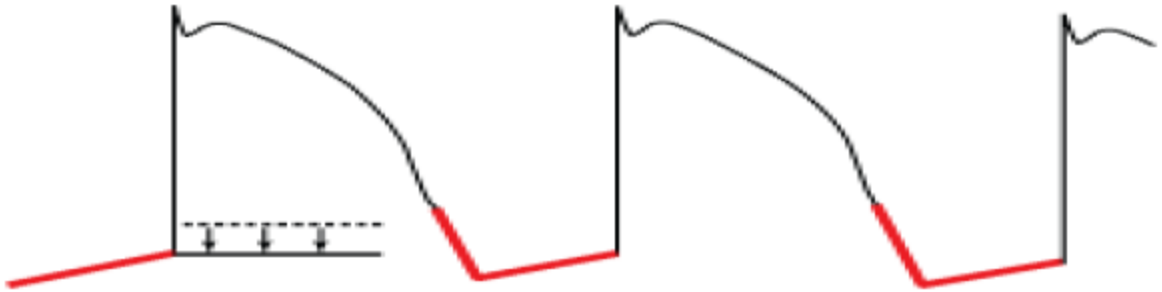
↓

Become ECTOPIC PACEMAKERS.(AV nodal rhythm, idioventricular rhythm, ectopic beats)

Ectopic pacemaker activity encouraged by

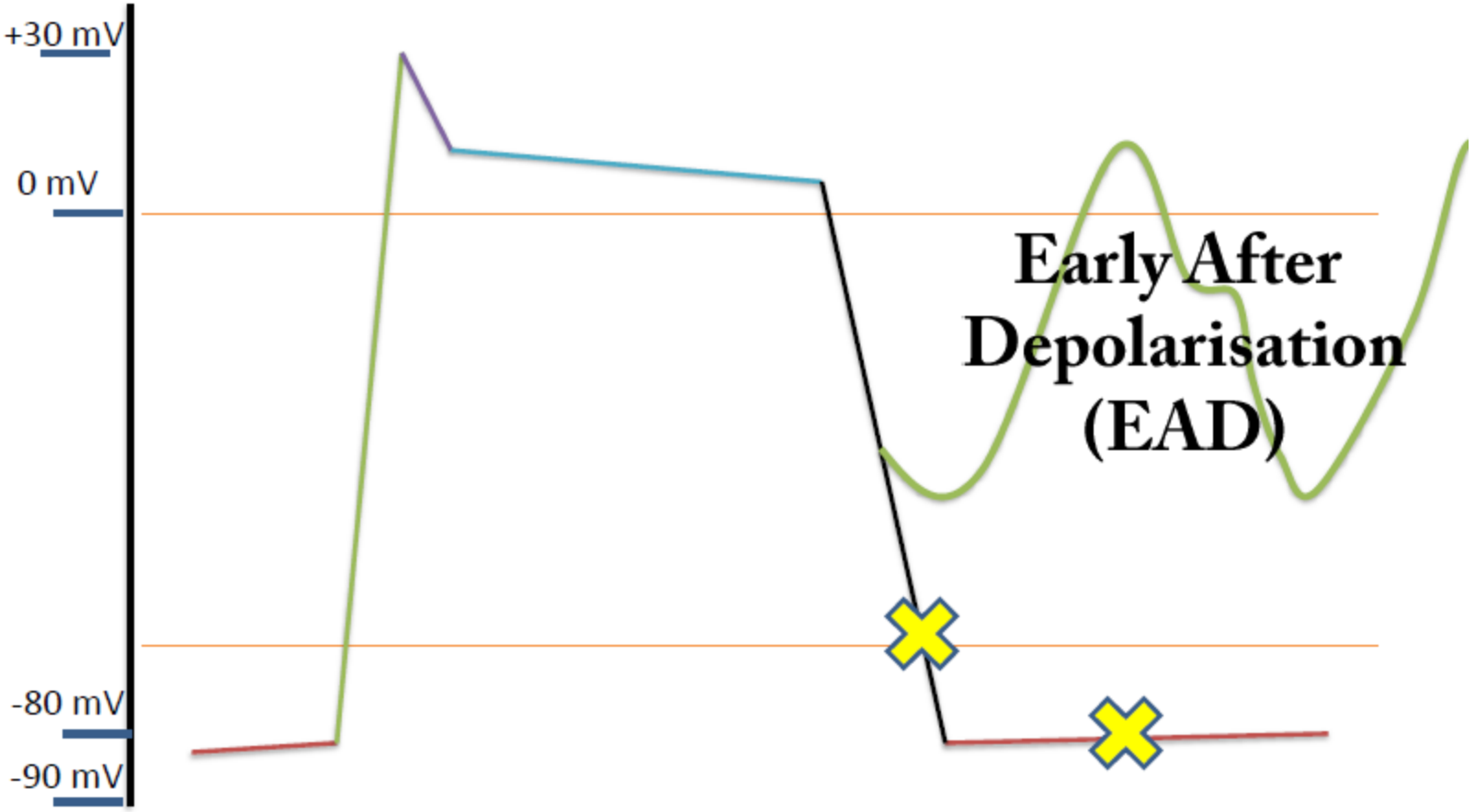
↑ Phase 4 slope

Less negative RMP

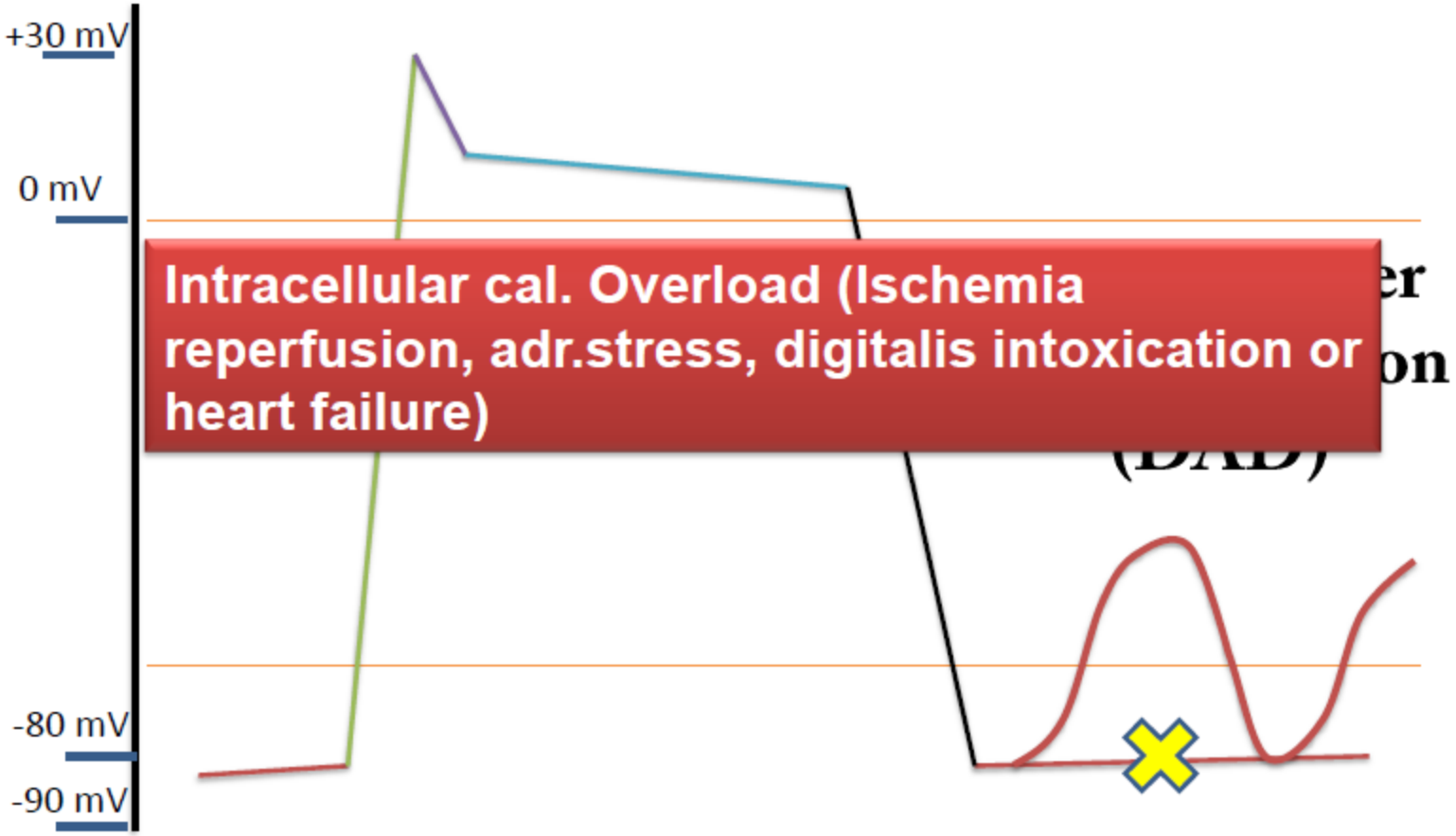


More negative TP

b) Trigerred automaticity



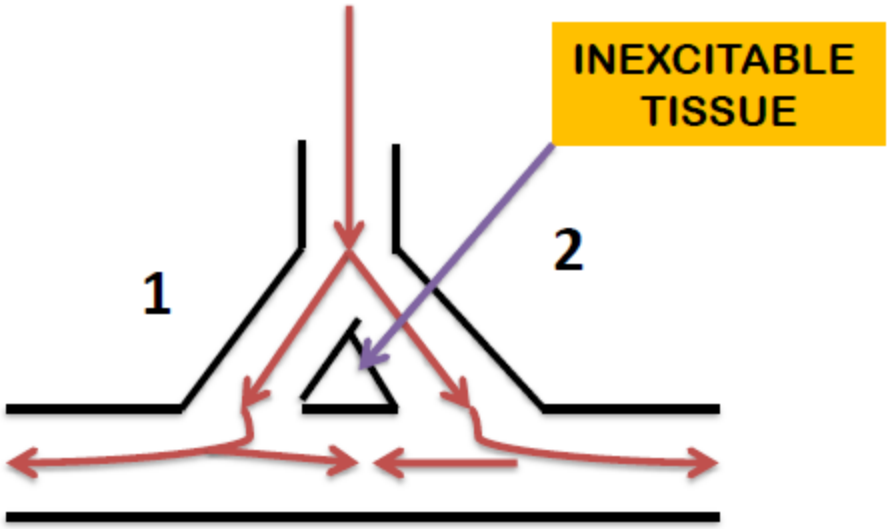
b) Trigerred automaticity



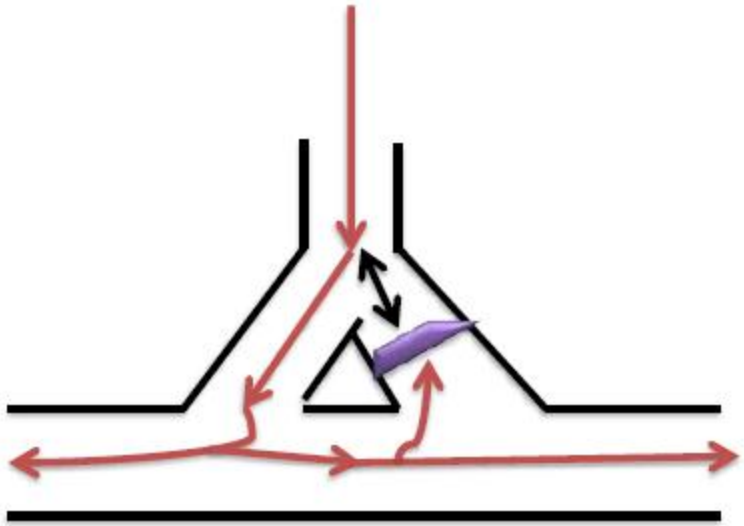
c. Abnormal impulse conduction

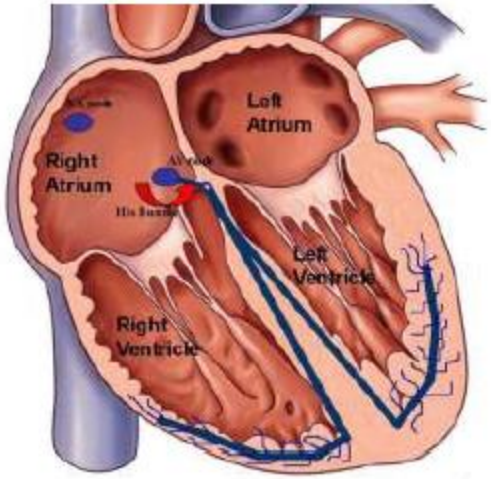
- Conduction block
  - First degree block
  - Second degree block
  - Third degree block
- Re-entry phenomenon
- Accessory tract pathways

Re-entry



Re-entry





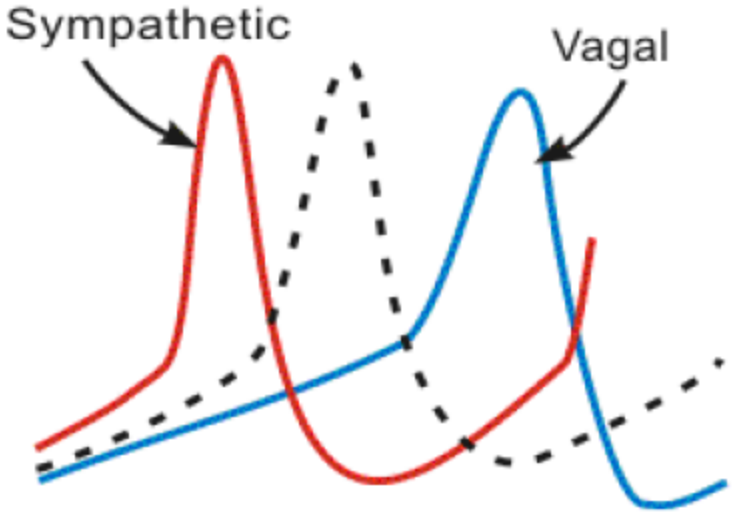
Regulation by autonomic tone

Parasympathetic/Vagus Nerve stimulation:

- Ach binds to M2 receptors
- Activate Ach dependent outward K^+ conductance (thus hyperpolarisation)
- ↓ phase 4 AP

Sympathetic stimulation:

- Activation of β1 receptors
- Augmentation of L-type Ca^{2+} current
- Phase 4 AP more steeper



AV Nodal Cell Action Potentials

Effects of Parasympathetic (Vagal) and Sympathetic Nerve Activation on AV Nodal Action Potentials

Classification of Anti-Arrhythmic Drugs (Vaughan-Williams-Singh..1969)

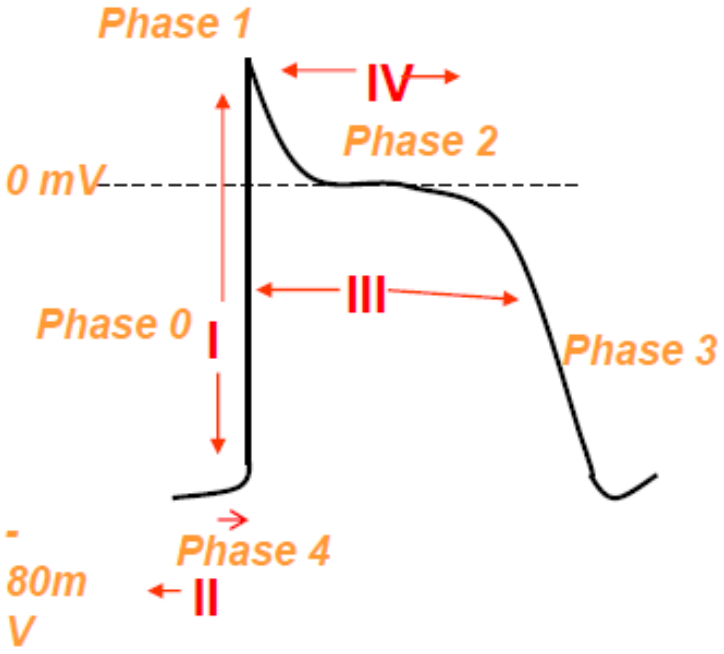
Class I: block Na^+ channels

Ia (quinidine, procainamide, disopyramide) (1-10s)
Ib (lignocaine) (<1s)
Ic (flecainide) (>10s)

Class II: ß-adrenoceptor antagonists (atenolol, sotalol)

Class III: prolong action potential and prolong refractory period (amiodarone, dofetilide, sotalol)

Class IV: Ca^{2+} channel antagonists (verapamil, diltiazem)



Classification based on clinical use

- Drugs used for supraventricular arrhythmia`s
  - Adenosine, verapamil, diltiazem
- Drugs used for ventricular arrhythmias
  - Lignocaine, mexelitine, bretylium
- Drugs used for supraventricular as well as ventricular arrhythmias
  - Amiodarone, β- blockers, disopyramide, procainamide

Na+ channel blocker

- Bind to and block Na+ channels (and K+ also)
- Act on initial rapid depolarisation (slowing effect)
- *Local Anaesthetic* (higher concentration): block nerve conduction
- Do not alter resting membrane potential *(Membrane Stabilisers)*
- At times, post repolarization refractoriness.
- Bind preferentially to the open channel state
- USE DEPENDENCE : The more the channel is in use, the more drug is bound

Ia	Ib	Ic
Moderate Na channel blockade	Mild Na channel blockade	Marked Na channel blockade
Slow rate of rise of Phase 0	Limited effect on Phase 0	Markedly reduces rate of rise of phase 0
Prolong refractoriness by blocking several types of K channels	Little effect on refractoriness as there is minimal effect on K channels	Prolong refractoriness by blocking delayed rectifier K channels
Lengthen APD & repolarization	Shorten APD & repolarization	No effect on APD & repolarization
Prolong PR, QRS	QT unaltered or slightly shortened	Markedly prolong PR & QRS

Class I: Na^+ Channel Blockers

IA: $\tau_{recovery}$ moderate (1-10sec)

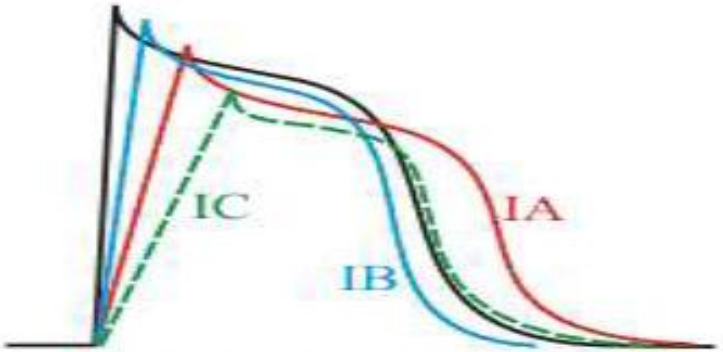
Prolong APD

IB: $\tau_{recovery}$ fast (<1sec)

Shorten APD in some heart tissues

IC: $\tau_{recovery}$ slow(>10sec)

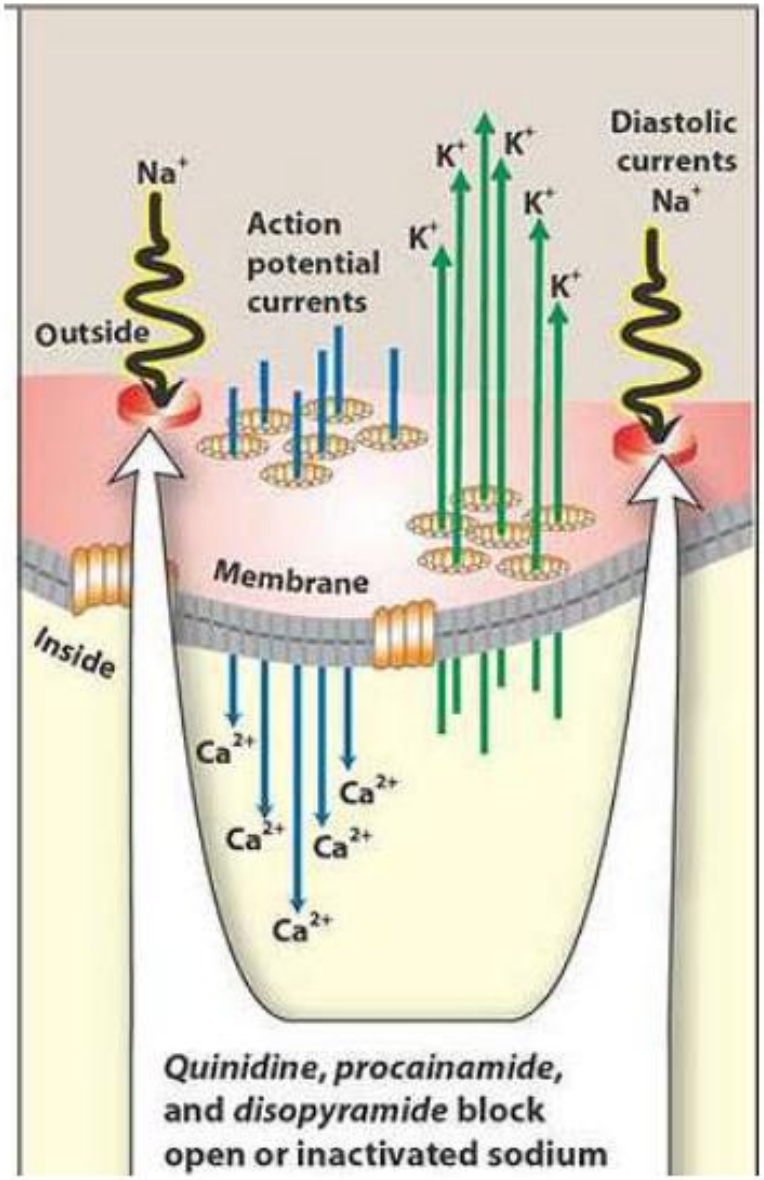
Minimal effect on APD

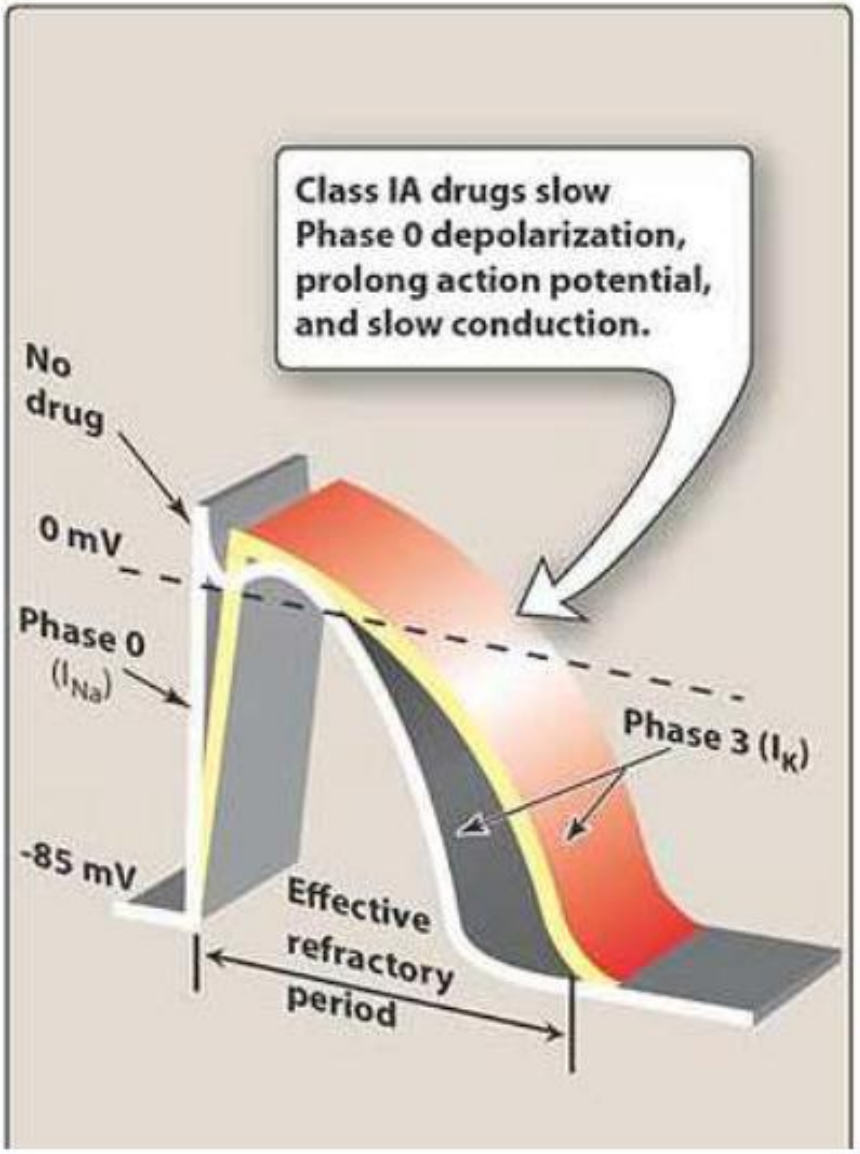


Ventricular Action Potential

- Class IA: e.g., quinidine
  - Moderate Na^+-channel blockade
  - ↑ ERP
- Class IB: e.g., lidocaine
  - Weak Na^+-channel blockade
  - ↓ ERP
- Class IC: e.g., flecainide
  - Strong Na^+-channel blockade
  - → ERP

Class IA


Na+
Action potential currents
K+
K+
K+
K+
K+
Diastolic currents
Na+
Outside
Membrane
Inside
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Quinidine, procainamide, and disopyramide block open or inactivated sodium


Class IA drugs slow Phase 0 depolarization, prolong action potential, and slow conduction.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period

Quinidine

- Historically first antiarrhythmic drug used.
- In 18th century, the bark of the cinchona plant was used to treat "rebellious palpitations“

pharmacological effects

↑ threshold for excitability

↓ automaticity

prolongs AP

Quinidine

- *Clinical Pharmacokinetics*
- well absorbed
- 80% bound to plasma proteins (albumin)
- extensive hepatic oxidative metabolism
- 3-hydroxyquinidine,
- is nearly as potent as quinidine in blocking cardiac Na^+ channels and prolonging cardiac action potentials.

Quinidine

- *Uses*
- to maintain sinus rhythm in patients with atrial flutter or atrial fibrillation
- to prevent recurrence of ventricular tachycardia or VF

Quinidine

Adverse Effects-

Non cardiac

- Diarrhea, thrombocytopenia,
- cinchonism & skin rashes.

cardiac

marked QT-interval prolongation &torsades de pointes (2-8%)

hypotension

tachycardia

Drug interactions

- Metabolized by CYP450
- Increases digoxin levels
- Cardiac depression with beta blockers
- Inhibits CYP2D6

Disopyramide

- Exerts electrophysiologic effects very similar to those of quinidine.
- Better tolerated than quinidine
- exert prominent anticholinergic actions
- Negative ionotropic action.
- A/E-
- precipitation of glaucoma,
- constipation, dry mouth,
- urinary retention

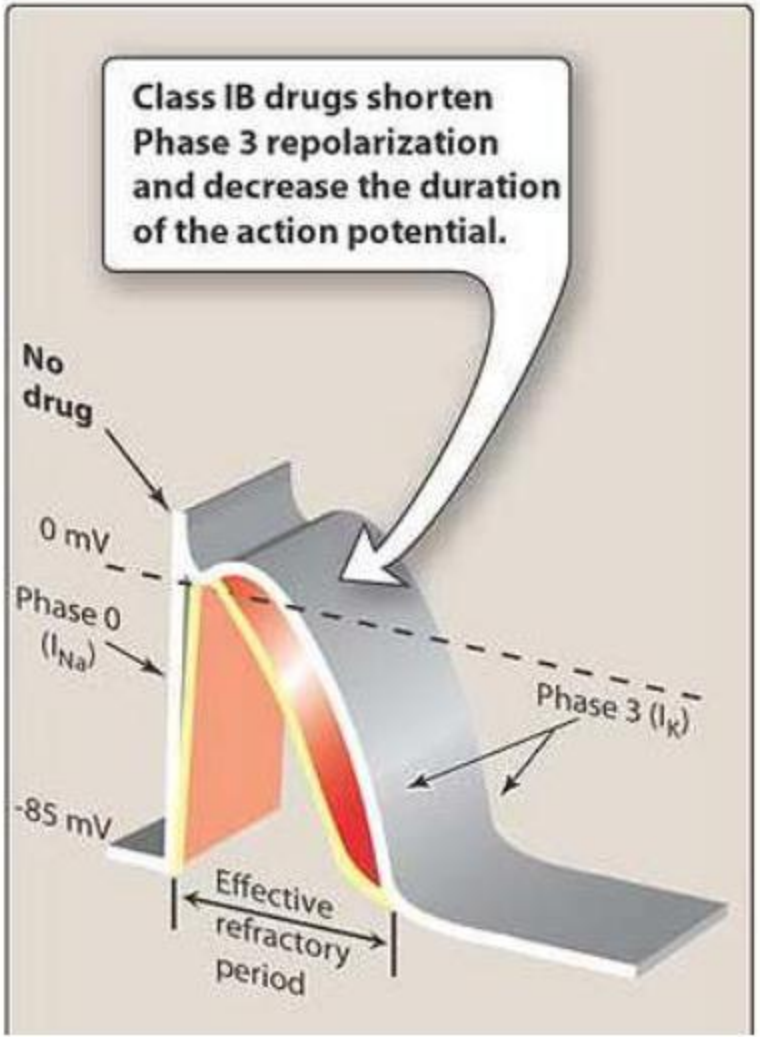
Procainamide

- Lesser vagolytic action , depression of contractility & fall in BP
- Metabolized by acetylation to N-acetyl procainamide which can block K+ channels
- Doesn’t alter plasma digoxin levels
- Cardiac adverse effects like quinidine
- Can cause SLE not recommended > 6 months
- Use: Monomorphic VT, WPW Syndrome

Class IB drugs

Lignocaine, phenytoin, mexiletine

Block sodium channels also shorten repolarization



Lignocaine

- Blocks inactivated sodium channels more than open state
- Relatively selective for partially depolarized cells
- Selectively acts on diseased myocardium
- Rapid onset & shorter duration of action
- Useful only in ventricular arrhythmias , Digitalis induced ventricular arrnhythmias

Lidocaine is not useful in atrial arrhythmias???

atrial action potentials are so short that the Na^+ channel is in the inactivated state only briefly compared with diastolic (recovery) times, which are relatively long

Pharmacokinetics

- High first pass metabolism
- Metabolism dependent on hepatic blood flow
- T ½ = 8 min – distributive, 2 hrs – elimination
- Propranolol decreases half life of lignocaine
- Dose= 50-100 mg bolus followed by 20-40 mg every 10-20 min i.v

Adverse effects

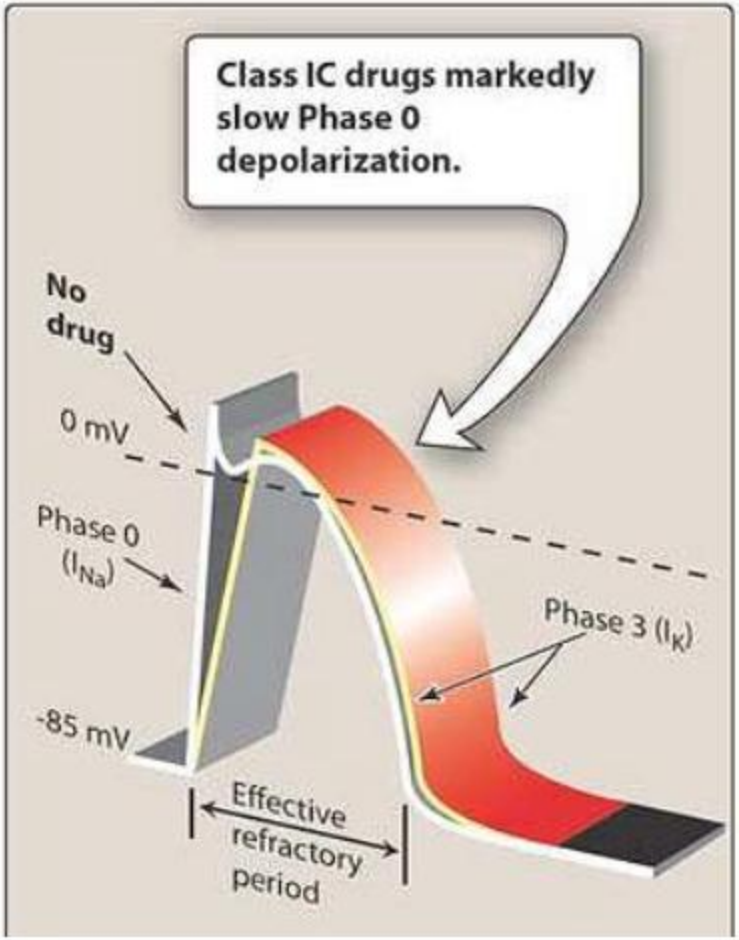
- Relatively safe in recommended doses
- Drowsiness, disorientation, muscle twitchings
- Rarely convulsions, blurred vision, nystagmus
- Least cardiotoxic antiarrhythmic

- Local anaesthetic
- Inactive orally
- Given IV for antiarrhythmic action
- Na+ channel blockade which occurs
- Only in inactive state of Na+ channels
- CNS side effects in high doses
- Action lasts only for 15 min
- Inhibits purkinje fibres and ventricles but
- No action on AVN and SAN so
- Effective in Ventricular arrhythmias only

Class I C drugs
Encainide, Flecainide, Propafenone

Have minimal effect on repolarization
Are most potent sodium channel blockers

- Risk of cardiac arrest , sudden death so not used commonly
- May be used in severe ventricular arrhythmias



Propafenone class 1c

- Structural similarity with propranolol & has β-blocking action
- Undergoes variable first pass metabolism
- Reserve drug for ventricular arrhythmias, re-entrant tachycardia involving accesory pathway
- Adverse effects: metallic taste, constipation and is proarrhythmic

Flecainde (Class Ic)

- Potent blocker of Na & K channels with slow unblocking kinetics
- Blocks K channels but does not prolong APD & QT interval
- Maintain sinus rhythm in supraventricular arrhythmias
- Cardiac Arrhythmia Suppression Test (CAST Trial):

When Flecainide & other Class Ic given prophylactically to patients convalescing from Myocardial Infarction it increased mortality by 2½ fold. Therefore the trial had to be prematurely terminated

Class II: Beta blockers

- β-receptor stimulation:
  - ↑ automaticity,
  - ↑ AV conduction velocity,
  - ↓ refractory period
- β-adrenergic blockers competitively block catecholamine induced stimulation of cardiac β- receptors

Beta blockers

- Depress phase 4 depolarization of pacemaker cells,
- Slow sinus as well as AV nodal conduction :
  - ↓ HR, ↑ PR
- ↑ ERP, prolong AP Duration by ↓ AV conduction
- Reduce myocardial oxygen demand
- Well tolerated, Safer

β Adrenergic Stimulation	β Blockers
↑ magnitude of Ca^{2+} current & slows its inactivation	↓ Intracellular Ca^{2+} overload
↑ Pacemaker current→↑ heart rate	↓Pacemaker current→↓ heart rate
↑ DAD & EAD mediated arrhythmias	Inhibits after-depolarization mediated automaticity
Epinephrine induces hypokalemia (β_2 action)	Propranolol blocks this action

Use in arrhythmia

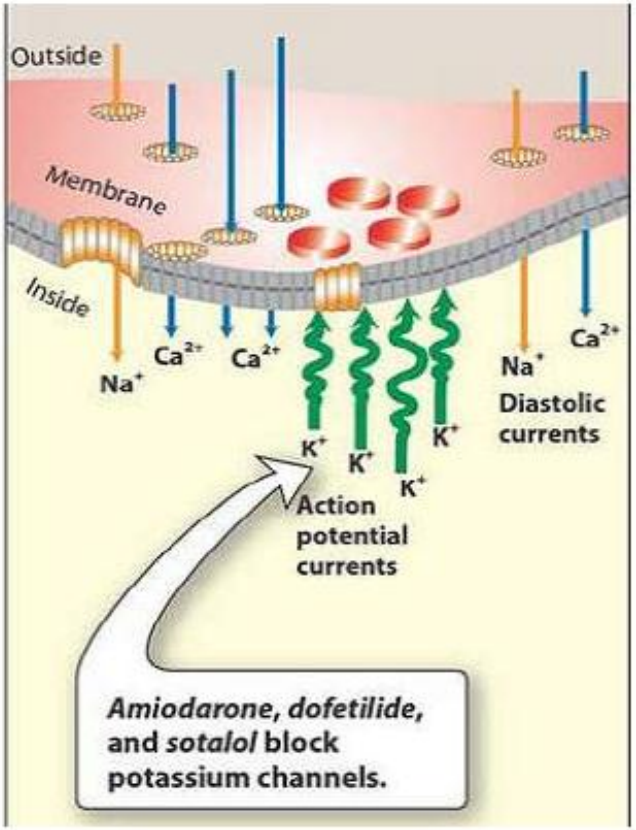
- Control supraventricular arrhythmias
  - Atrial flutter, fibrillation, PSVT
- Treat tachyarrhythmias caused by adrenergic +
  - Hyperthyroidism Pheochromocytoma, during anaesthesia with halothane
- Digitalis induced tachyarrythmias
- Prophylactic in post-MI
- Ventricular arrhythmias in prolonged QT syndrome

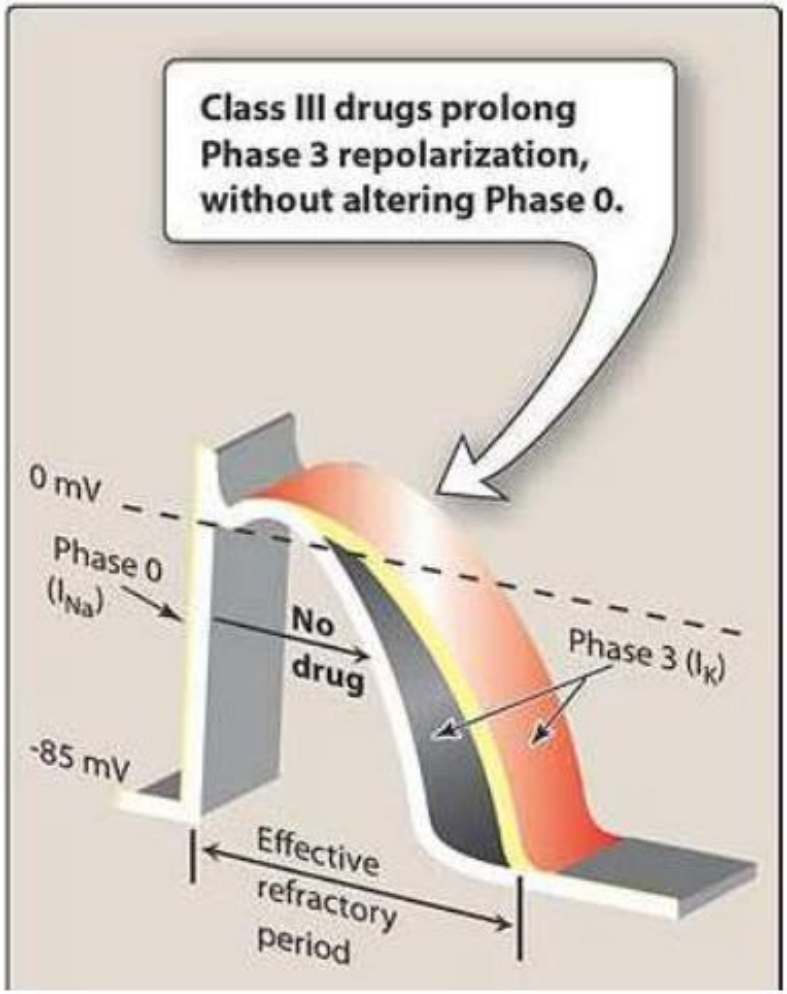
Esmolol

- β1 selective agent
- Very short elimination t1/2 :9 mins
- Metabolized by RBC esterases
- Rate control of rapidly conducted AF
- Use:
  - Arrythmia associated with anaesthesia
  - Supraventricular tachycardia

Class III drugs

↑APD & ↑RP by blocking the K^+ channels





Amiodarone

- Iodine containing long acting drug
- Mechanism of action: (Multiple actions)
  - Prolongs APD by blocking K^+ channels
  - blocks inactivated sodium channels
  - β blocking action , Blocks Ca^{2+} channels
  - ↓ Conduction, ↓ectopic automaticity

Amiodarone

- Pharmacokinetics:
  - Variable absorption 35-65%
  - Slow onset 2days to several weeks
  - Duration of action : weeks to months
- Dose
  - Loading dose: 150 mg over 10min
  - Then 1 mg/min for 6 hrs
  - Then maintenance infusion of 0.5 mg/min for 24 hr

Amiodarone

- Uses:
  - Can be used for both supraventricular and ventricular tachycardia
- Adverse effects:
  - Cardiac: heart block , QT prolongation, bradycardia, cardiac failure, hypotension
  - Pulmonary: pneumonitis leading to pulmonary fibrosis
  - Bluish discoloration of skin, corneal microdeposits
  - GIT disturbances, hepatotoxicity
  - Blocks peripheral conversion of T4to T3 can cause hypothyroidism or hyperthyroidism

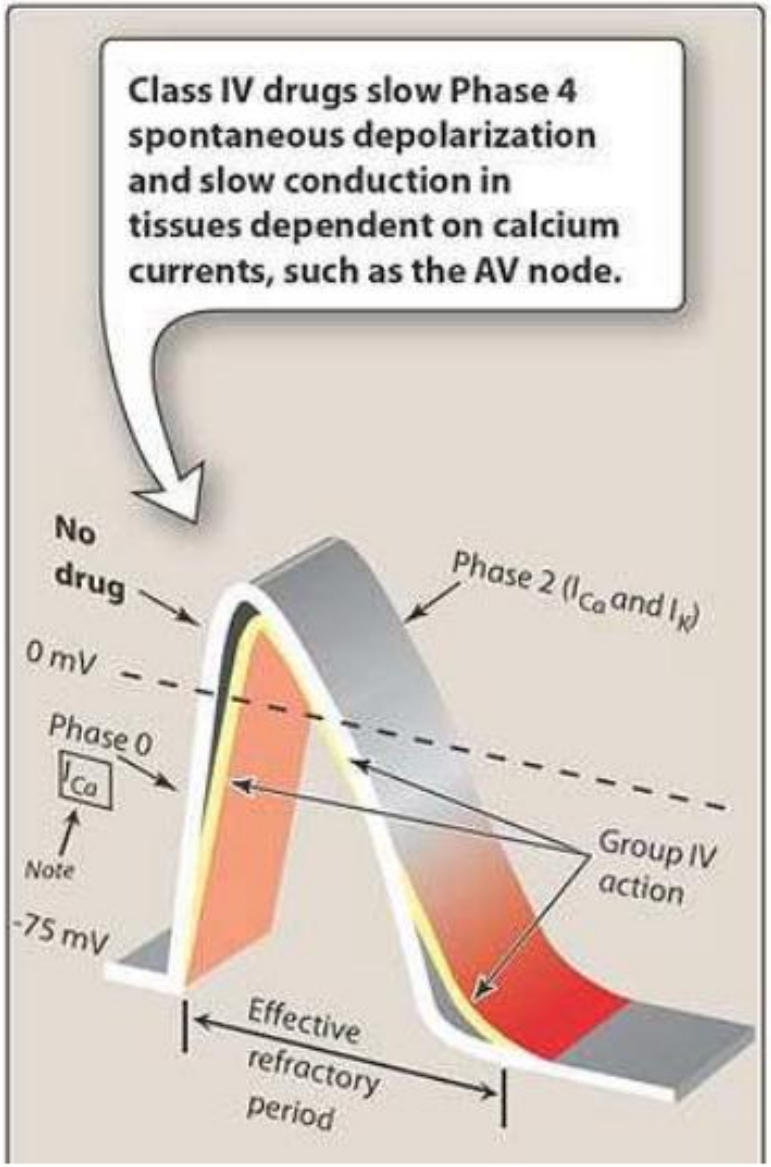
- Antiarrhythmic
- Multiple actions
- Iodine containing
- Orally used mainly
- Duration of action is very long (t ½ = 3-8 weeks)
- APD & ERP increases
- Resistant AF, V tach, Recurrent VF are indications
- On prolonged use- pulmonary fibrosis
- Neuropathy may occur
- Eye : corneal microdeposits may occur

Newer class III drugs

- Dronedarone
- Vernakalant
- Azimilide
- Tedisamil

Calcium channel blockers (Class IV)

- Inhibit the inward movement of calcium ↓ contractility, automaticity , and AV conduction.
- Verapamil & diltiazem



Verapamil

- Uses:
  - Terminate PSVT
  - control ventricular rate in atrial flutter or fibrillation
- Drug interactions:
  - Displaces digoxin from binding sites
  - ↓ renal clearance of digoxin

Other antiarrhythmics

- Adenosine :
  - Purine nucleoside having short and rapid action
  - IV suppresses automaticity, AV conduction and dilates coronaries
  - Drug of choice for PSVT
  - Adverse events:
    - Nausea, dyspnoea, flushing, headache

Adenosine

- Acts on specific G protein-coupled adenosine receptors
- Activates AcH sensitive K+ channels channels in SA node, AV node & Atrium

↓

- Shortens APD, hyperpolarization & ↓ automaticity

↓

- Inhibits effects of ↑ cAMP with sympathetic stimulation

↓

- ↓ Ca currents

↓

- ↑AV Nodal refractoriness & inhibit DAD's

Other antiarrhythmics

- Atropine: Used in sinus bradycardia
- Digitalis: Atrial fibrillation and atrial flutter
- Magnesium SO_4: digitalis induced arrhythmias

Drugs of choices

S. No	Arrhythmia	Drug
1	Sinus tachycardia	Propranolol
2	Atrial extrasystole	Propranolol,
3	AF/Flutter	Esmolol, verapamil ,digoxin
4	PSVT	Adenosine ,esmolol
5	Ventricular Tachycardia	Lignocaine , procainamide , Amiodarone
6	Ventricular fibrillation	Lignocaine, amiodarone
7	A-V block	Atropine , isoprenaline