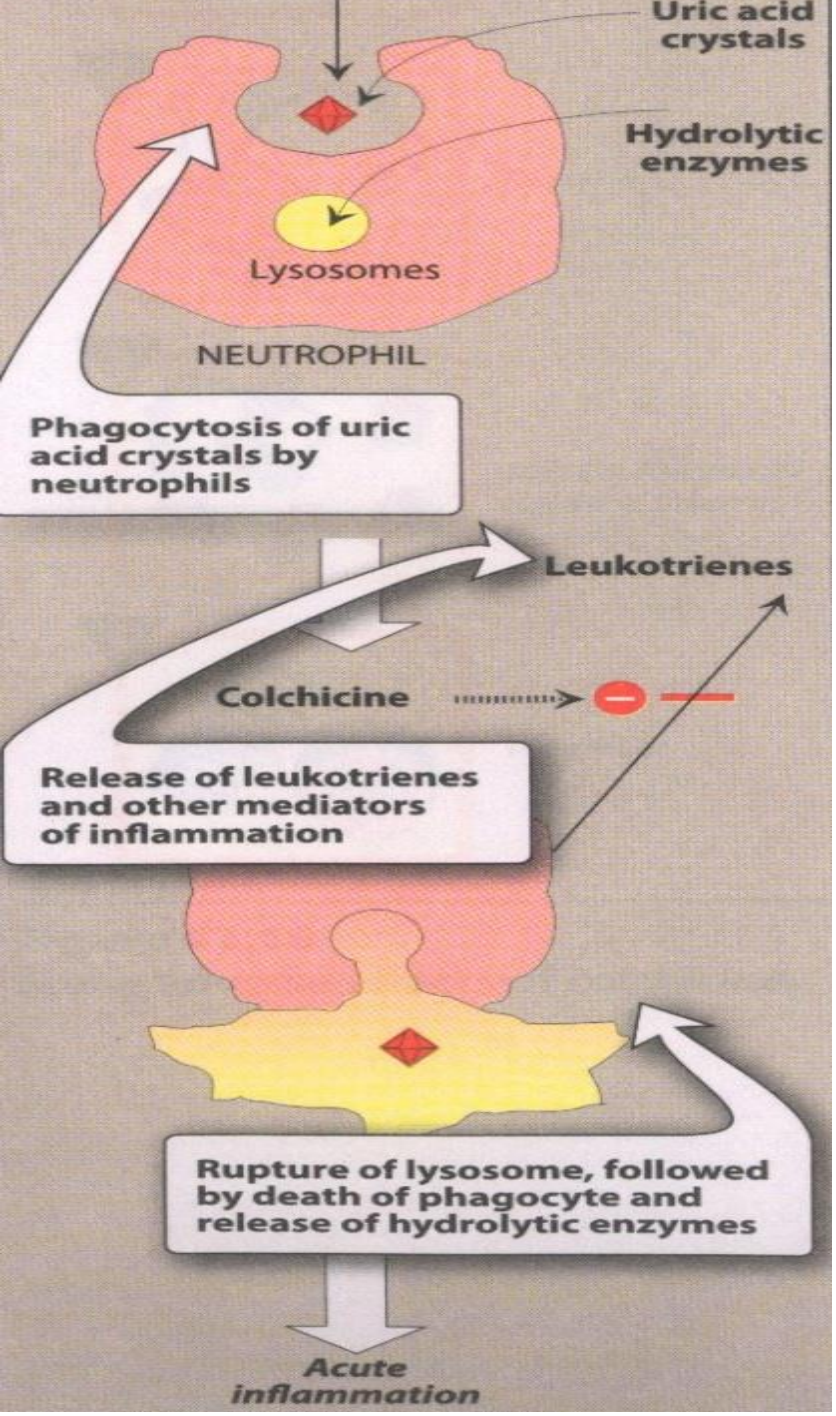
Gout and hyperuricemia

- B) write down the mechanism of action of Allopurinol
- B) what is the rationale for the use of ALLOPURINOL for lowering of urates?

4 syndromes of hyperuricaemia

- Acute urate synovitis --- gout
  - Acute attack involve joint inflammation initiated by precipitation of uric acid crystals
- Chronic polyarticular gout
- Chronic tophaceous gout
- Interstitial nephritis and Urate renal stone formation

Mechanism of damage by the uric acid crystals



Treatment

- Reduce inflammation during **acute attack**
  - **NSAIDs, clochicine, or** glucocorticoids
- **Prophylaxis of gout**
- **Reduce formation of uric acid from purines**
  - Allopurinol, febuxostat
- **Increase excretion of uric acid by uricosuric drugs**
  - Sulphenpyrazone
  - Probenecid

Treatment

- Reduce inflammation during **acute attack**
  - **NSAIDs, clochicine, or** glucocorticoids
- **Prophylaxis of gout**
- ↑ **renal excretion** of uric acid with uricosuric drugs
  - Probenecid , Sulfinpyrazone
- ↓ **synthesis** of uric acid
  - Reduce the conversion of purines to uric acid by xanthine oxidase
  - **Allopurinol**, febuxostat

Treatment of an acute gouty arthritis

- **NSAIDs** (high doses) and Corticosteroids
  - Corticosteroids used only when use of NSAIDs are contraindicated
- **Colchicine** is an alternative
- Aspirin is not indicated in gout
- Allopurinol and uricosurics are **not effective in treating an acute attack** and may prolong it indefinitely if started during an acute attack

Mechanism of action of NSAIDs

- By Inhibition COX Inhibit inflammation of acute gouty arthritis
- Act through the reduction of PG formation and inhibition of crystal phagocytosis by macrophages

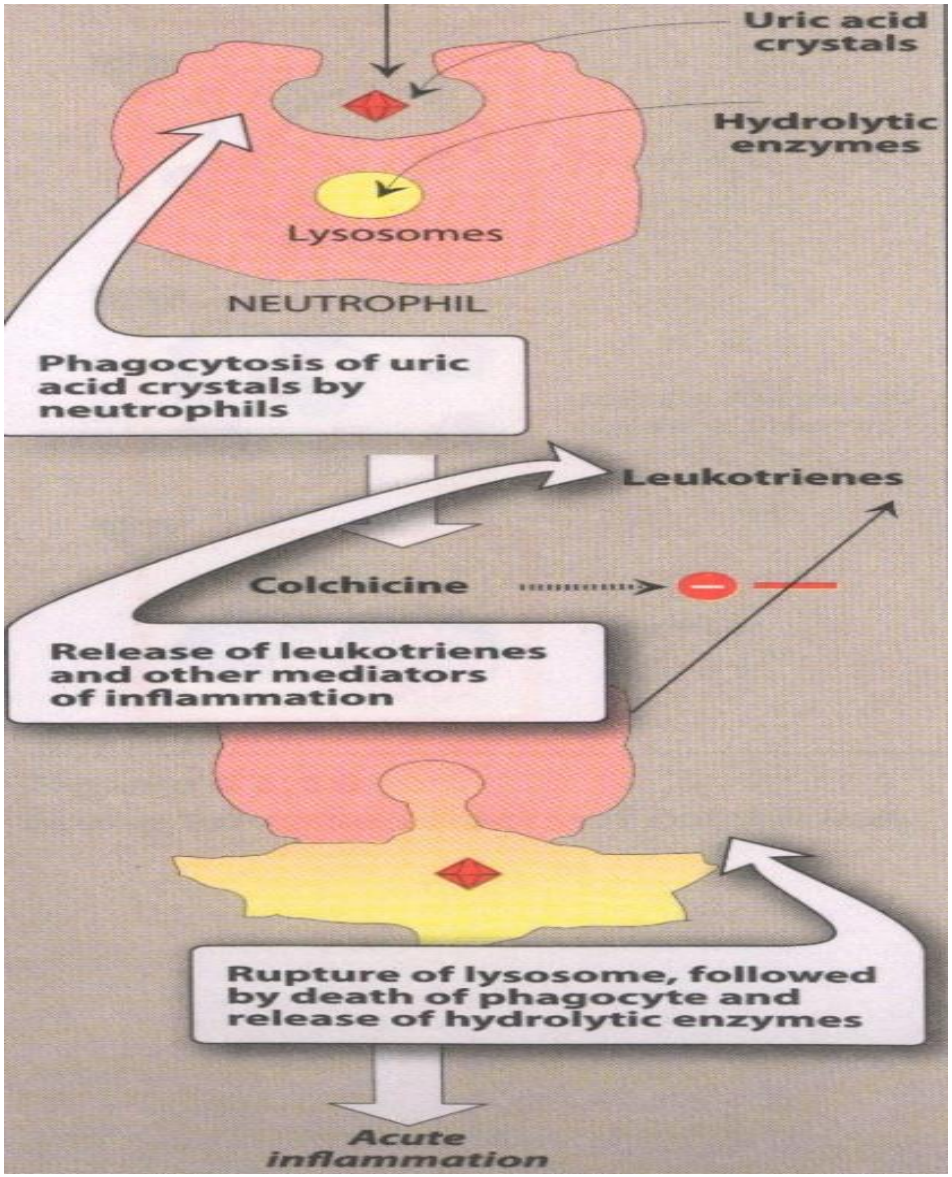
High dose NSAIDs

- **High dose NSAIDs**
  - Diclofenac, **indomethacin**, ketoprofen, naproxen, piroxicam
- **Indomethacin**
  - 75 mg immediately, then 50 mg every 6-8 hourly
- Naproxen
  - 750 mg immediately, then 500 mg every 8-12 hours
- Diclofenac
  - 75-100 mg immediately, then 50 mg every 6-8 hours
- After 24-48 hours, reduce doses are given for a further week

Colchicine

- **Acute gout**
- **Short term prophylaxis**
  - during initial therapy with allopurinol and uricosuric drugs
- Lower doses of colchicine are used to prevent attacks of gout in patients with a history of multiple acute attacks
- **Prophylaxis of familial Mediterranean fever** (recurrent polyserositis)
- mild beneficial effect in sarcoid arthrits and in hepatic cirrhosis

Mechanism of action of colchicine



- **An inhibitor of microtubule assembly**, reduces leukocytes migration and phagocytosis
- It also reduce synthesis and release of **L B_4** and
- Decrease free radical formation

Colchicine

- Treatment of acute gout
  - 1 mg initially, followed by 500 µ g every 2-3 hours until
    - relief of pain is obtained or
    - vomiting or diarrhoea occurs, or
    - a total dose of **6 mg** has been reached
- The course should not be repeated within 3 days
- **Short term prophylaxis**
  - 500 µ g 2-3 times daily
- For prevention of recurrent attacks
  - 500 µ g daily

Adverse effects (colchicine)

- Oral
  - Occur in 80% of patients at dose near that necessary to relieve gout, include **nausea, vomiting , abdominal pain, and particularly diarrhea**
  - Chronic administration
    - Myopathy, agranulocytosis, aplastic anemia and alopecia
- Overdose may be fatal – liver damage and blood dyscrasias
- I/v preparation decrease the risk of GIT disturbances but increase the risk of sloughing skin and SC tissue

Long term prophylaxis

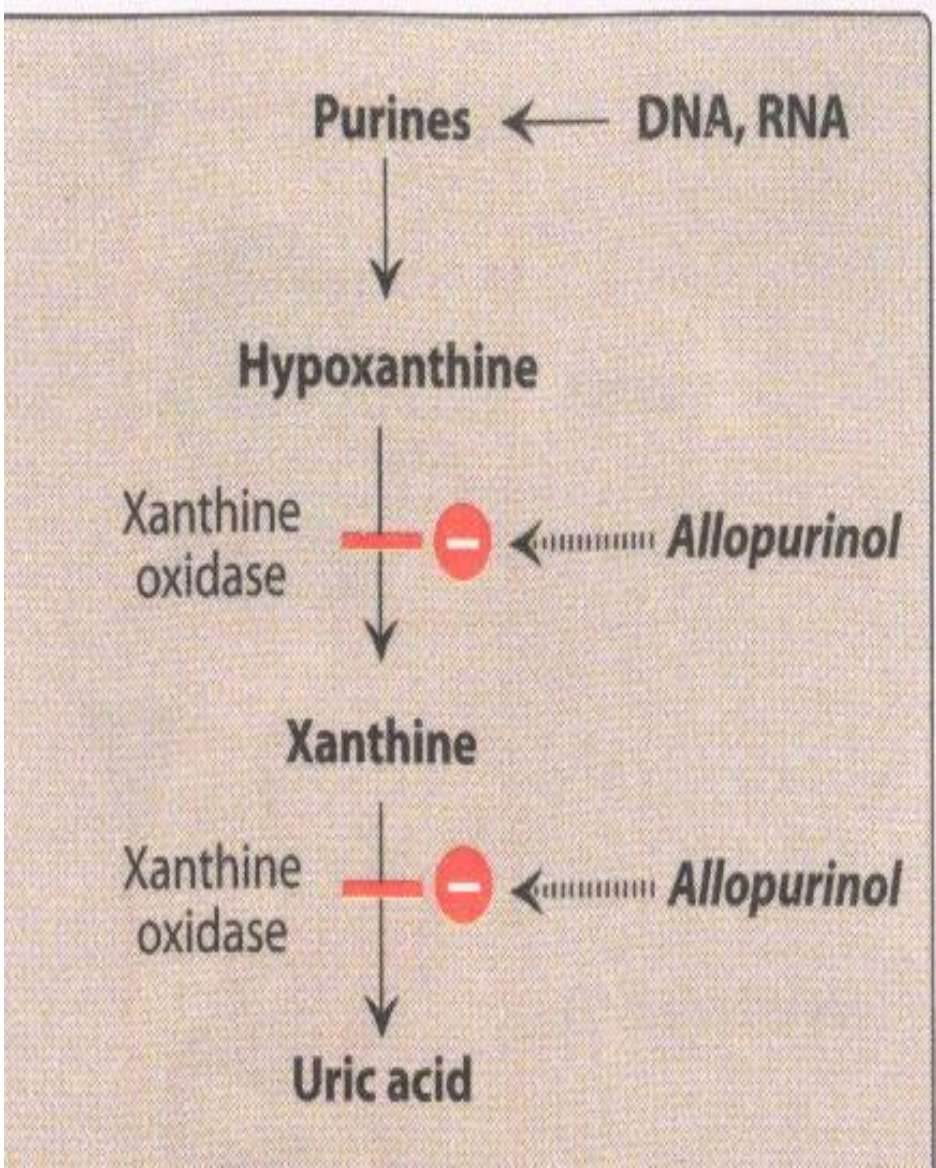
- Indication
  - Frequent recurrence of acute attacks
  - The presence of tophi or
  - the signs of chronic gouty arthritis
- **Reduce formation of uric acid from purines**
  - Allopurinol
- **Increase excretion of uric acid by uricosuric drugs**
  - Sulphenpyrazone
  - Probenecid

Long term control of gout

- Treatment should be continued indefinitely
- **These drugs should never be started during an acute attack**
  - They are usually started 2-3 weeks after the attack has settled
- The initiation of treatment may precipitate an acute attack therefore
  - **Colchicine or a NSAIDs should be used as a prophylactic** (**Short term prophylaxis**) and continued for at least one month after the hyperuricemia has been corrected (usually about three months of prophylaxis)

Mechanism of action of allopurinol

- It is a xanthine oxidase inhibitor
  - xanthine oxidase coverts hypoxanthine to xanthine and xanthine to uric acid
- Allopurinol is metabolized by xanthine oxidase to alloxanthine, which also inhibit xanthine oxidase
- Allopurinol also inhibit de novo purine synthesis



Therapeutic uses of Allopurinol

- Primary hyperuricemia of gout (**chronic, tophaceous gout)**
  - It reduces the size of the tophi
  - Colchicine is administered concomitantly for the first week of the therapy to prevent the gouty arthritis
- Hyperuricemia secondary to certain malignancy (particularly with chemotherapy)
- Renal disease ---- Especially useful in patients with renal impairment or urate stones where uricosuric drugs cannot be used
- **It is not indicated** for the treatment of asymptomatic hyperuricemia
- 100- 300 mg daily

Allopurinol -- adverse effects

- Hypersensitivity – skin rashes -- 3%
- GIT disturbances
- Rarely hypersensitivity
  - Fever hepatic dysfunction, and blood dyscrasias
  - To be used with caution in patients with liver disease or bone marrow depression
- Drug interaction – interfere with the metabolism of (require reduction in dose of these drugs)
  - 6-mercaptopurine -- anti cancer drug
  - Azathioprine -- immunosuppressant

- 24 hour urine for uric acid
- < 800 mg/day
  - Under secretion of uric acid
  - Uricosuric agent
- > 800mg/day
  - Over production of uric acid
  - Allopurinol

Uricosuric agents

- **Sulfinpyrazone & Probenecid**
- At therapeutic doses they block proximal tubular resorption of uric acid
  - At low doses block proximal tubular secretion of uric acid
- Used for chronic gout
- Both drugs under go rapid oral absorption
- ↑ incidence of urolithiasis can be prevented
  - ↑ water intake > 2000 ml/day
  - Alkalinization of urine with potassium citrate

Uricosuric agents

- Low doses of uricosuric agents and salicylates inhibit uric acid secretion
- Common adverse effects include **GIT disturbances** and dermatitis, rarely blood dyscrasias
- Inhibit the secretion of other drugs that are secreted by the renal tubules
  - Penicillin, NSAIDs, cephalosporins and methotrexate

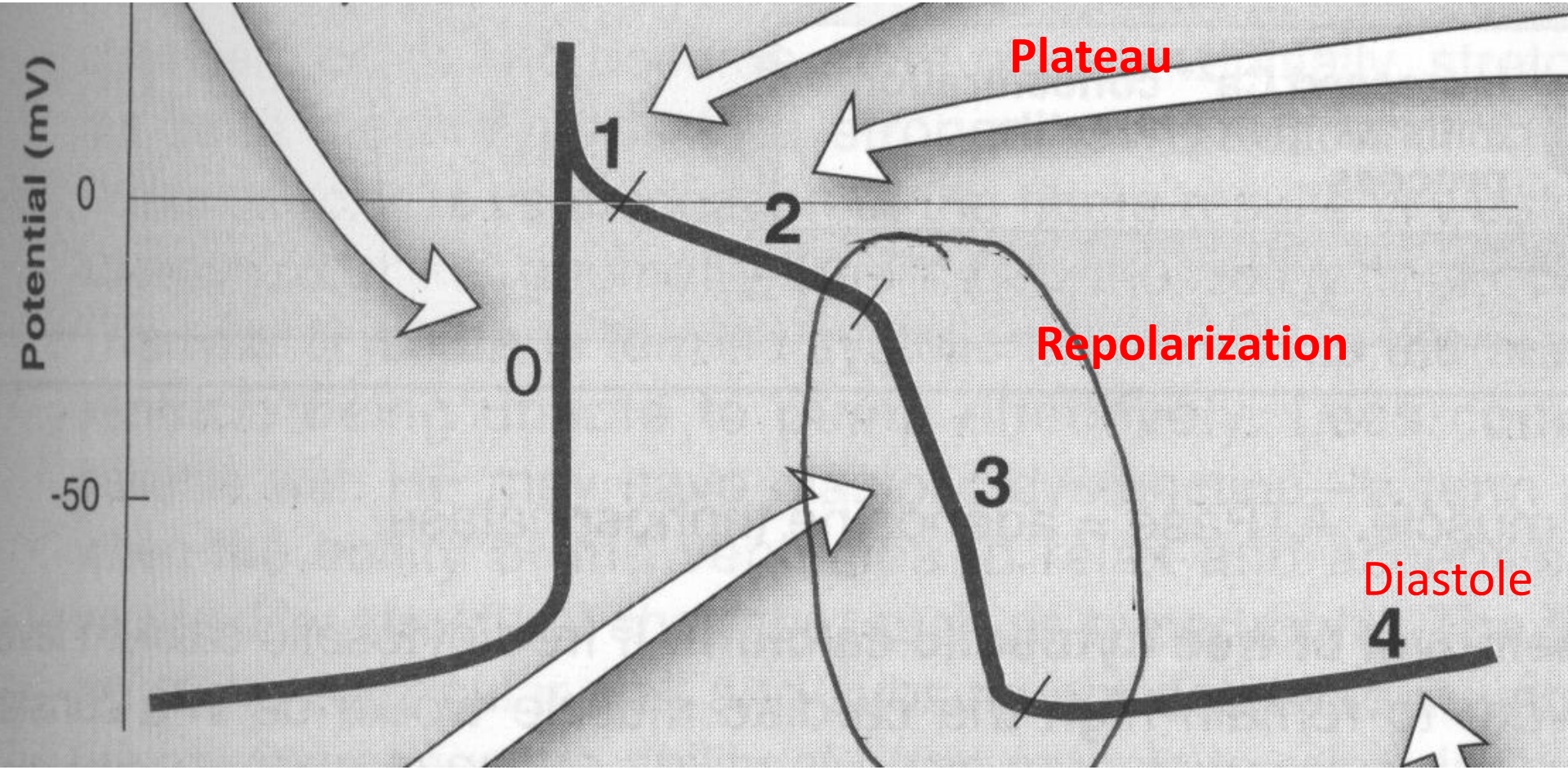
Antiarrhythmic drugs

Vaughan williams and singh (1969),
4 class system

Harrison (1979)- subgrouping of class I

Early fast partial repolarization

Fast upstroke

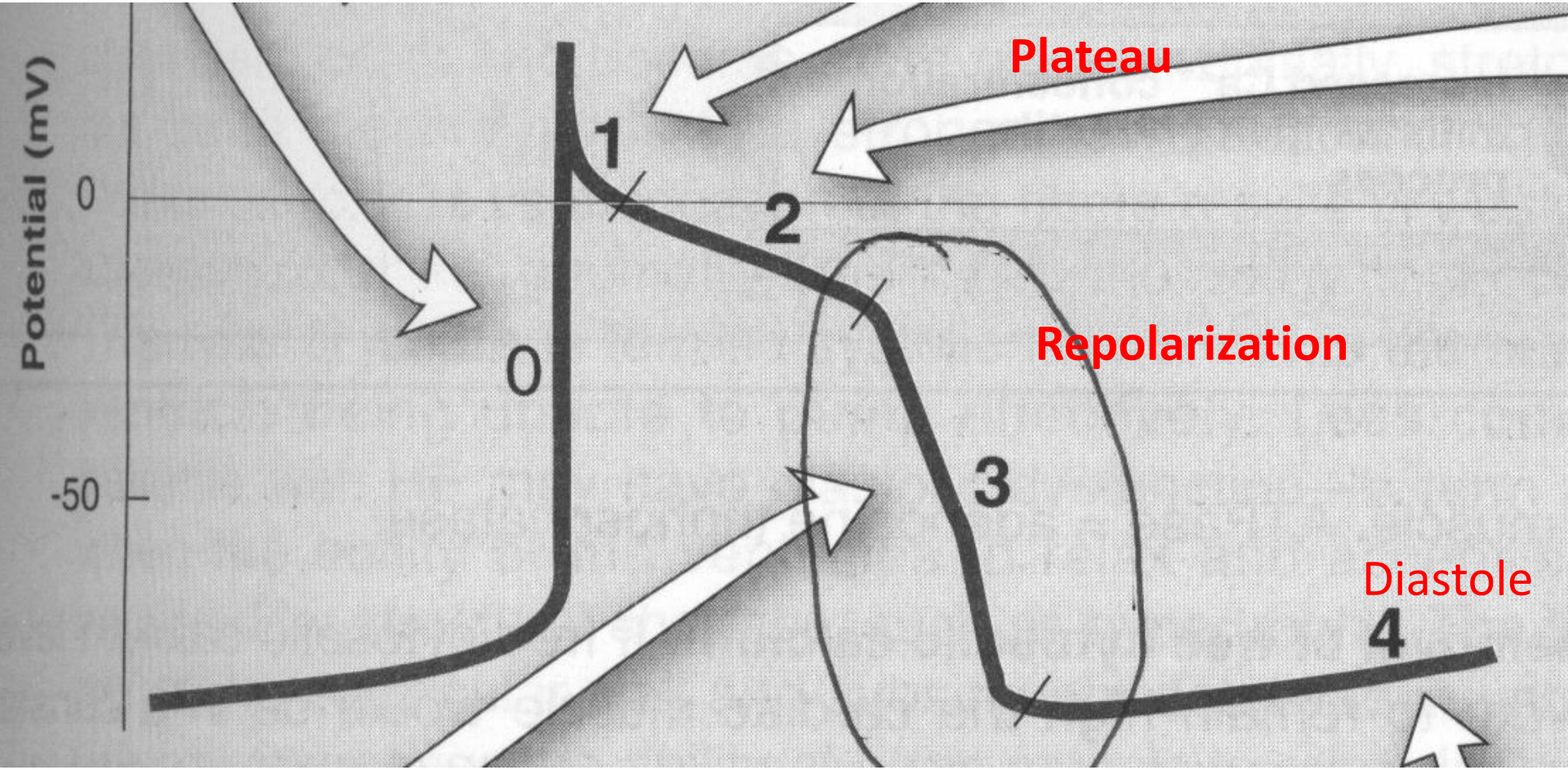


Early fast partial repolarization

Fast upstroke

Fast Na^+ channels open

Blocked by “Quinidine”



Fast upstroke

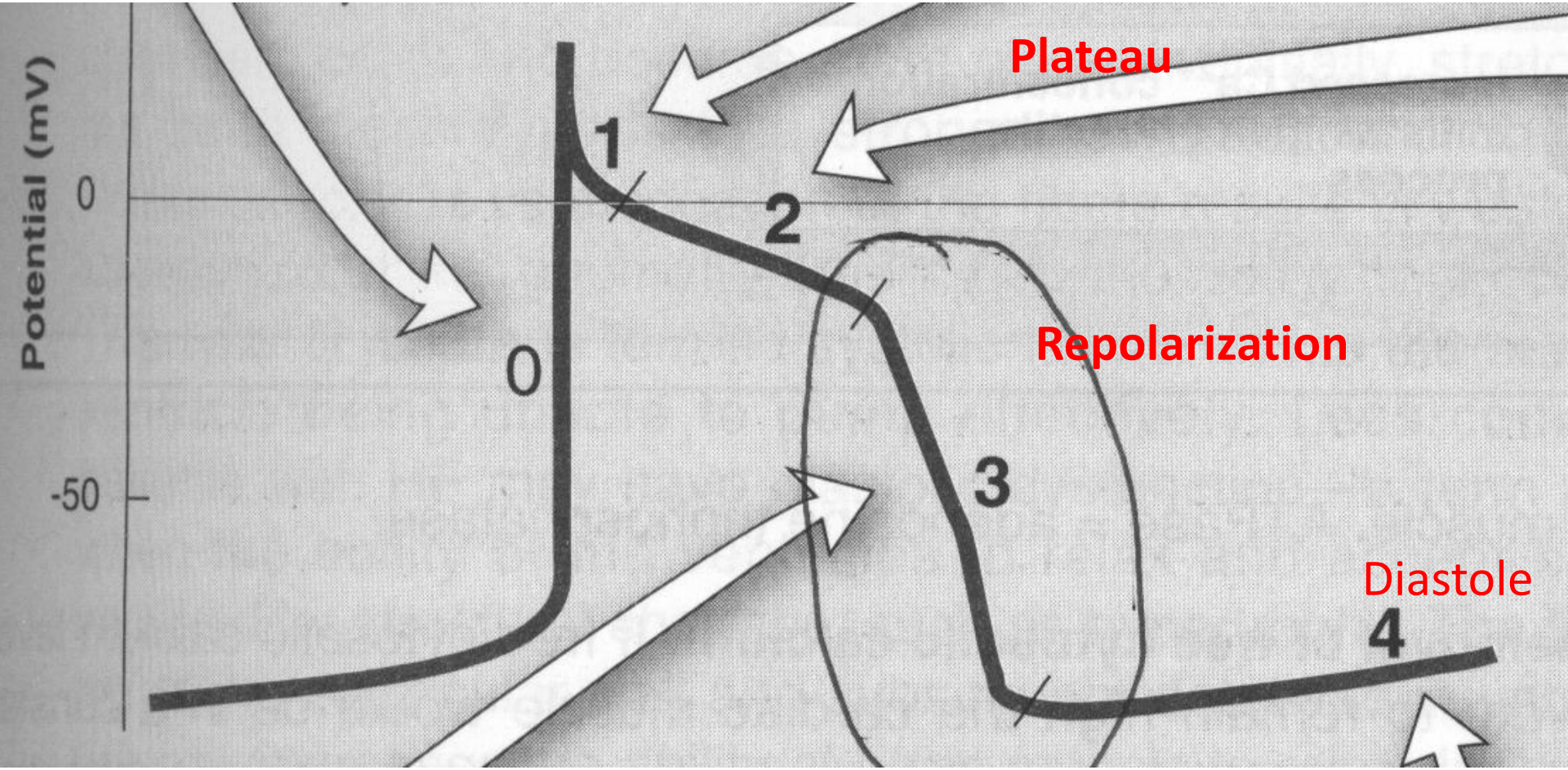
Fast Na^+ channels open

Blocked by “Quinidine”

Early fast partial repolarization

Na^+ channel inactivate

K^+ channels rapidly open



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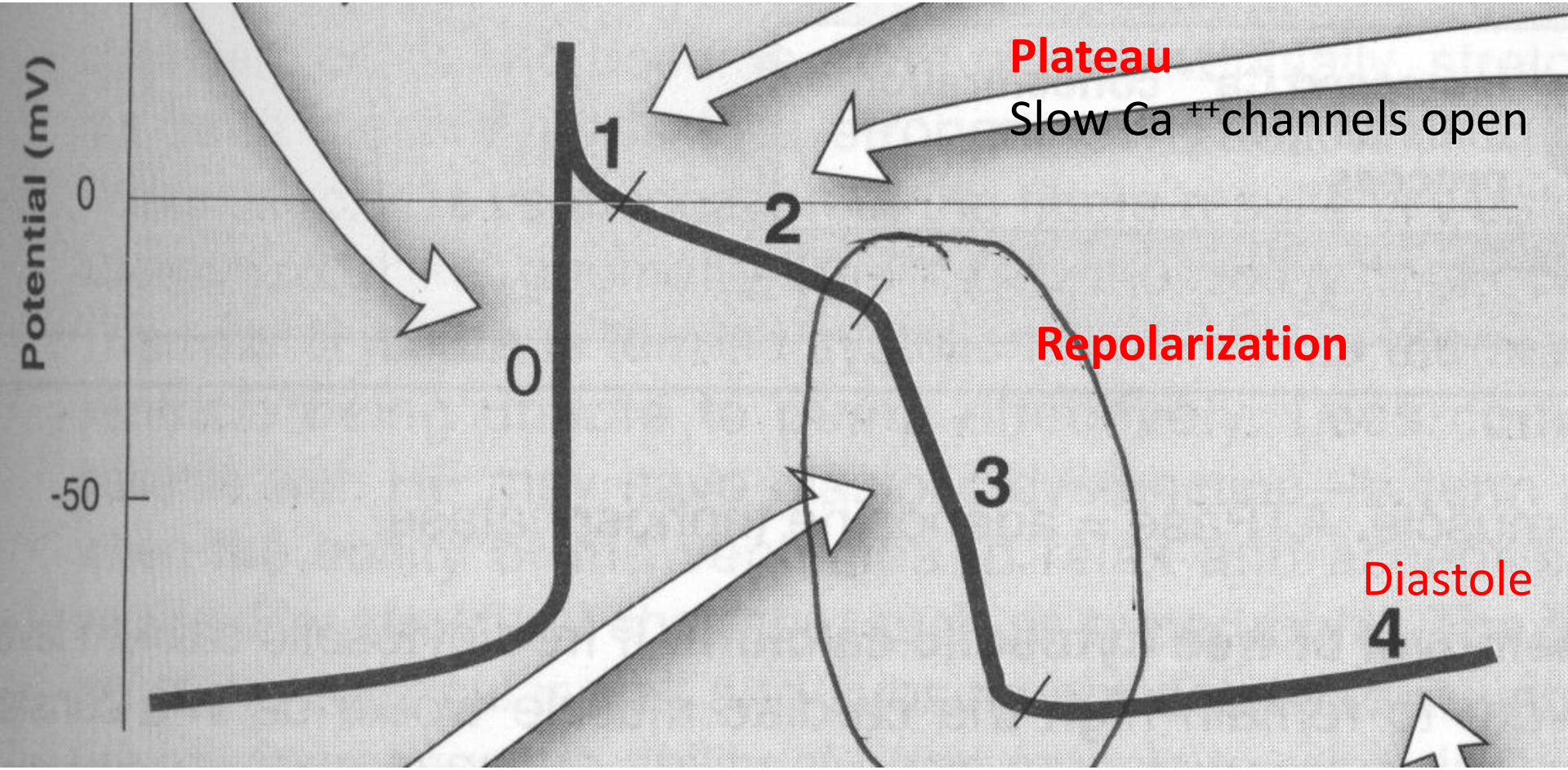


Fast upstroke

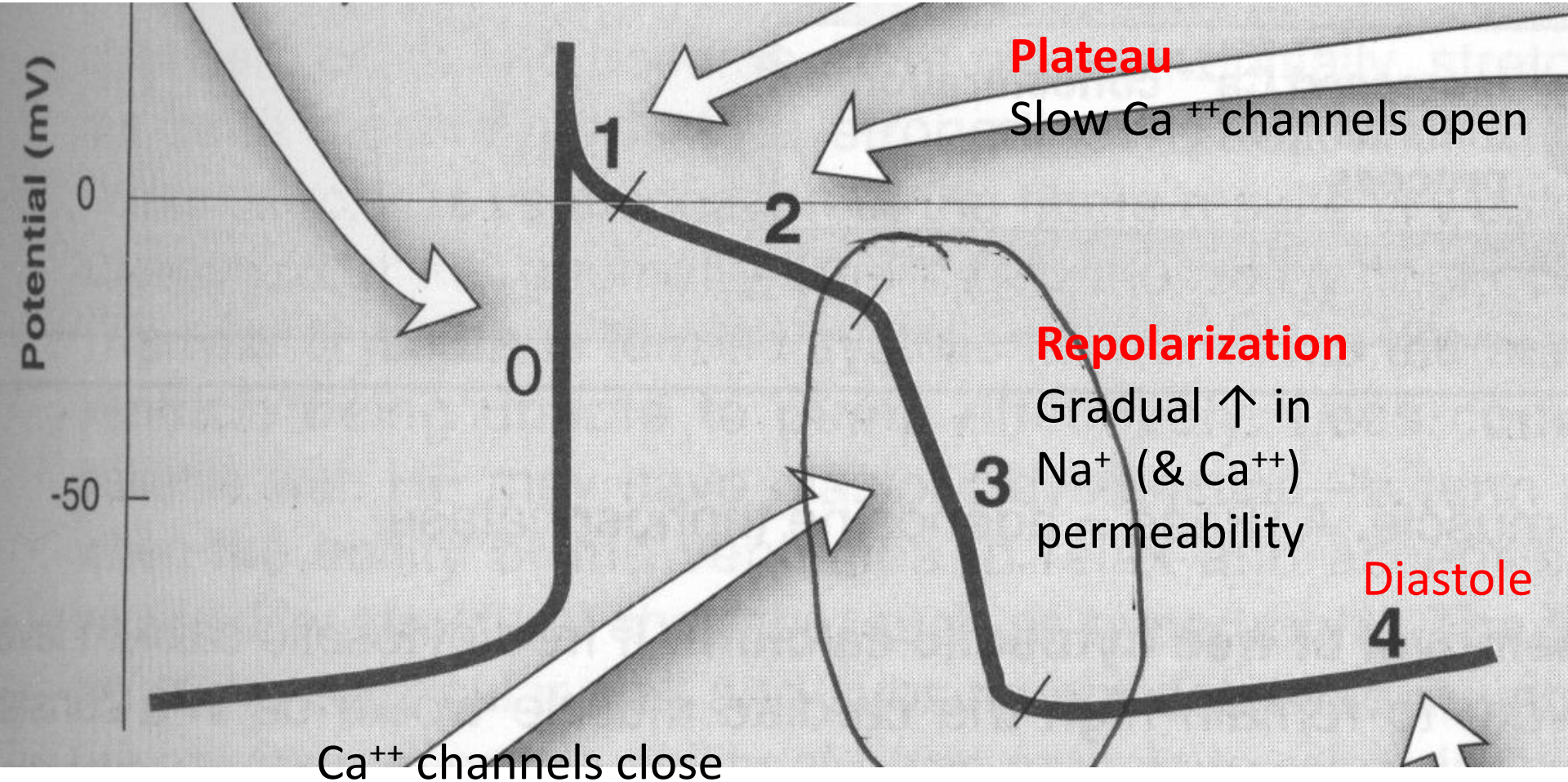
Fast Na^+ channels open

Blocked by “Quinidine”

Early fast partial repolarization

Na^+ channel inactivate

K^+ channels rapidly open



Fast upstroke

Fast Na^+ channels open

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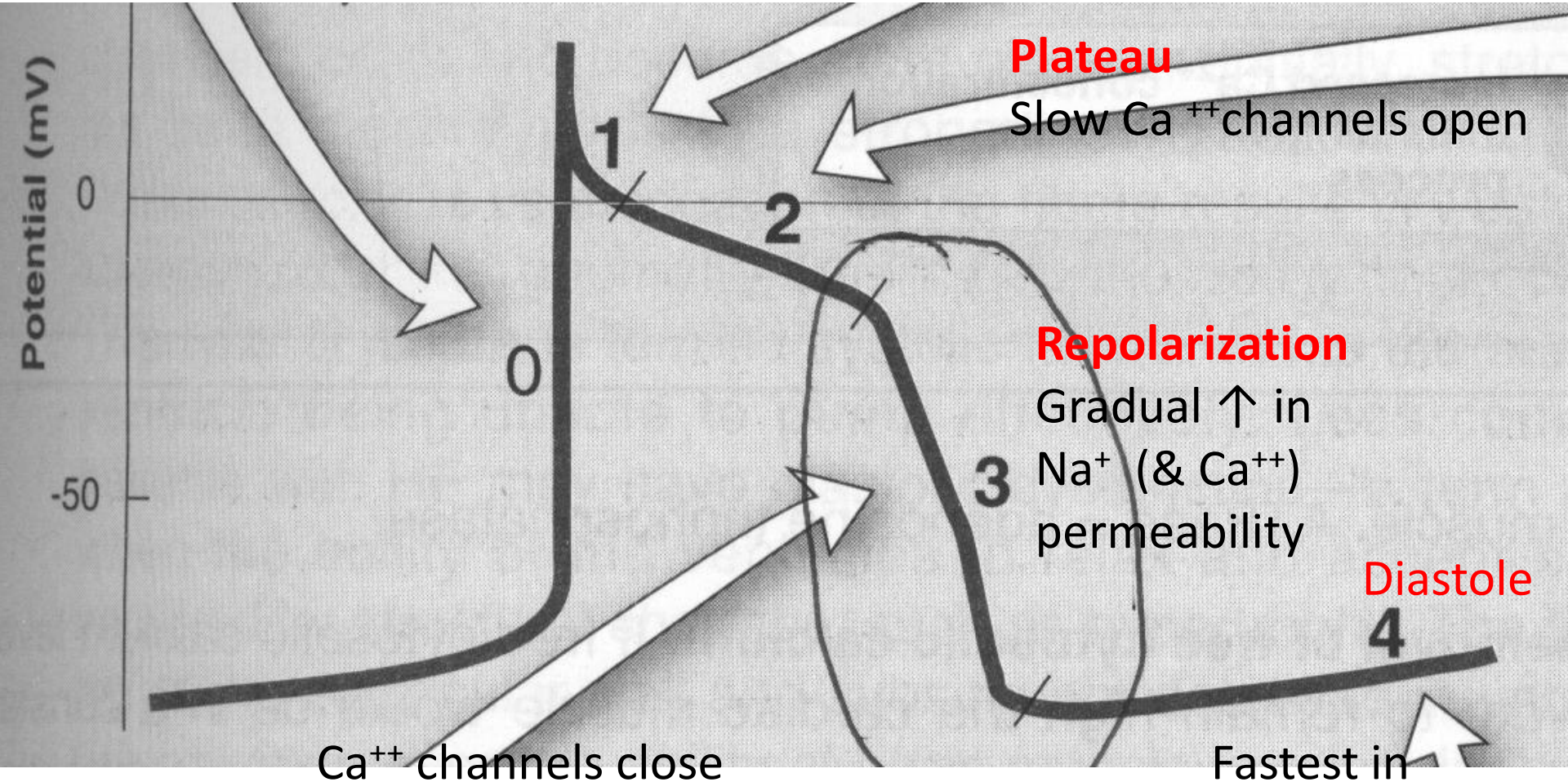
Na^+ channel inactivate

K^+ channels rapidly open



Ca^{++} channels close

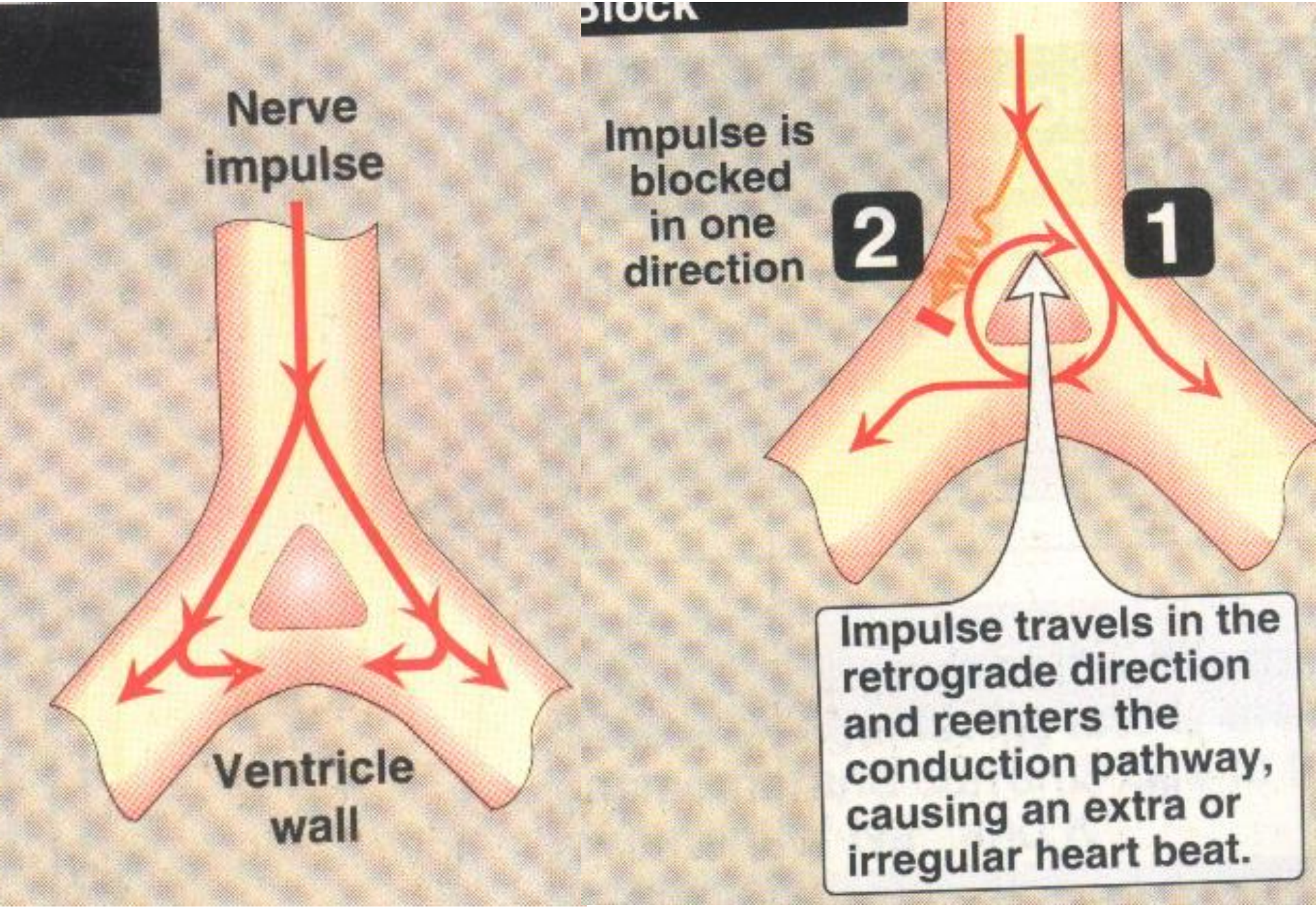
K+ channels open

Fastest in pacemaker cells

Most common mechanisms of arrhythmias

- **Abnormal automaticity**
  - Pacemaker activity that originates anywhere other than in the SA node
- **Abnormal (reentrant) conduction**
  - Conduction of impulse that does not follow the path defined or reenters tissue previously excited

Abnormal (reentrant) conduction



Arrhythmia (dysrhythmia)

- **Any rhythm that is not a normal sinus rhythm** is an arrhythmia
- Clinically most important arrhythmias
  - Atrial fibrillation, Atrial flutter,
  - SVT (A-V nodal reentery)
  - VPCs, VT and VF
  - Torsade de pontis
    - Antiarrhythmic drugs and drugs that prolong the QT interval
    - Heritable --- Long QT syndromes

Treatment of arrhythmias

- **Nonpharmacological** (physical) means of treatment of cardiac arrhythmias
  - Pacemakers or
  - Electrical **cardioversion** by applying a D C shock to the chest or
  - via an implanted device (implanted defibrillators) Implantable cardioverter-defibrillator (ICD)
  - Radiofrequency catheter ablation
- **Drugs**

Classification of antiarrhythmic drugs (Vaughan williams and singh)

- Based on channel or receptor involved

Class I	Na+ channel blockers, membrane depressant drugs
	Ia, Ib, Ic
Class II	β-adrenoceptor blockers
Class III	K+ channel blockers
	amiodarone, sotalol
Class IV	Ca++ channel blockers
	Verapamil, diltiazem

Antiarrhythmic drugs unclassified in the Vaughan Williams system

Drug	use
Adenosine	S V T
Digoxin	rapid **AF, Afl** and PSVT
Atropine	sinus bradycardia
Adrenaline	cardiac arrest
Isoprenaline	heart block
Calcium chloride	V T due to hyperkalemia
Magnesium chloride	V F, digoxin toxicity

Summary

Class	Example	Mechanism
• Ia	**Disopyramide**	Na+ channel block **(intermediate dissociation)**
• Ib	**Lidocaine**	Na+ channel block **(fast dissociation)**
• Ic	**Flecainide**	Na+ channel block **(slow dissociation)**
• II	**Propranolol**	β blockade
• III	**Amiodarone, Sotalol**	K+ channel block
• IV	**Verapamil**	Ca++ channel block

Summary

- Class I agents also have Class III properties
- Propranolol has Class I action as well
- Sotalol and bretylium have both Class II and Class III action

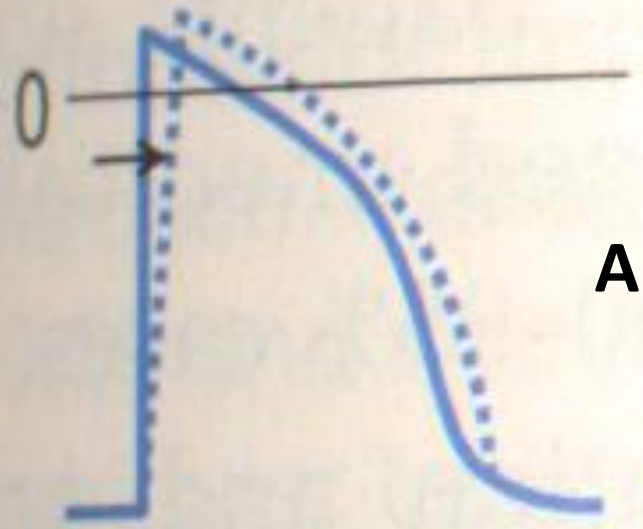
Class I anti arrhythmic drugs

- Na+ channel blockers (membrane depressant drugs)
  - » (**Use-dependence or state dependence)** Drugs binds more rapidly to open or inactivated Na + channels --- fast tachycardia or hypoxia
- Cause a ↓ in excitability and conduction velocity
- Use declining due to their possible **proarrhythmic effects**, particularly in patients with reduced LVF and IHD

Class I antiarrhythmics

- Class IA
  - Also reduce K+ current
  - **Prolong the AP**
  - Procainamide , quinidine, disopyramide
- Class IB -- (fast dissociation)
  - **Shorten the AP**
  - Lidocaine (lignocaine), mexilitine , phenytoin
- Class I C -- (slow dissociation)
  - **No effect on duration of AP**
  - Flecainide, propafenone

Procainamide
Disopyramide,
Quinidine

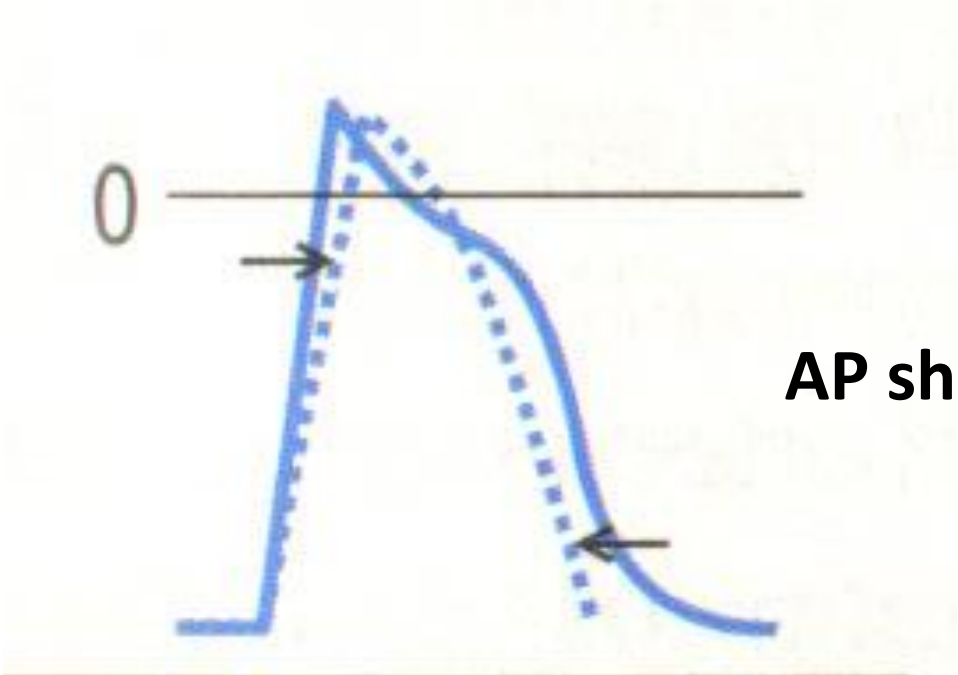


AP prolonged

Class Ia agents

Reduce rate of rise of phase 0
Lengthen action potential and slows the conduction

Lidocaine
Mexilitine
Phenytoin

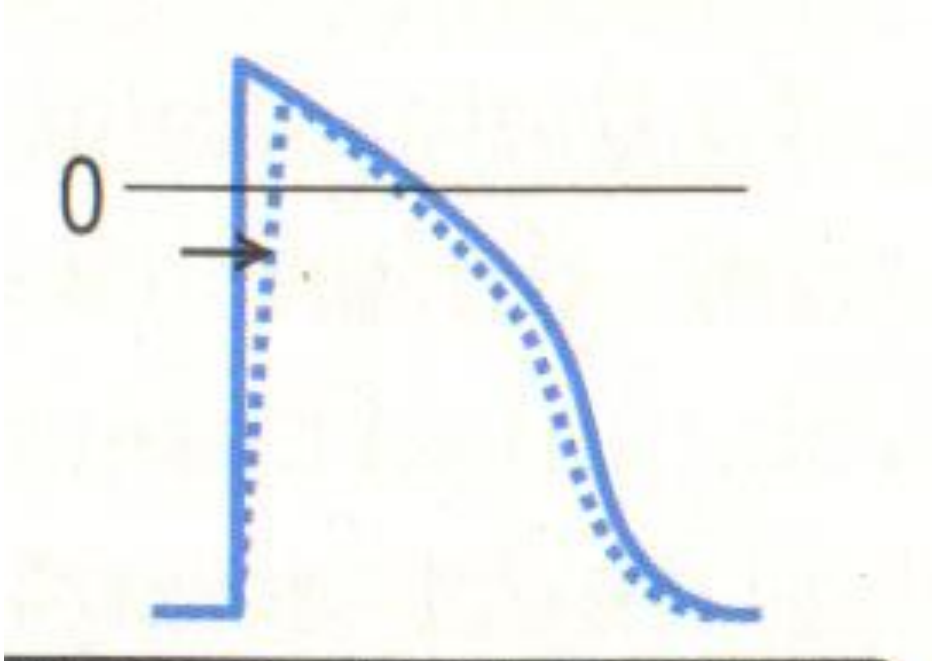


AP shortened

Class Ib agents

Reduce rate of rise of phase 0
Shorten action potential

flecainide

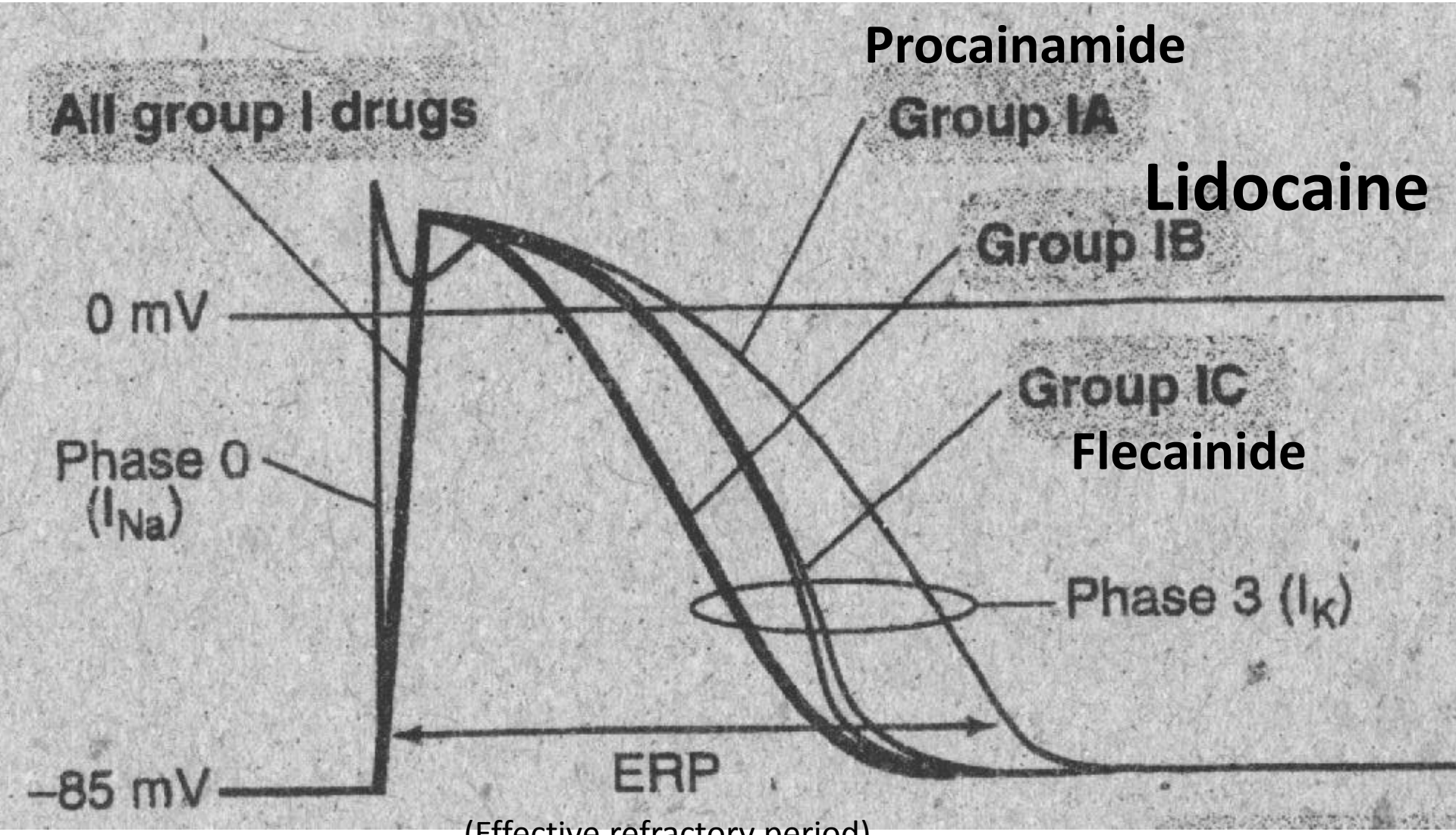


Class Ic agents

Reduce rate of rise of phase 0

No effect on duration of action potential

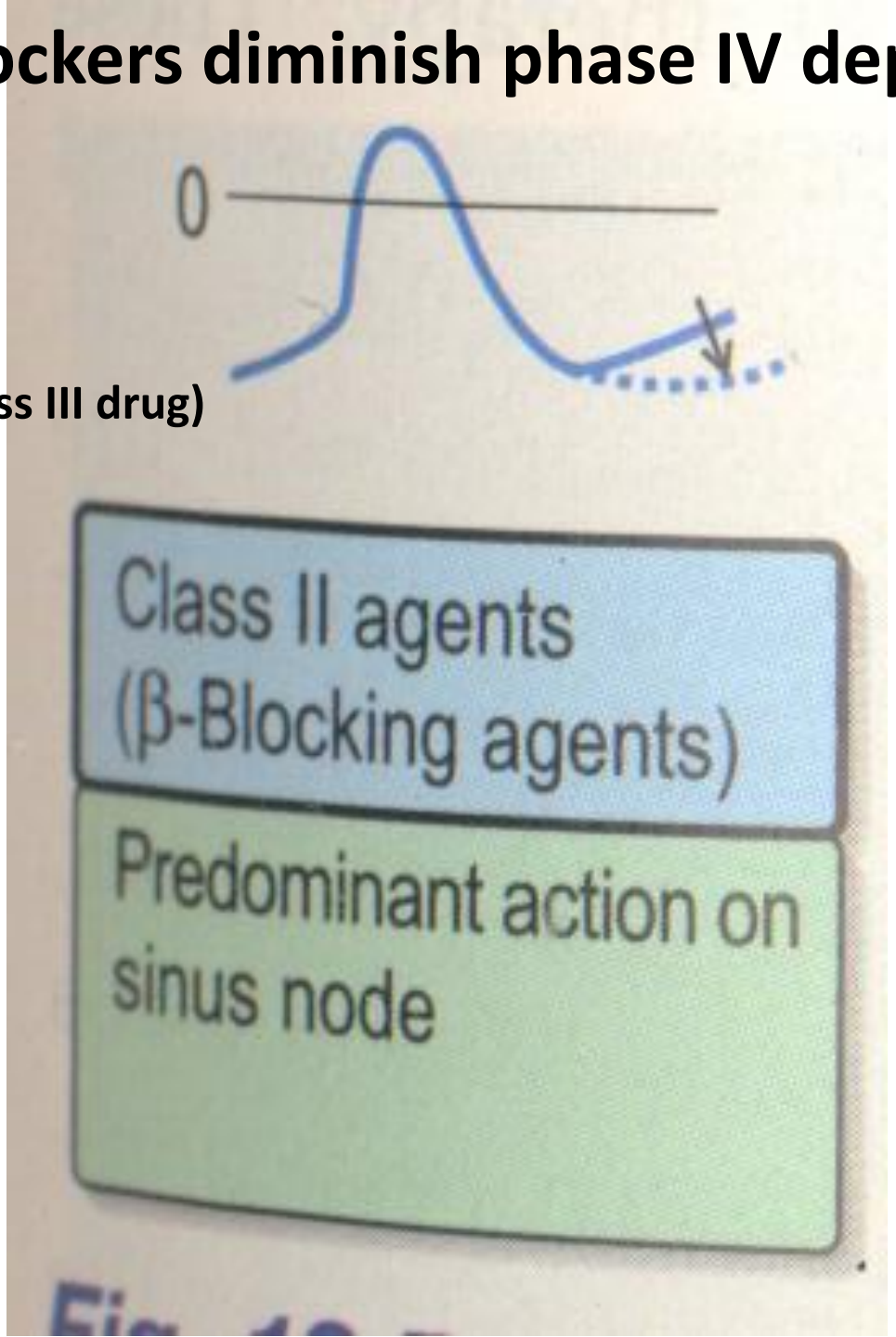
Ib & Ic have no effect on K + current and thus shorten or have no effect on AP duration

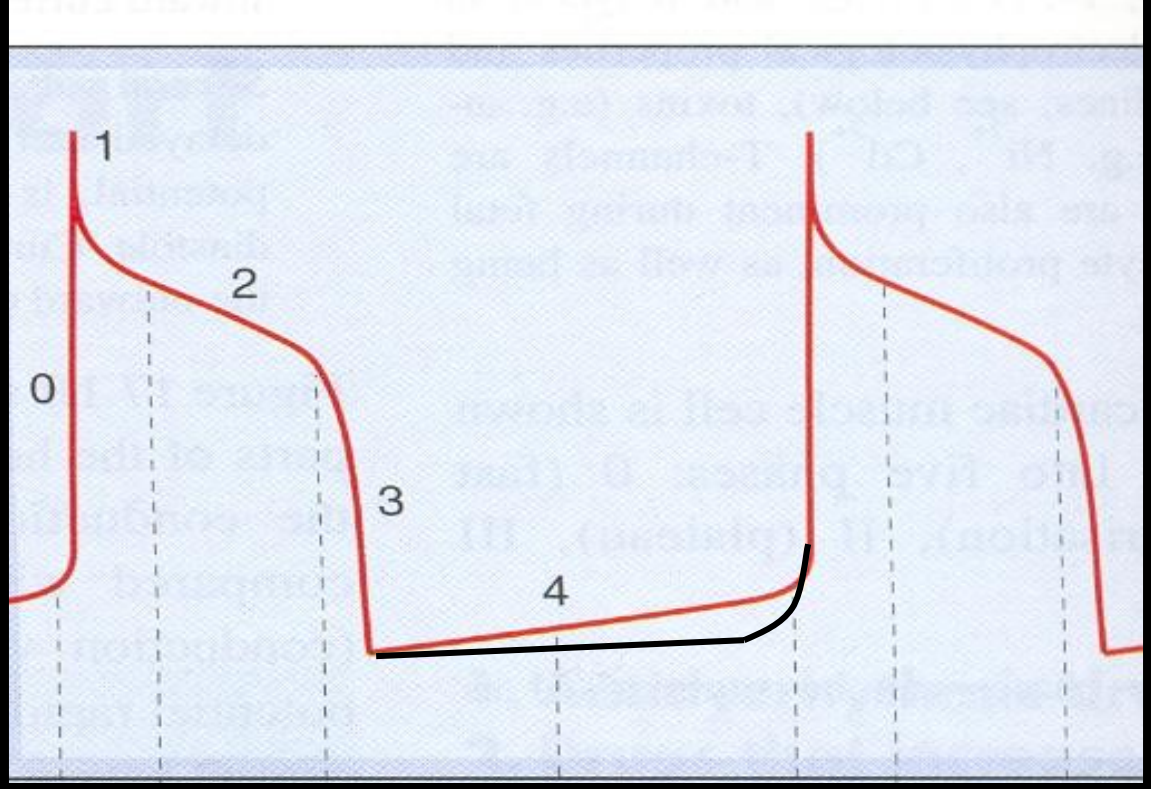


(Effective refractory period)

β blockers diminish phase IV depolarization

Propranolol,
Esmolol,
Sotalol **(also class III drug)**



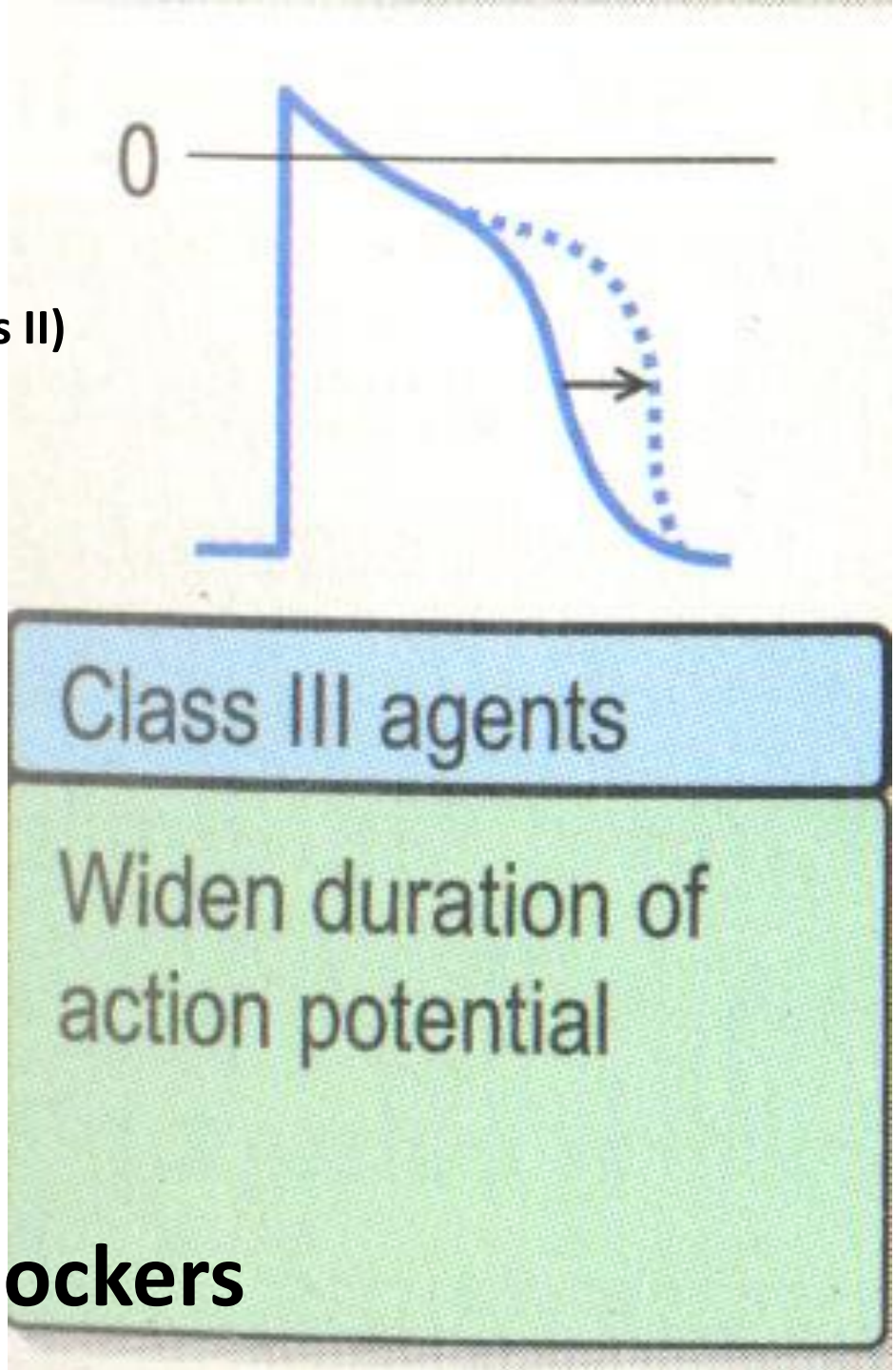


Phase 4 slope decreased

Beta Blockers,

Na+ & Ca++ Blockers

Amiodarone,
Bretylium **(also class II)**



K^+ channel blockers

Amiodarone

Sotalol

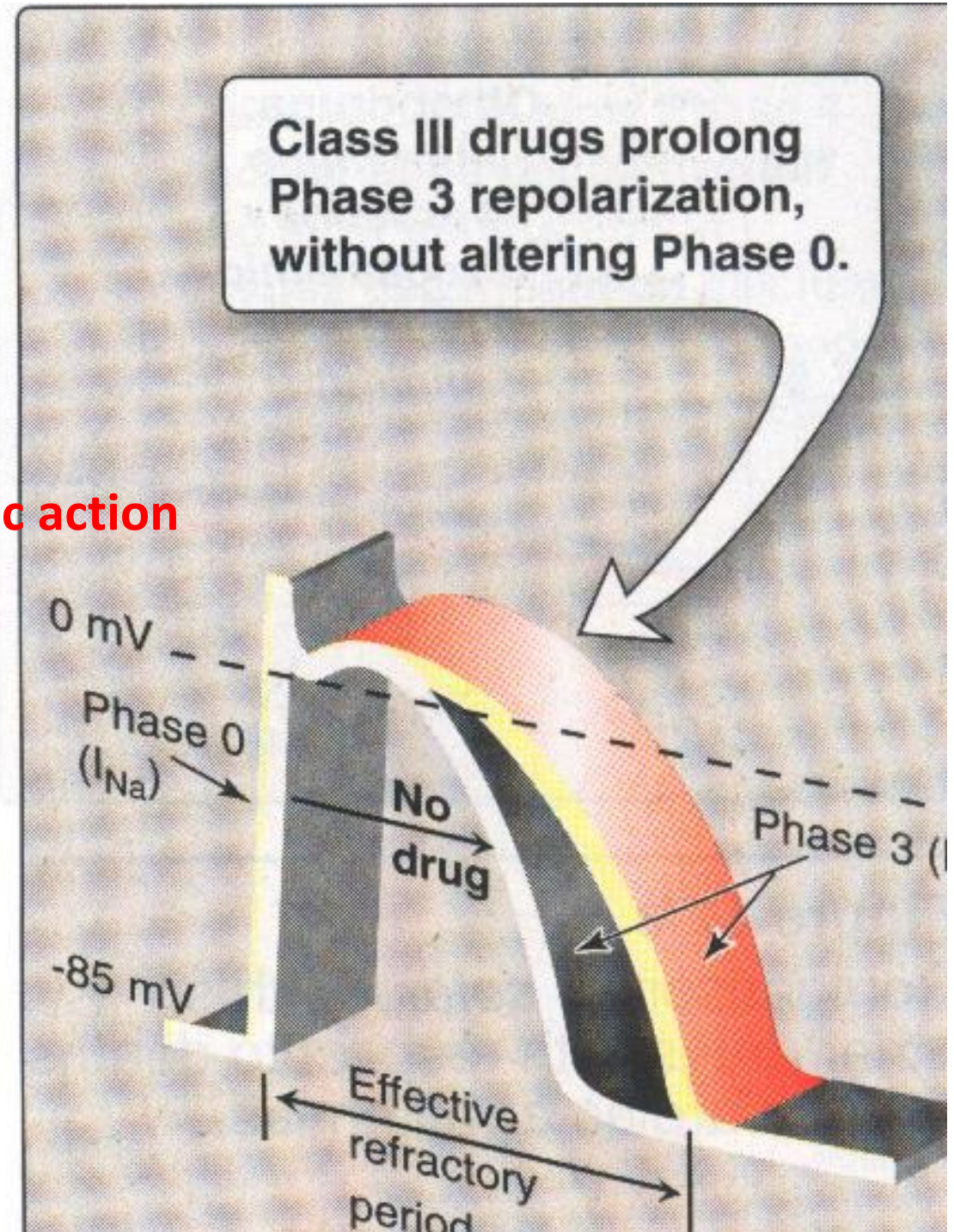
chiral compound

One isomer – β blocker

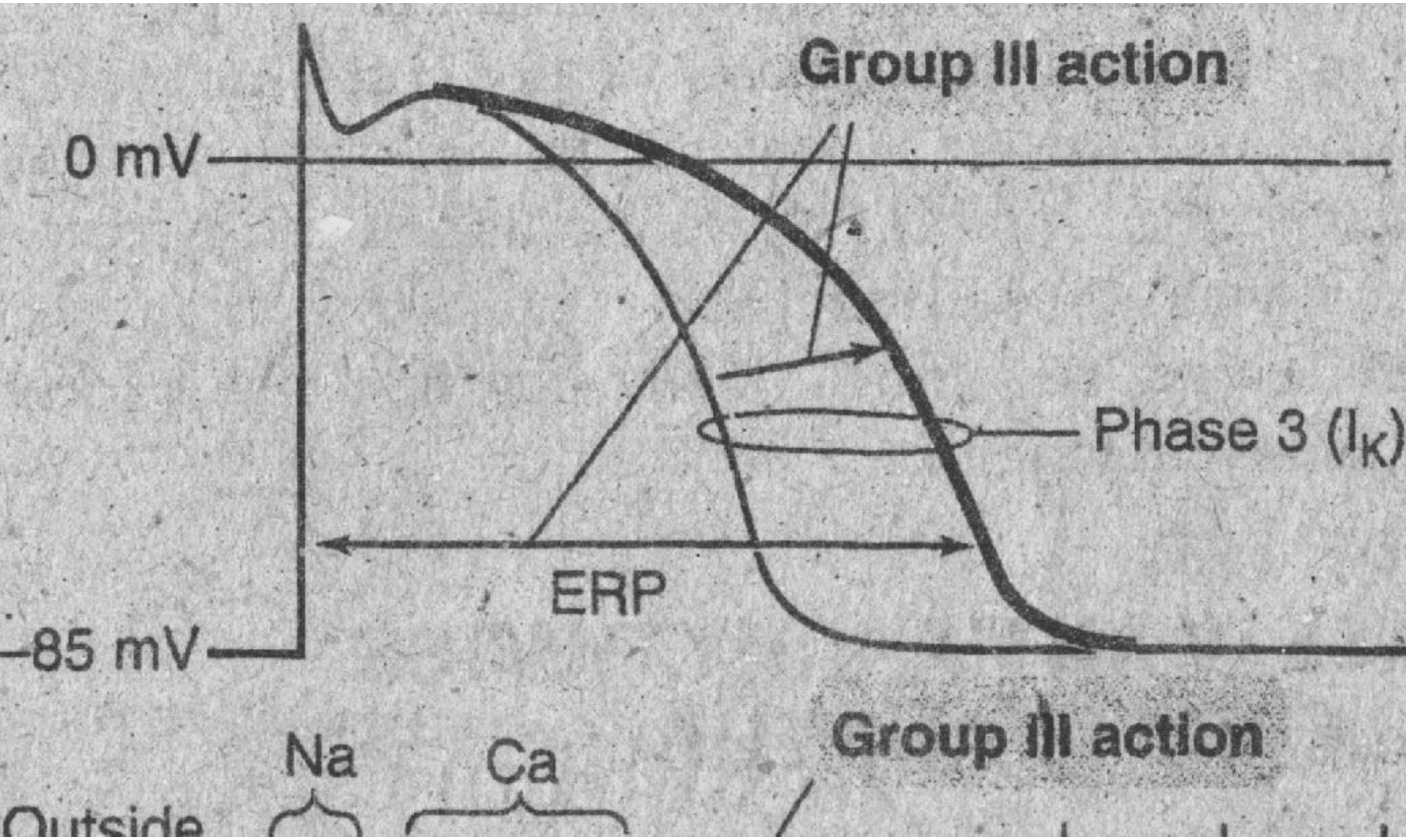
Both isomer – antiarrhythmic action

Ibutilide

Dofetilide

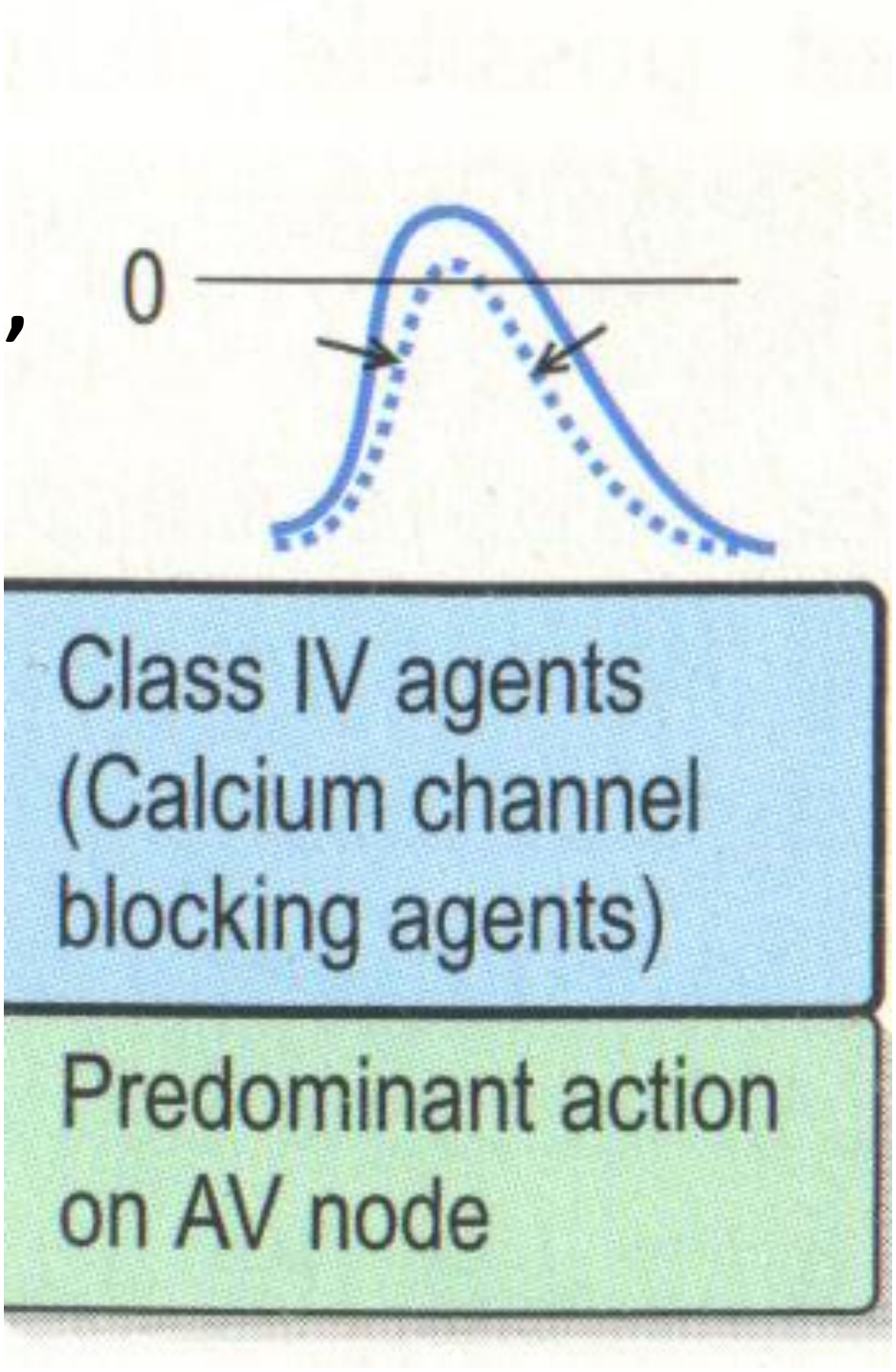


The main effect is to prolong the effective refractory period



Verapamil,

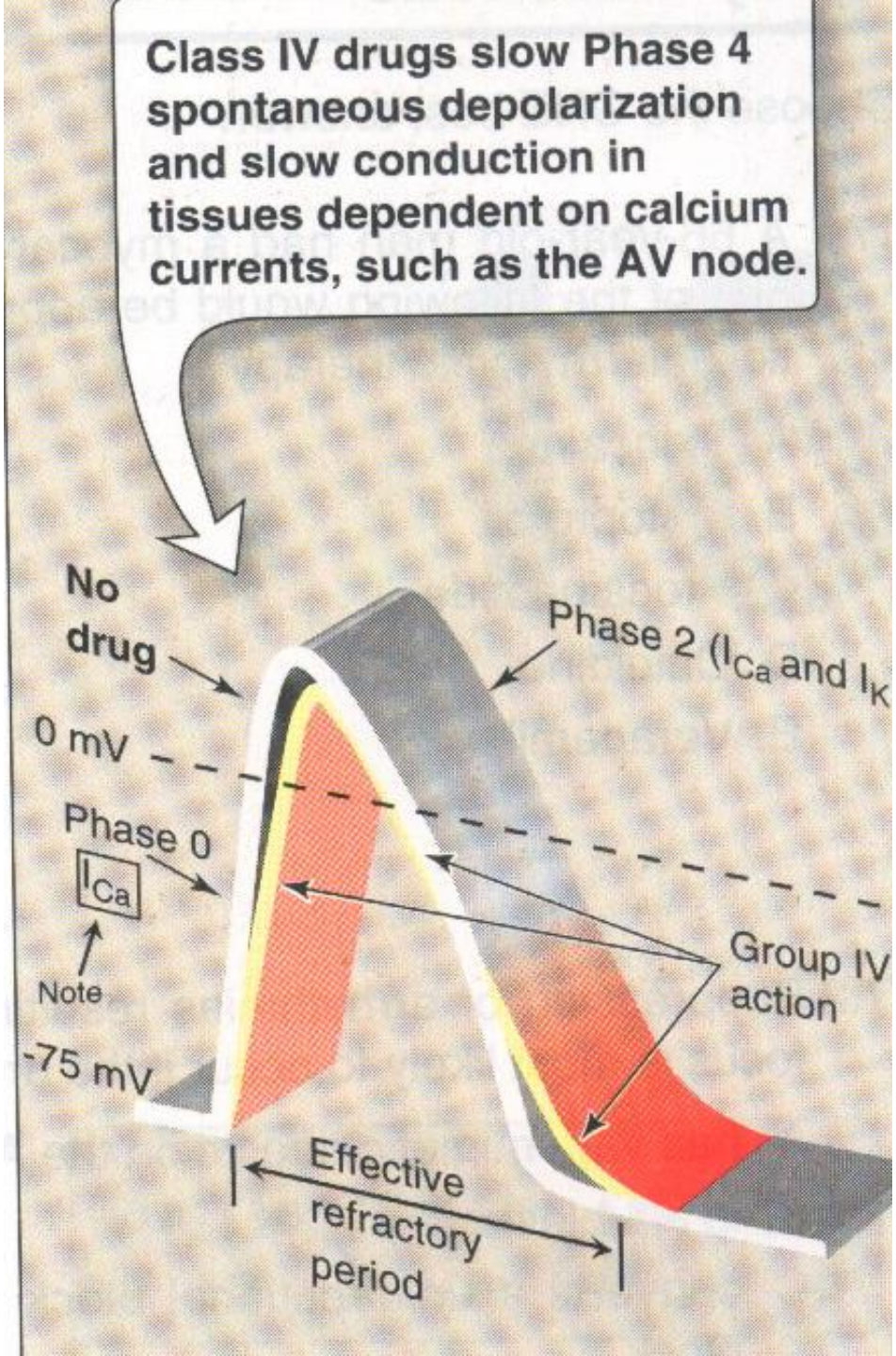
Diltiazem

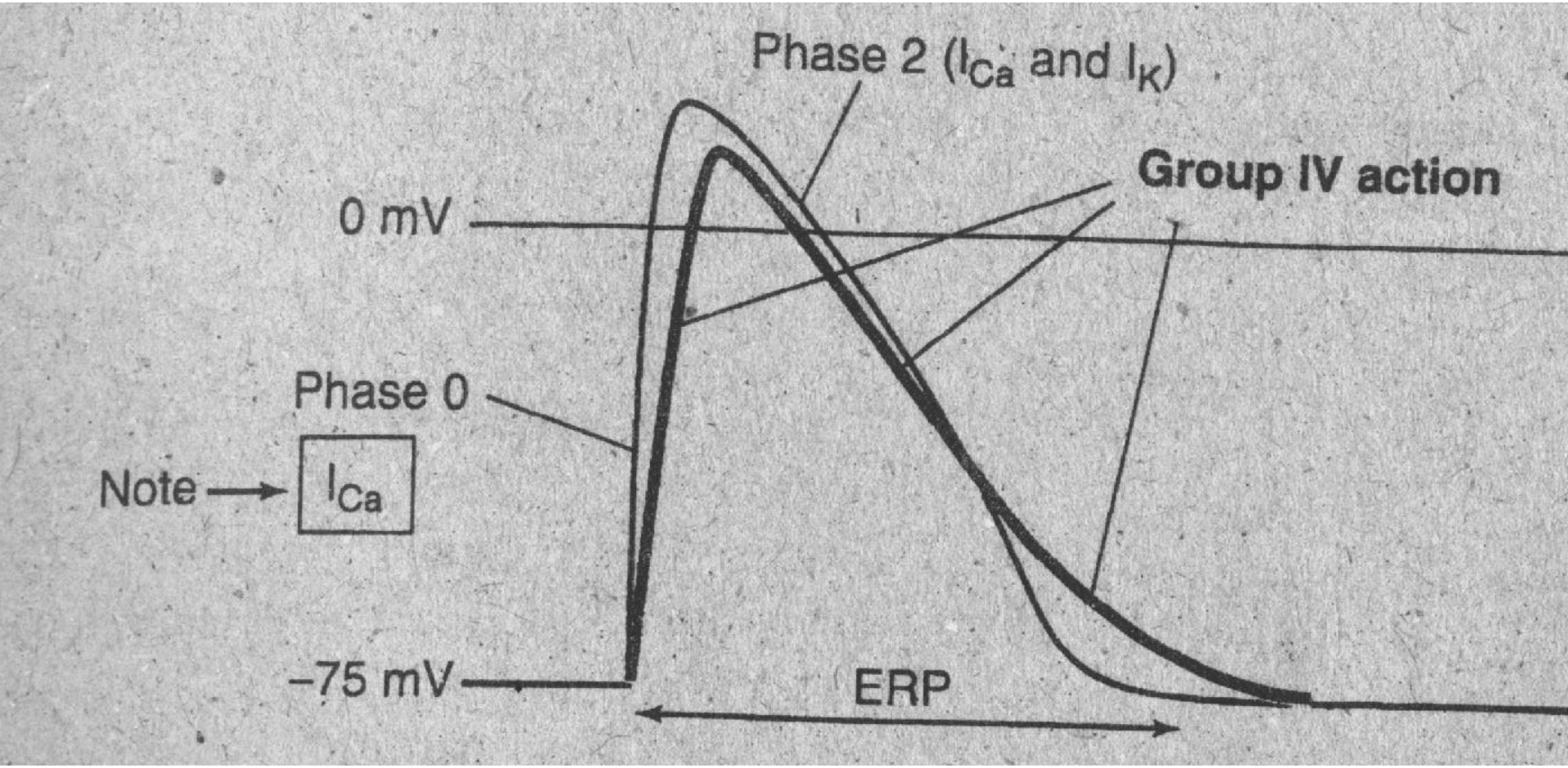


Verapamil,

Diltiazem

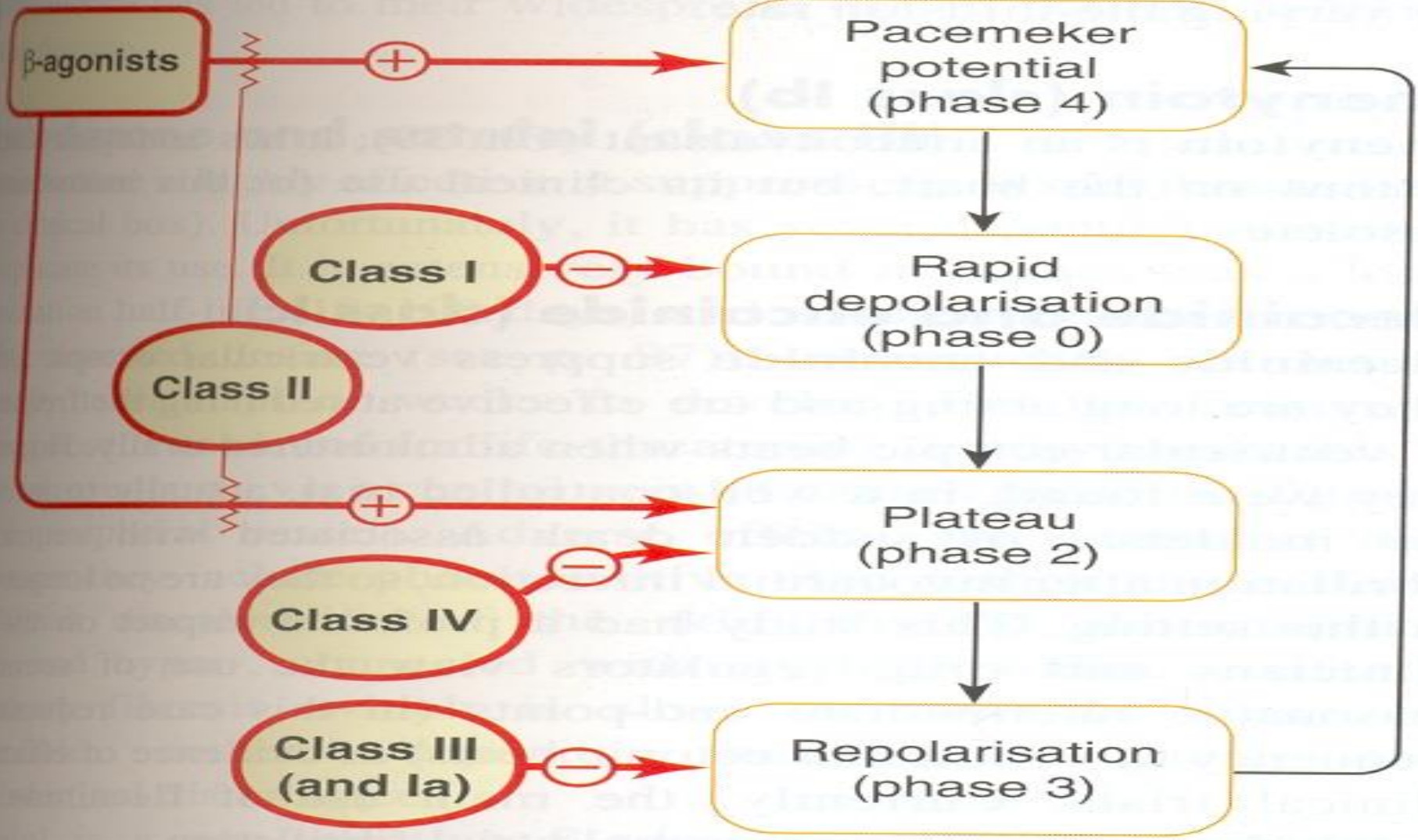
Upstroke in AV node is due mainly to CA^{++} current





Effects of Ca+ blockers on A V node

↓ conduction velocity, ↑ refractoriness



Effects of antidysrhythmic drugs on the different phases (as defined in Fig. 17.1) of the cardiac action potential.

Class of drug	Mechanism of action	comment
IA	Na+ channel blocker	Slows phase 0 depolarization
IB	Na+ channel blocker	Shortens phase III repolarization
IC	Na+ channel blocker	Markedly slows phase 0 depolarization
II	β blockers	Suppresses phase IV depolarization
III	K+ channel blocker	Prolongs phase III repolarization
IV	CCBs	↓ AV conduction

Asymptomatic

or

Minimally Symptomatic Arrhythmias

are usually ***not treated***

because

anti-arrhythmic drugs themselves

can precipitate lethal arrhythmias;

Treatment of arrhythmias

is needed only

if

- **cardiac output is reduced,**

  or if

- ***some arrhythmias can precipitate serious / lethal rhythm disturbances***

  e.g., ventricular fibrillations.

Cardiac Output is decreased due to:

Increased rate of contraction

Decreased rate of contraction

Asynchronised rate of contraction

Clinical uses of class I drugs

- Class Ia (e.g., **procainamide**, disopyramide)
  - Ventricular dysrhythmias
  - Prevention of recurrent paroxysmal AF triggered by vagal overactivity
- Class Ib (e.g., I/V lidocaine)
  - treatment and prevention of V T and V F during and immediate post MI
- Class Ic
  - To prevent paroxysmal AF (**flecainide**)
  - Recurrent tachyarrhythmias associated with abnormal conducting pathways (e.g., WPW syndrome)

Clinical uses of class II drugs

- **Esmolol,** a very short acting β blocker, given used exclusively in acute arrhythmias
- **Propranol**ol, metoprolol, and timolol
- To reduce mortality **following MI**
- To prevent recurrence of tachyarrhythmias (e.g., **paroxysmal A F**) provoked by increased sympathetic activity

Clinical uses of class III drugs

- **Amidarone** has a broad spectrum (effective in most type of arrhythmias) and is most efficacious of all antiarrhythmic drugs
- Tachycardia associated with the WPW syndrome.
- It blocks Na, Ca, and K channels and β adrenoceptors

Clinical uses of class III drugs

- **Sotalol (racemic) -- chiral compound**
- **One isomer – β blocker**
- **Both isomer – antiarrhythmic action**
- Combines class III with class II actions
- It is used in paroxysmal supraventricular dysrhythmias and suppresses ventricular ectopic beats and short runs of V T

Clinical uses of class IV drugs

- **Verapamil** is the main drug. It is used
  - To prevent recurrence of **paroxysmal SVT**
  - To reduce ventricular rate in patient with **AF**, provided they do not have WPW syndrome or a related disorder
  - Contraindicated in WPW syndrome
  - Dangerous and ineffective in Ventricular dysrrhythmias
- Verapamil was previously given I/V to terminate S V T, it is now seldom used for this because **adenosine** is safer
- Diltiazem has relatively more smooth muscle relaxing effect and produce less bradycardia

Contraindication

- **CCF**
  - **Disopyramide, Flecainide, beta blocker**
- **SA node/AV node dysfunction**
  - **Beta blockers, Ca++ channel blockers, Digoxin**
- **MI**
  - **Flecainide**
- **Prolong Q-T interval**
  - **Quinidine, procaineamide, disopyramide, sotalol, bretyllium, amidarone, ibutilide**

Adverse effects

- **Quinidine**
  - **GIT, Cinchonism, Idiosyncracy**
- **Procainamide**
  - **SLE, GIT, Allergic**
- **Disopyramide**
  - **Atropine like** (antimuscarinic effects and may precipitate HF)
- **Lidocaine**
  - **CNS --- drowsiness, disorientation and convulsions**
- **Propofenone**
  - **taste, constipation, arrhythmias**

- **Amiodarone**
  - Accumulation in heart, liver, skin, tears
  - Microcrystal deposits in the cornea and skin
  - Thyroid dysfunction -- **hypo or hyperthyroidism, vasodilatation**
  - Paresthesias, tremors and pulmonary fibrosis
- **Bretyllium**
  - **Ganglion blockade**
- **Sotalol**
  - **beta blockade like**
- **Adenosine**
  - **vasodilatation, bronchospasm, heart block**

Adenosine

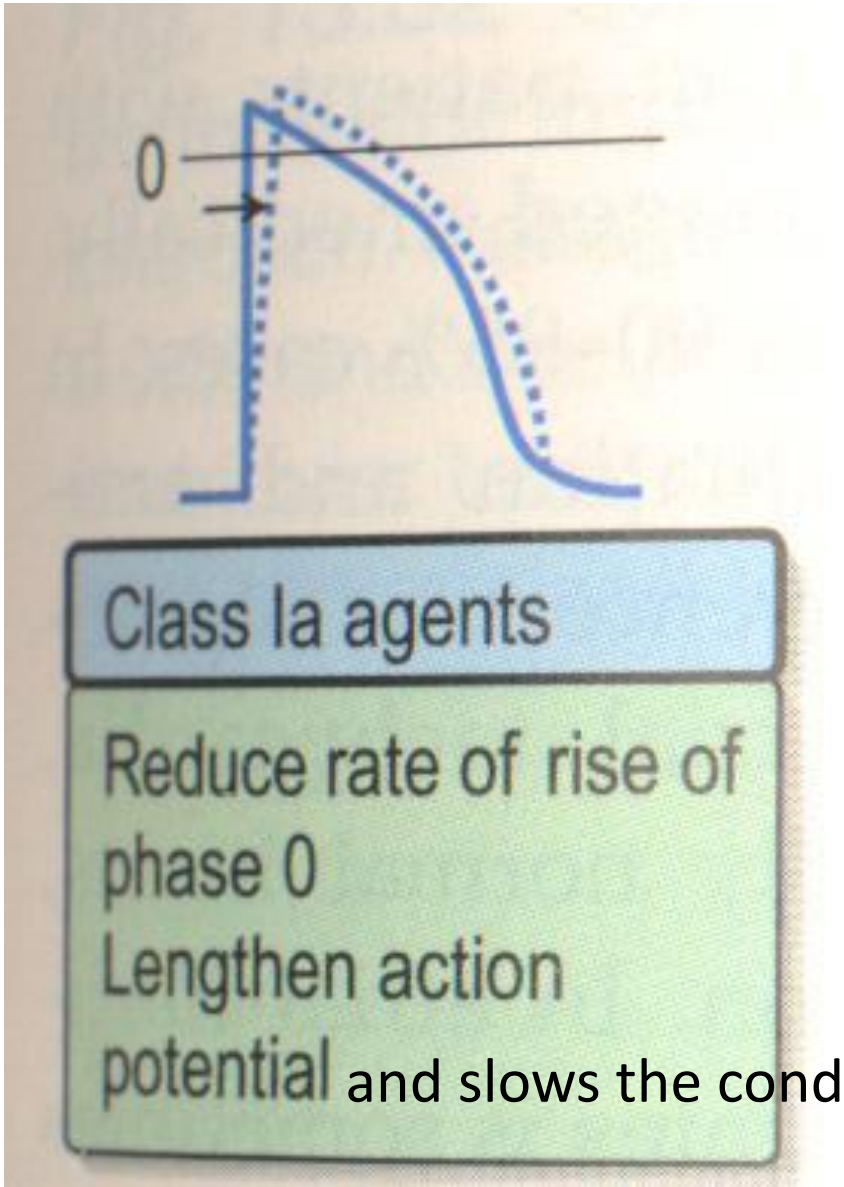
- **I/V adenosine is the drug of choice for acute SVT**
  - It markedly slows or completely blocks conduction in the AV node
  - prolongs the refractory period and
  - decreases automaticity in the AV node
- Act probably by hyperpolarizing this tissue (through increase I_{KI} and by ↓ Ca^{++} current)
- It has extremely short duration of action (about 15 seconds), given I/V bolus (6-12 mg)
- It has low toxicity
  - Flushing, chest pain, and hypotension

Class I anti arrhythmic drugs

- Na+ channel blockers
- Generally cause a ↓ in excitability and conduction velocity
- Use declining due to their possible proarrhythmic effects, particularly in patients with reduced LVF and IHD
- **Use-dependence or state dependence**
  - Drugs binds more rapidly to open or inactivated Na + channels --- shows a greater degree of blockade in tissues that are frequently depolarizing (during tachycardia)

Quinidine (class I A)

- Inhibits ectopic arrhythmias caused by increased automaticity
- Can induce tachycardia --- **anticholinergic effect**
- Atrial , A-V junctional , and V. tachyarrhythmias
- To maintain sinus rhythm after D-C cardioversion of AF and Afl
- To prevent frequent VT



Quinidine adverse effects

- Exacerbation of arrhythmia
- Quinidine may cause SA and AV block or asystole
- At toxic dose may induce VT
- Toxic effects exacerbated by hypokalemia
- N,V, diarrhoea
- Symptoms of cinchonism
  - Tinitis, headache, blurred vision, disorientation and psychosis
  - Mild alpha adenergic action as well as atropine like effects
  - Interaction with digoxin, phenytoin

Procainamide (class I A)

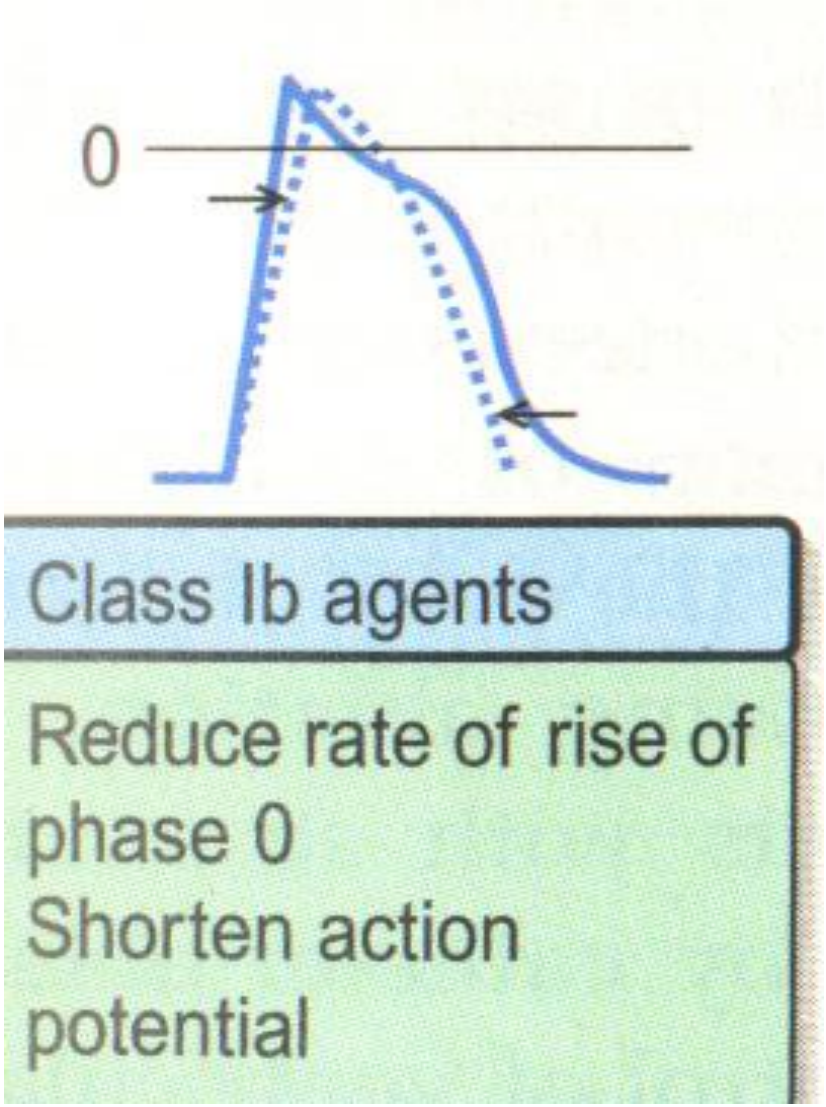
- A derivative of local anesthetic procaine
- Actions similar to those of quinidine
- Adverse effects
  - High incidence (25-30 %) of reversible SLE like syndrome
- Toxicity
  - Asystoe or induction of ventricular arrhythmia
  - CNS --- depression, hallucinations and psychosis

Diasopyramide (class I A)

- Actions similar to qunidine
- Negative inotropic effect
- Cause peripheral vasoconstriction
- Used in treatment of ventricular Arrhythmias as an alternative to procainamide or quinidine
- Adverse efrfects-- anticholinergic activity
- Use contraindicated in patient with HF

Lidocaine (class I B)

- Class I B drugs **rapidly associate and dissociate** from Na+ channels
- **Ventricular arrhythmia arising during MI**
- Little effect on atrial or A-V junctional arrhythmias
- Given I/V
- Fairly wide toxic -to-therapeutic ratio
- No negative inotropic effect
- CNS effects– drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsion
- Cardiac arrhythmias may occur

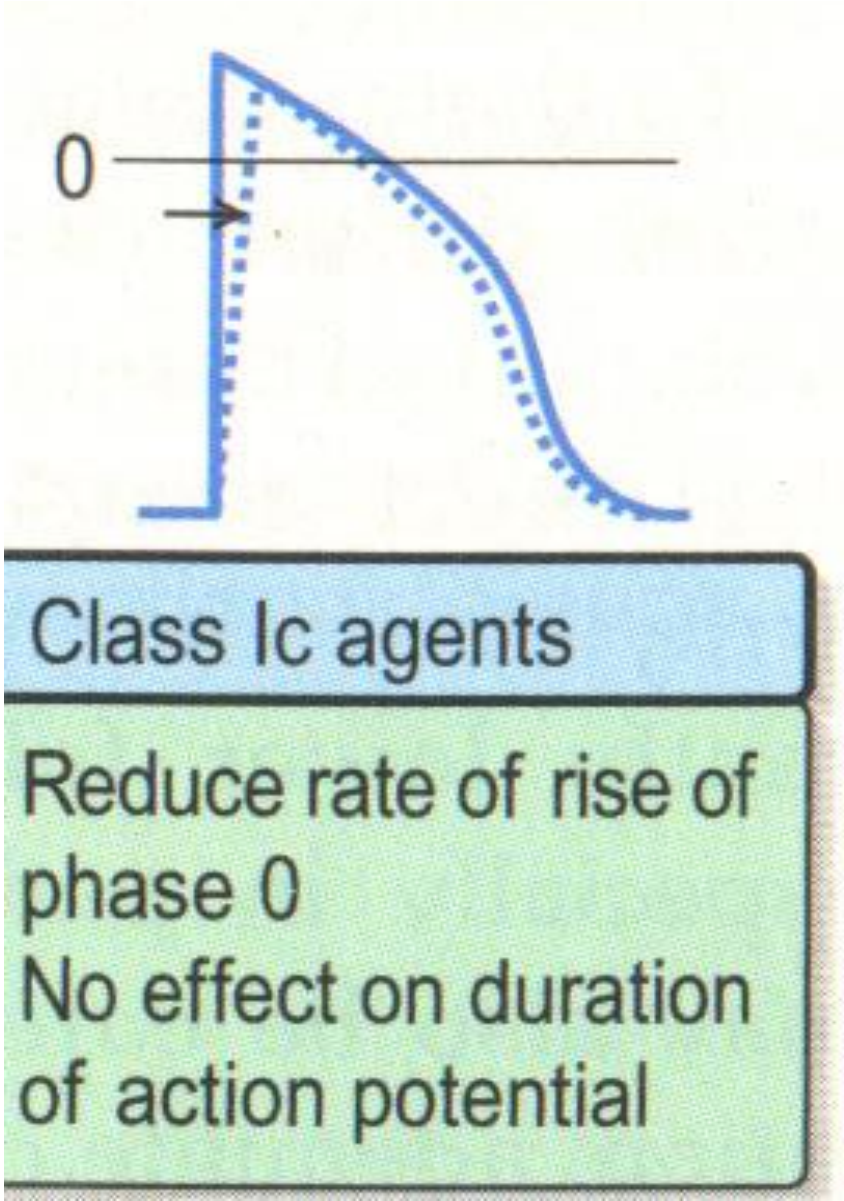


Class I B

- **Mexiletine**
  - Used in chronic treatment of arrhythmia associated with previous MI
- **Tocainide**
  - Used in treatment of ventricular tachyarrhythmias
  - May cause pulmonary fibrosis

Flecainide (class I C)

- **Slowly dissociate** from resting Na+ channel, and show prominent effects even at normal heart rates
- Approved **for use only for refractory ventricular arrhythmias**
- VPCs
- Negative inotropic effect and can aggravate HF

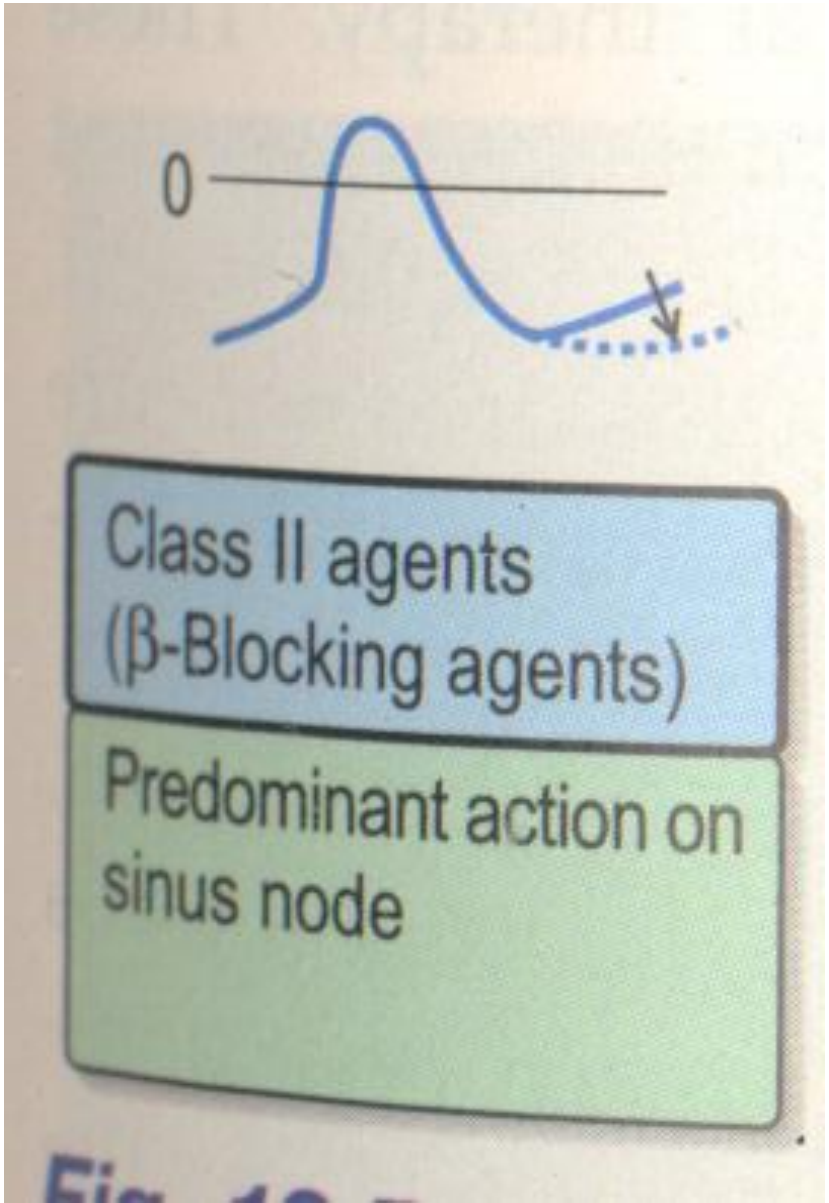


Flecainide (class I C)

- Adverse effects – dizziness, blurred vision, headache ,and nausea
- Can aggravate preexisting arrhythmia or induce life threatening VT that is resistance to treatment
- **Propafenone**
  - Class I C drug shows actions similar to flecainide

Class II(β blockers)

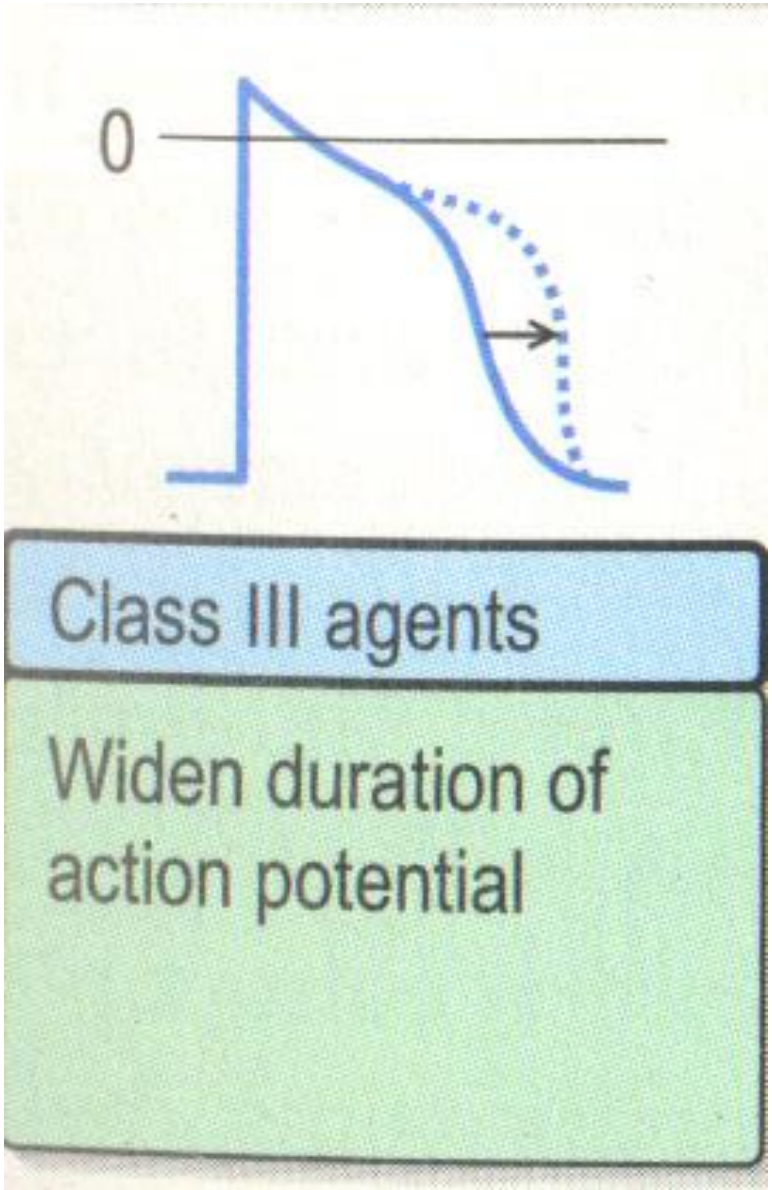
- These drugs **diminish phase IV depolarization**
- Depress automaticity
- Prolong A-V conduction
- Decrease heart rate and contractility
- Prevent the effect of cathecholeamines on the AP
  - Useful in treating arrhythmias caused by increased sympathetic activity
- AF, AFl, A-V nodal reentrant tachycardia



- Suppress A-v nodal conduction
  - Prevent attack **of junctional tachycardia**
  - Control ventricular rate during paroxysms of SVT (e.g., **AF)**
- Anti-ischemic and anti androgenic
  - Post MI
  - CHF
- Used either alone or in combination with other antiarrhythmic drugs
  - Tachyarrhythmia + coronary artery disease

- Reduce the incidence of sudden arrhythmic death after MI
- Cardioselective drugs are preferred
  - Atenolol, metaprolol
- Esmolol
  - Very short acting β blocker
  - Used I/V in acute arrhythmias that occur during surgery or emergency

Class III(amiodarone, sotalol)



Amiodarone

- Contains iodine and structurally similar to thyroxine
- Shows class I, II, III, IV actions
- Dominent effect is prolongation of AP and refractory period
- **Half life of several weeks**
- does not prolong QT interval
- Adverse effects
  - interstitial **pulmonary fibrosis, hypo- or hyperthyroidism**, tremor, ataxia, liver toxicity, photosensitivity, neuropathy, muscle weakness, and blue skin coloration caused by iodine accommodation in the skin

Sotalol

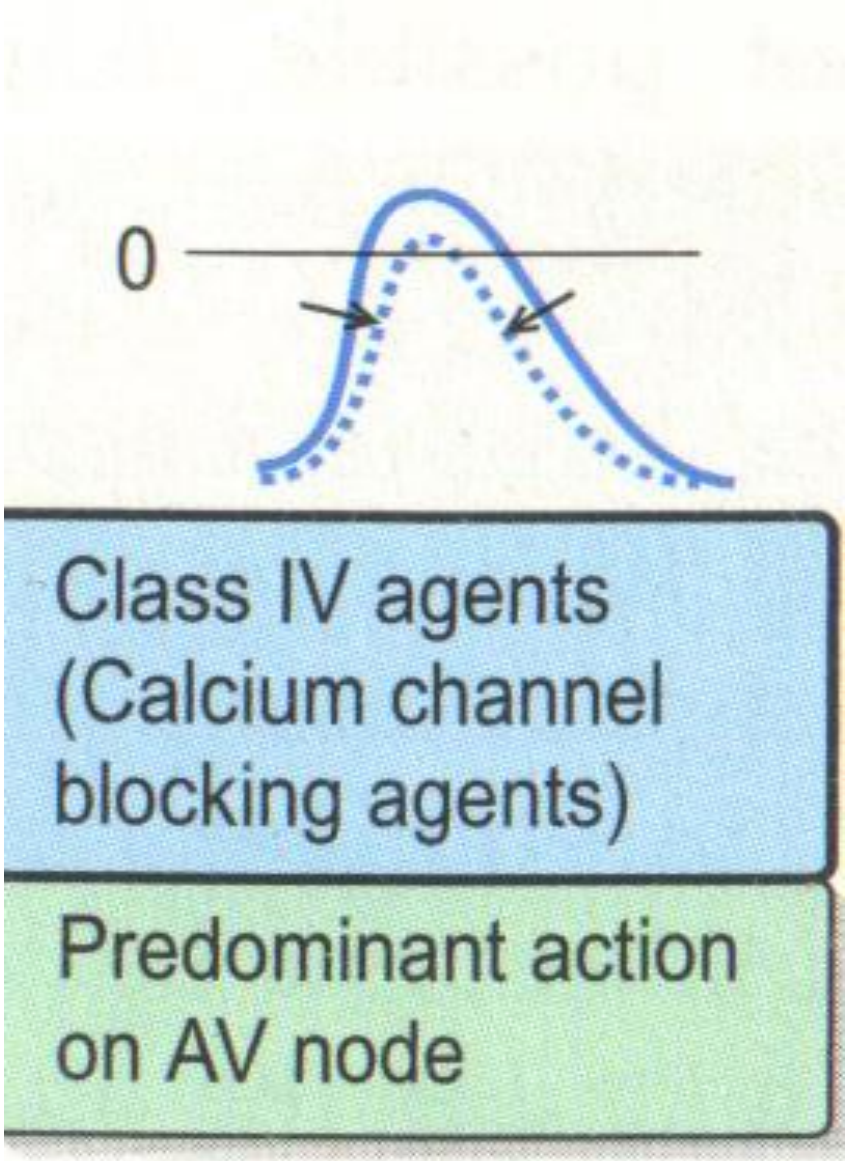
- Class III + non selective beta blocker
- Unlike other beta agonists it prolongs the cardiac AP and QT interval by delaying the slow outward current
- This class III activity is present in both L and D isomers
- Beta blocker decrease the rate of sudden death following an acute MI
- Suppress ectopic beats and reduce myocardial Oxy demand
- Adverse effect
  - All drugs that prolong the QT interval , the syndrome of torsade de pontis is a serious potential adverse effects, seen in 3 to 4 % of patients

Dofetilide

- Risk of pro arrhythmia
  - Initiation limited to the inpatient setting + specialist
- Can be used as first line anti-arrhythmic agent in patients with persistent AF and HF

Class IV (CCBs) Verapamil, diltiazem

- ↓ inward Ca++ current act on L-type channels
- conduction is slowed and effective refractory period is prolonged
- More effective against atrial than ventricular dysarrhythmias
- Reentrant SVT
- AF, Afl --- reduce Ventricular rate
- HTN and angina



CCBs

- Negative ionotropic
  - Contra indicated in patients with CHF
- Beneficial in patients with HTN and angina
- Contraindicated in patients with WPW syndrome, and is ineffective and dangerous in ventricular arrhythmias

Digoxin

- Excites the myocardium and depresses the conducting tissue
  - Shortens the refractory period in myocardial cells
  - prolonging the refractory period and decrease conduction velocity in purkinji fibers
- Used in AF and Afl
  - to control ventricular response rate
- In toxic concentration causes VPc that may lead to VT and VF (treated by lidocaine or phenytoin)

Adenosine

- I/V adenosine is the drug of choice for acute SVT
  - It decreases conduction velocity
  - prolongs the refractory period and
  - decreases automaticity in the AV node
- It has low toxicity
  - Flushing, chest pain, and hypotension

Torsades de pointes

- Class I A
  - Quinidine, Disopyramide, procainamide,
- Sotalol, amiodarone
- Amitriptyline(and other tricyclic antidepressants)
- Chlorpromazine (and other phenothiazines)
- Erythromycine and other macrolides and
- fluoroquinolones

Classification of antiarrhythmic drugs (unclassified in Vaughan williams)

- Miscellaneous group

  1. for PSVT **Adenosine,** digitalis

  2. for A-V block

     Atropine anticholinergic
     Isoprenaline sympathtomimetic

  3. **digitalis** is used in

  AF, Afl and PSVT to control ventricular rate