Antiarrhythmic Drugs

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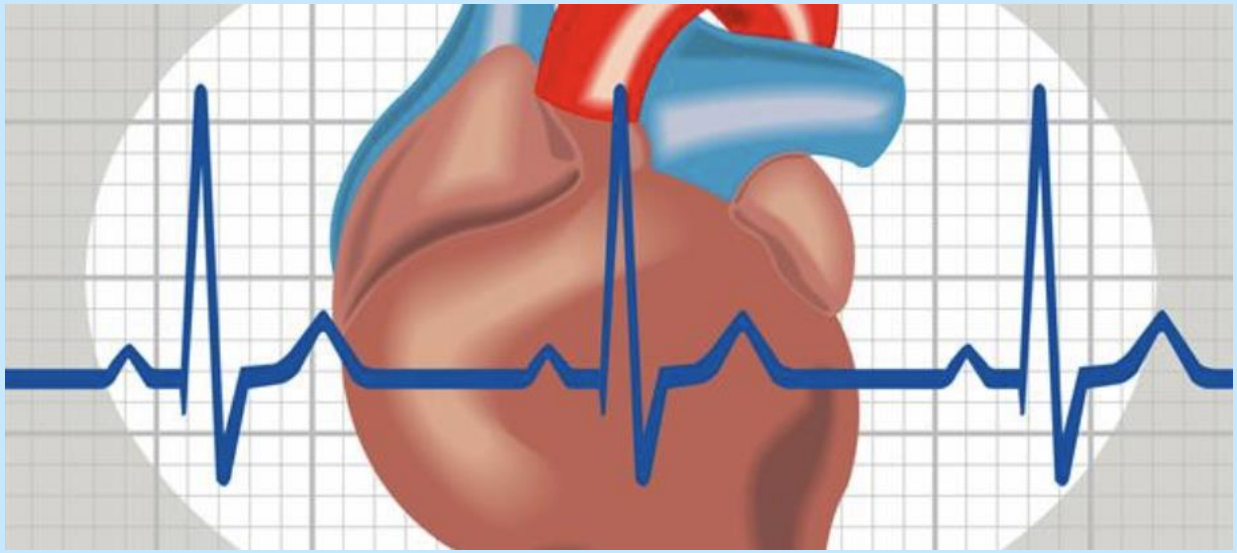


Cardiovascular Pharmacology

- Antiarrhythmic drugs
- Drugs in heart failure
- Antihypertensive drugs
- Antianginal drugs
- Antihyperlipidemic drugs

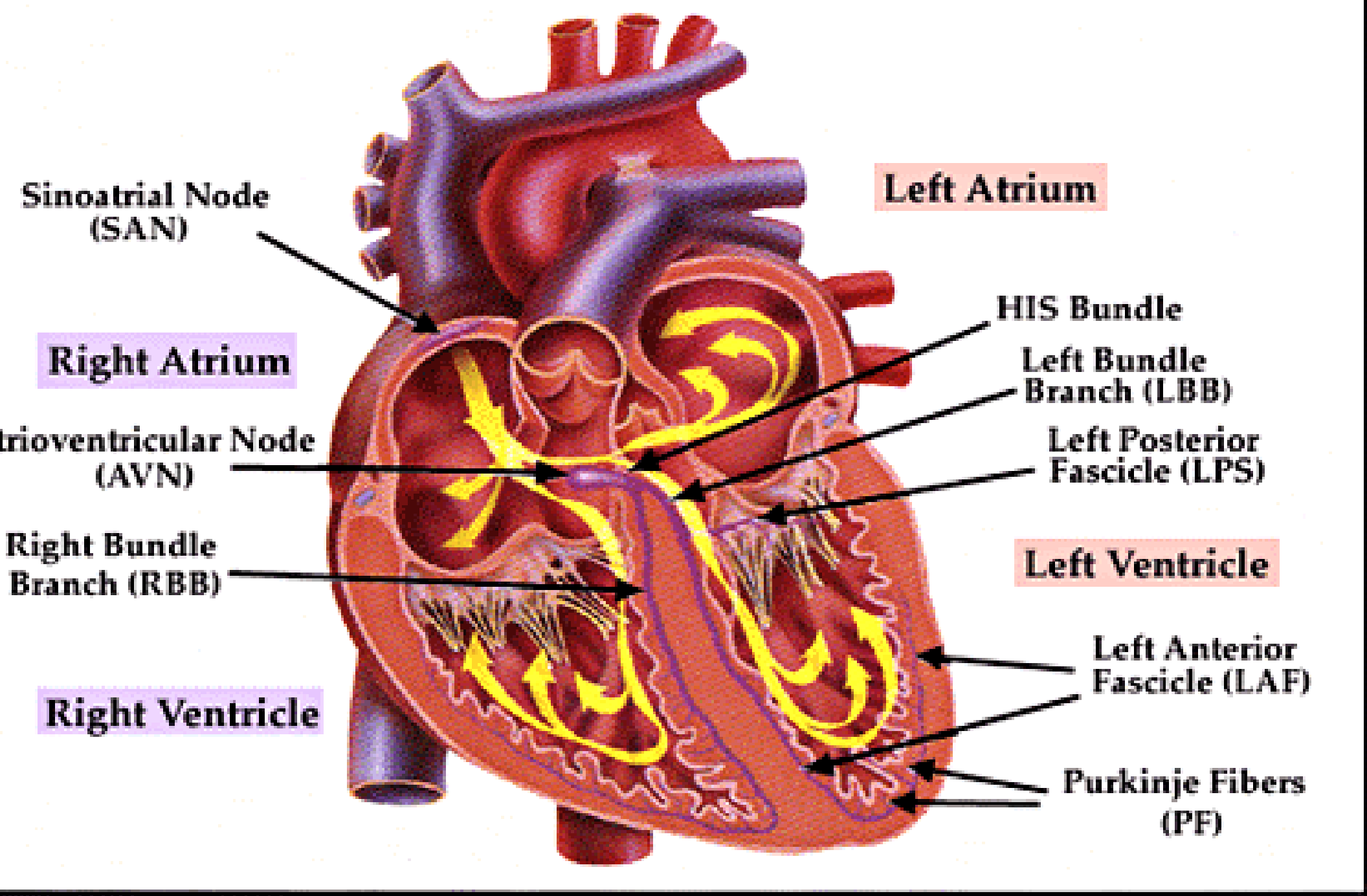
Learning objectives

By the end of this lecture, students should be able to:

- Understand definition of **arrhythmias** & their different types

- Describe different classes of **Antiarrhythmic drugs** & their mechanism of action

- Understand their pharmacological actions, clinical uses, adverse effects & their interactions with other drugs.

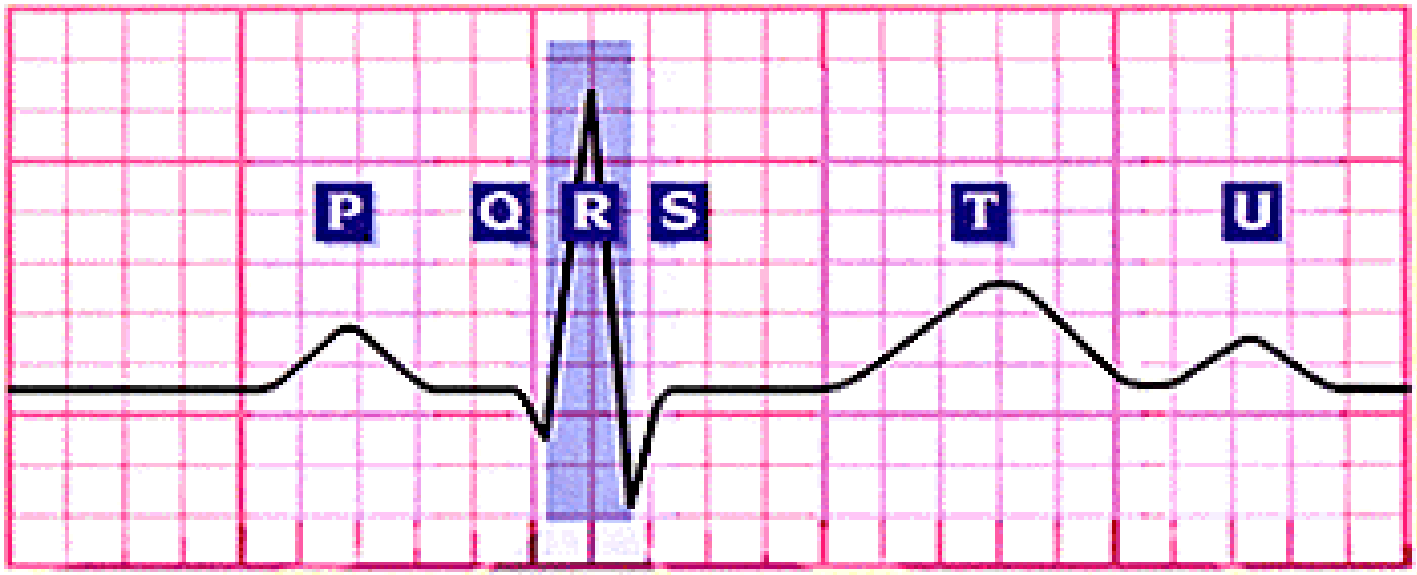


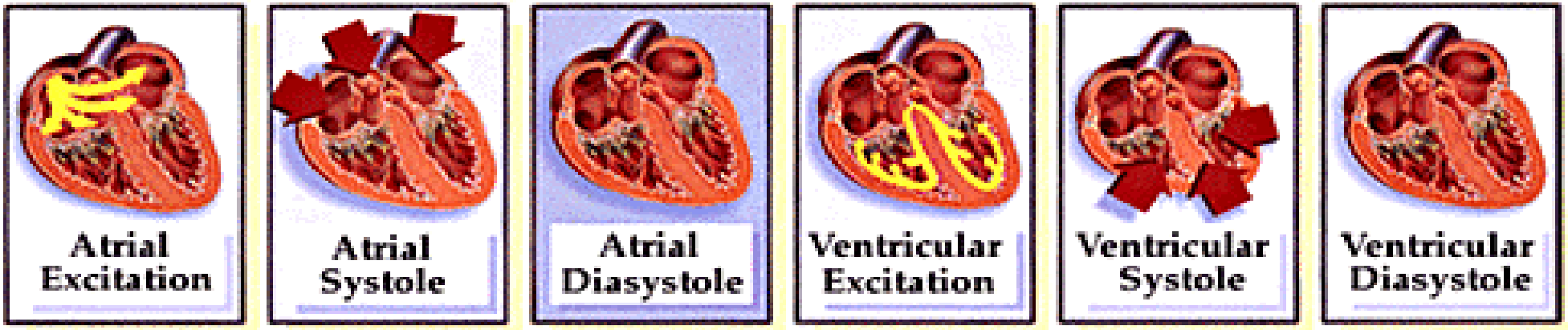
Cardiac Conduction System

CARDIAC CONDUCTION SYSTEM

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

Electrocardiogram (ECG)

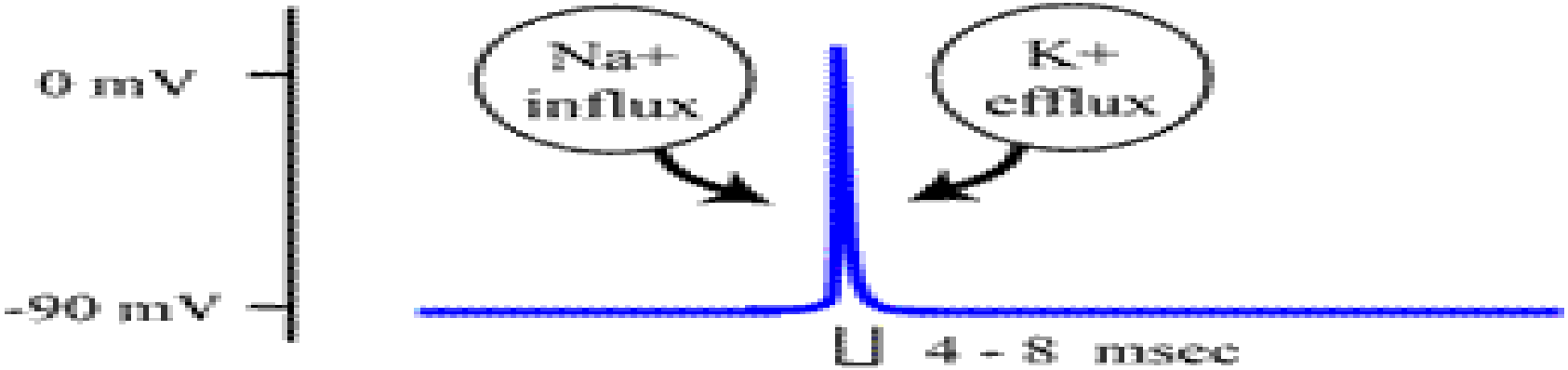




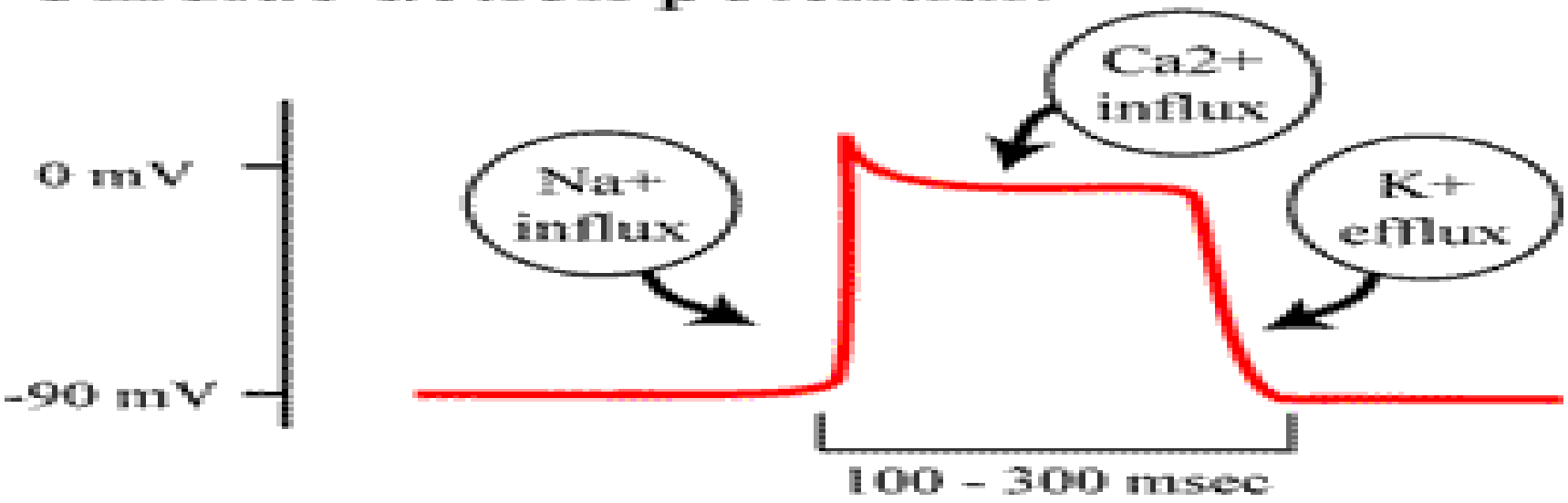
Electrical and Mechanical Events

CARDIAC ACTION POTENTIAL

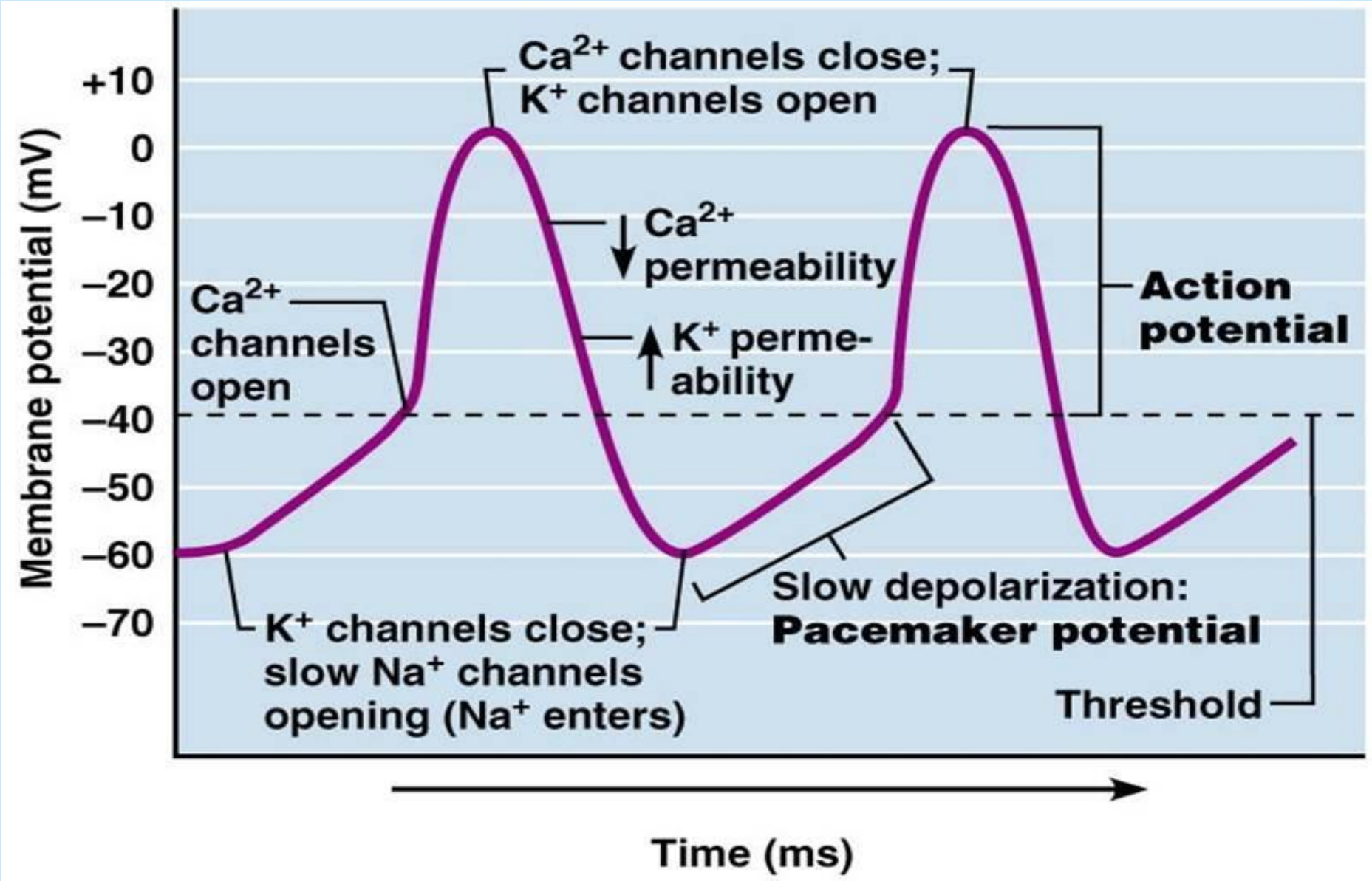
Skeletal action potential:



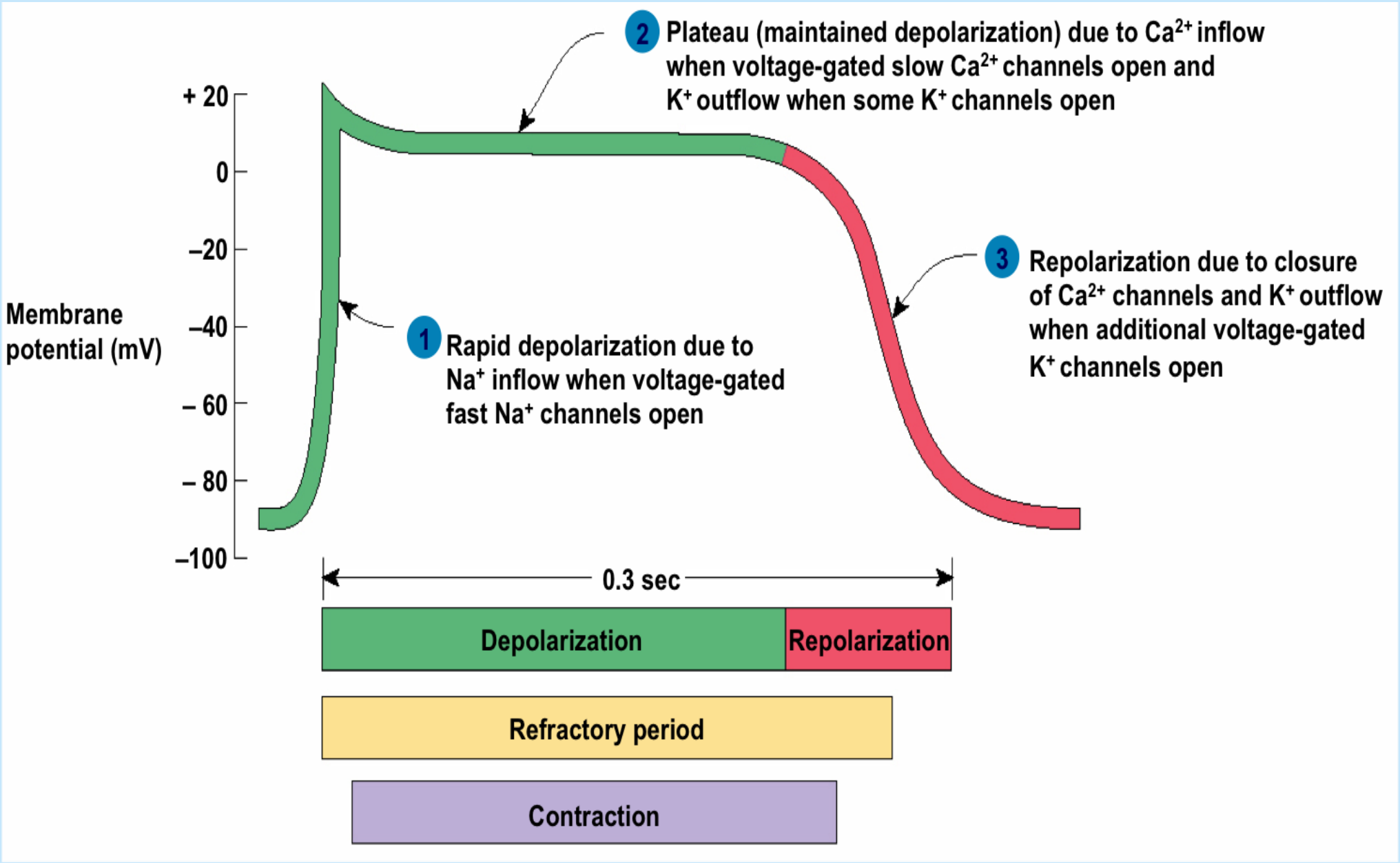
Cardiac action potential:



CARDIAC ACTION POTENTIAL
Pacemaker (SA node)

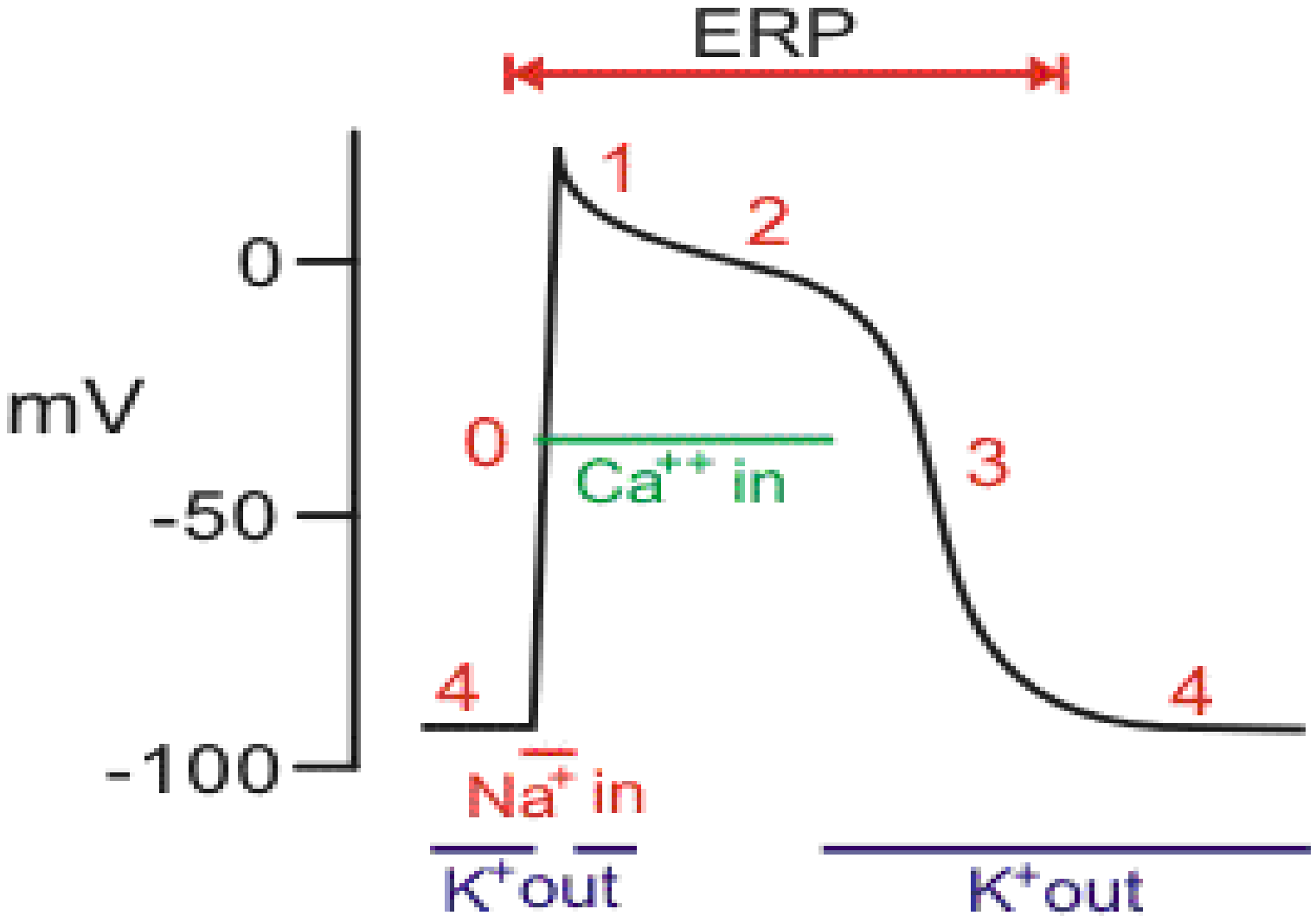


CARDIAC ACTION POTENTIAL
Non-pacemaker (ventricular muscle)

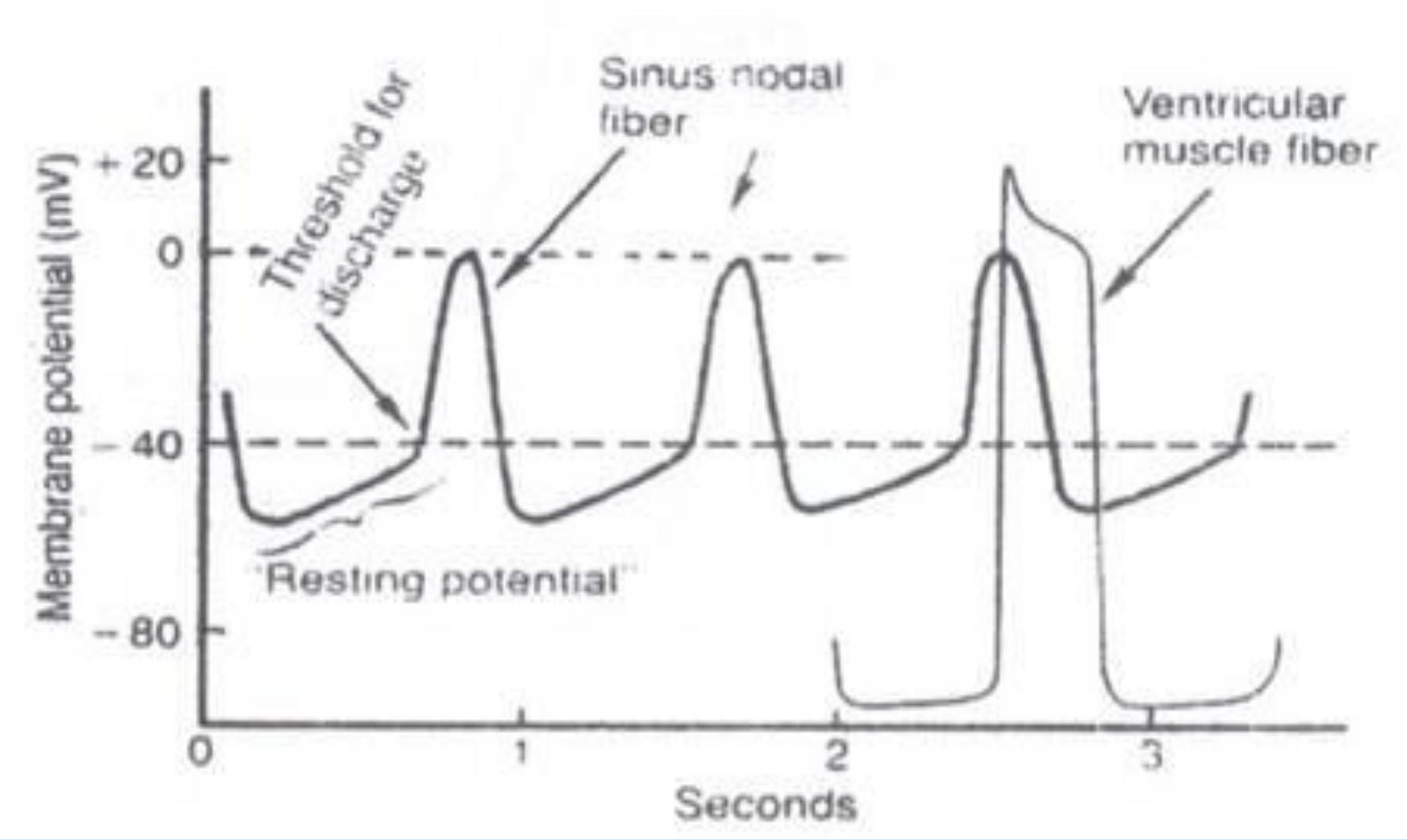


Fast-Response Action Potential

(e.g., ventricular myocyte)



Difference between pacemaker and non-pacemaker action potential



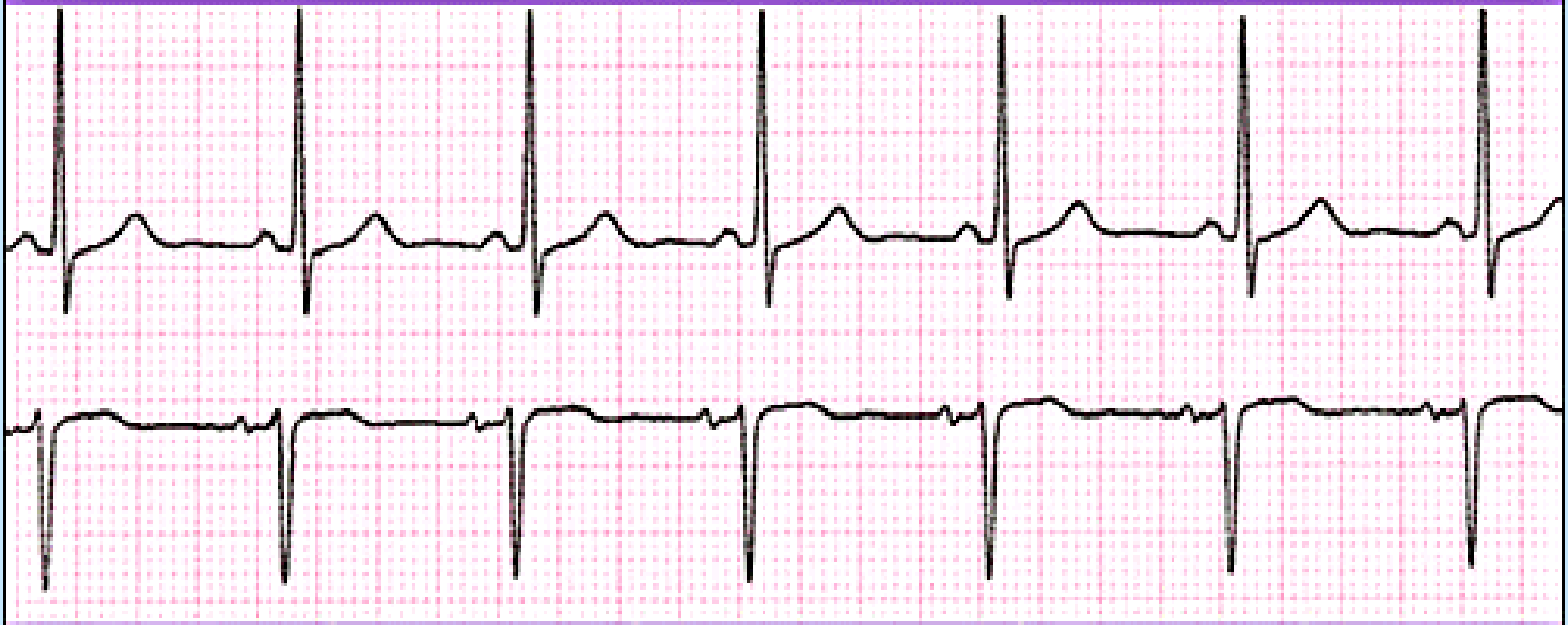
WHAT IS ARRHYTHMIA?

An abnormality in the :

- **rate ..... high= tachycardia**

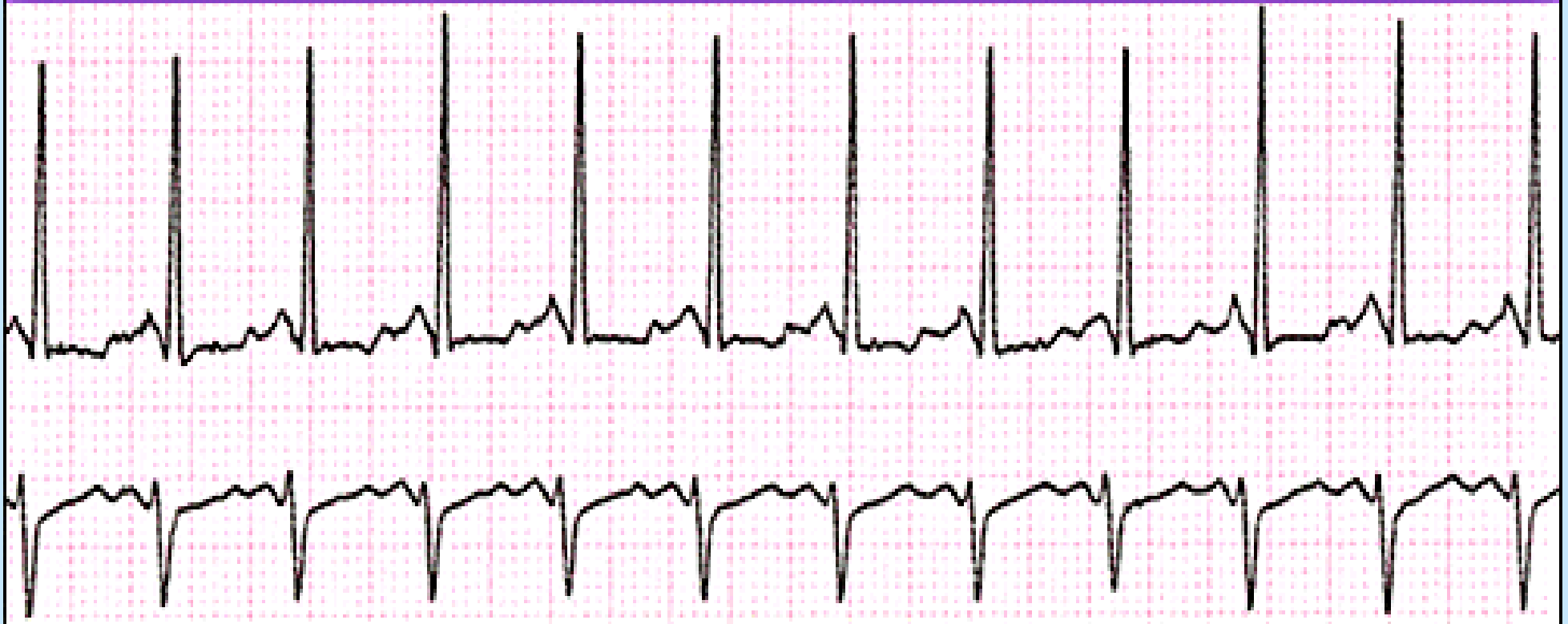
low = bradycardia

Normal Sinus Rhythm



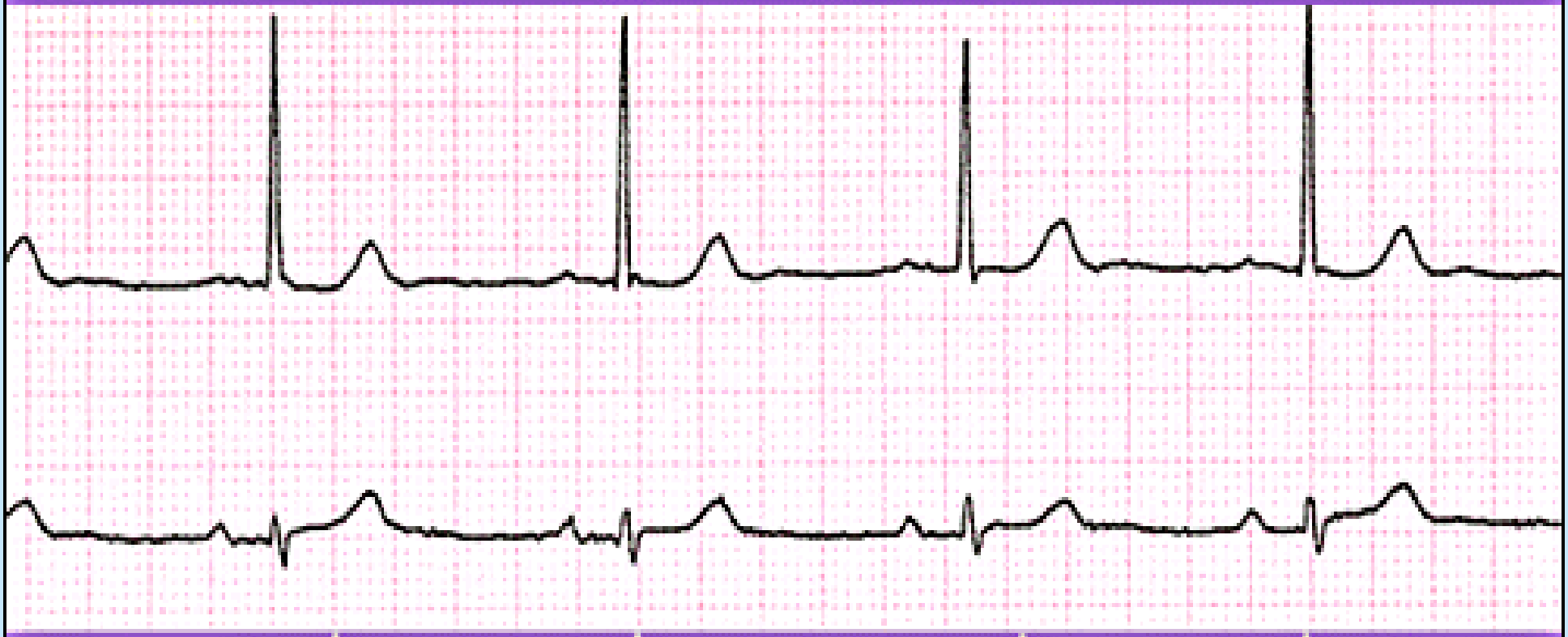
Heart Rate	Rhythm	P Wave	PR interval (in seconds)	QRS (in seconds)
60-100 bpm	Regular	Before each QRS, identical	.12 to .20	<.12

Sinus Tachycardia



Heart Rate	Rhythm	P Wave	PR interval (in seconds)	QRS (in seconds)
> 100 bpm	Regular	Before each QRS, identical	.12 to .20	<.12

Sinus Bradycardia



Heart Rate	Rhythm	P Wave	PR interval (in seconds)	QRS (in seconds)
< 60 bpm	Regular	Before each QRS, identical	.12 to .20	<.12

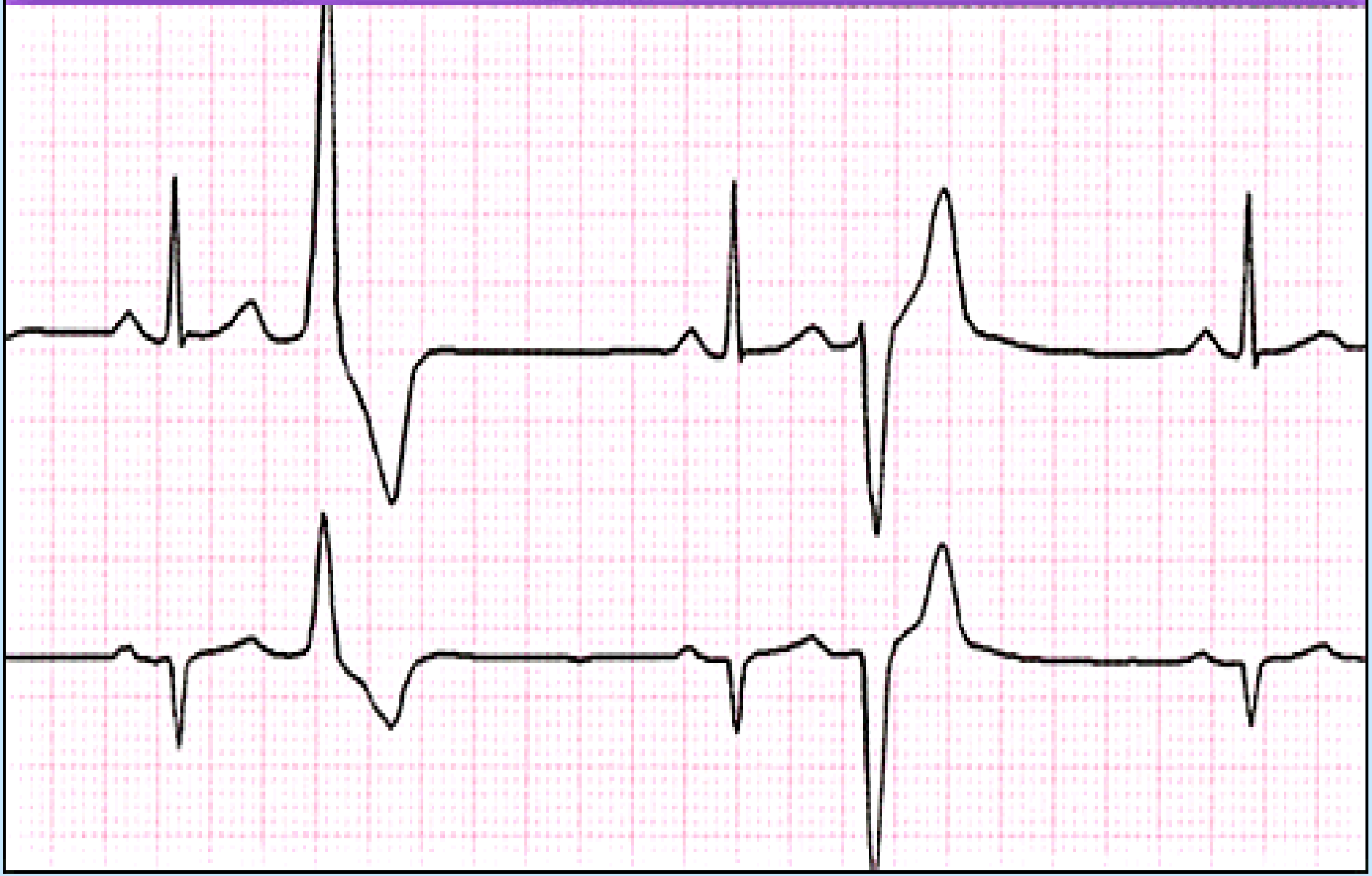
WHAT IS ARRHYTHMIA?

An abnormality in the :

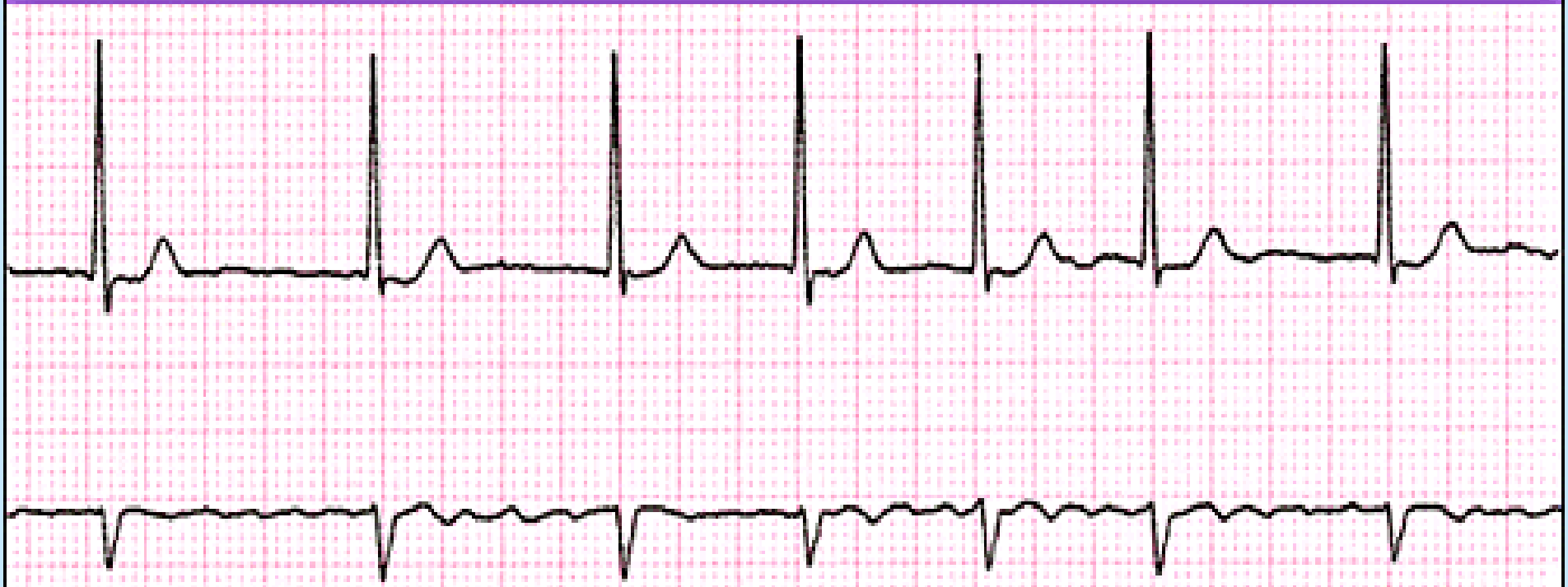
- **rate ..... high= tachycardia**
  low = bradycardia

- **regularity ..... Extrasystoles**
  (PAC, PVC)

Multifocal PVC's: more than one shape



Atrial Fibrillation



Heart Rate	Rhythm	P Wave	PR interval (in seconds)	QRS (in seconds)
A: 350-650 bpm V: Slow to rapid	Irregular	Fibrillatory (fine to course)	N/A	<.12

WHAT IS ARRHYTHMIA?

An abnormality in the :

- **rate ..... high= tachycardia**

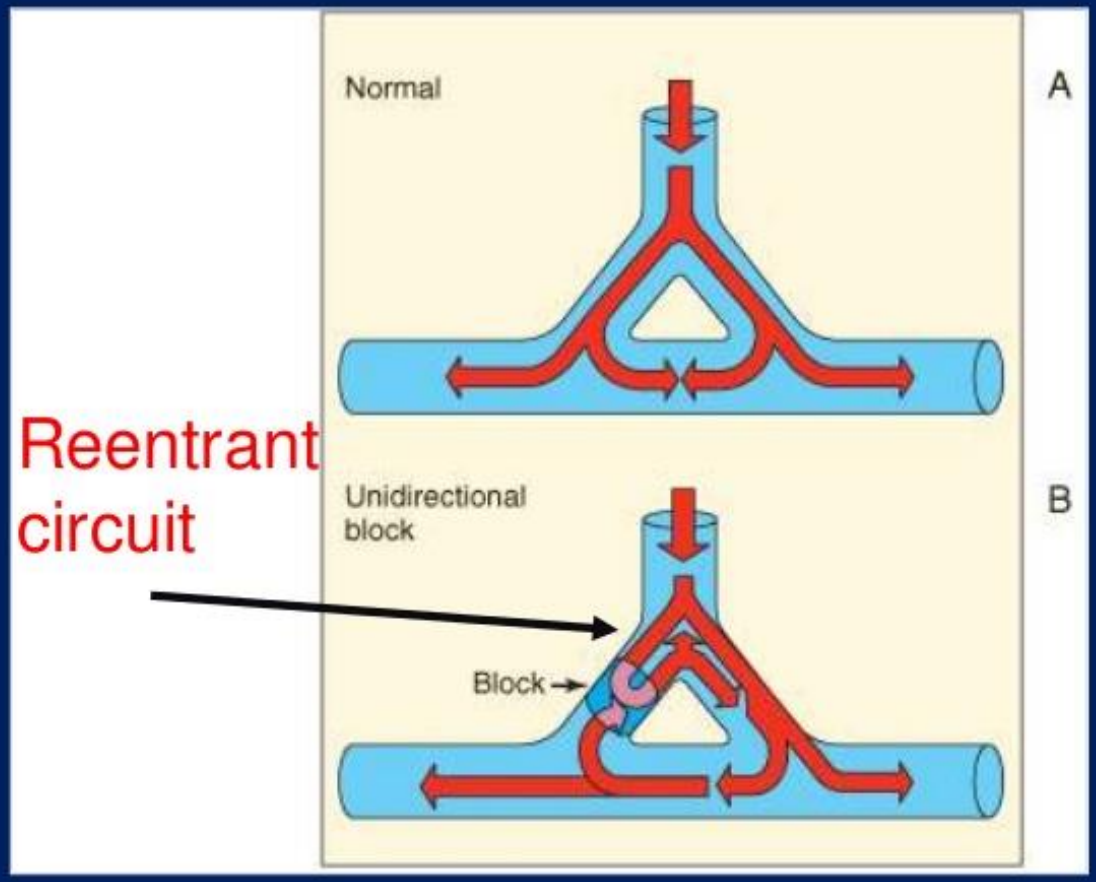
  low = bradycardia

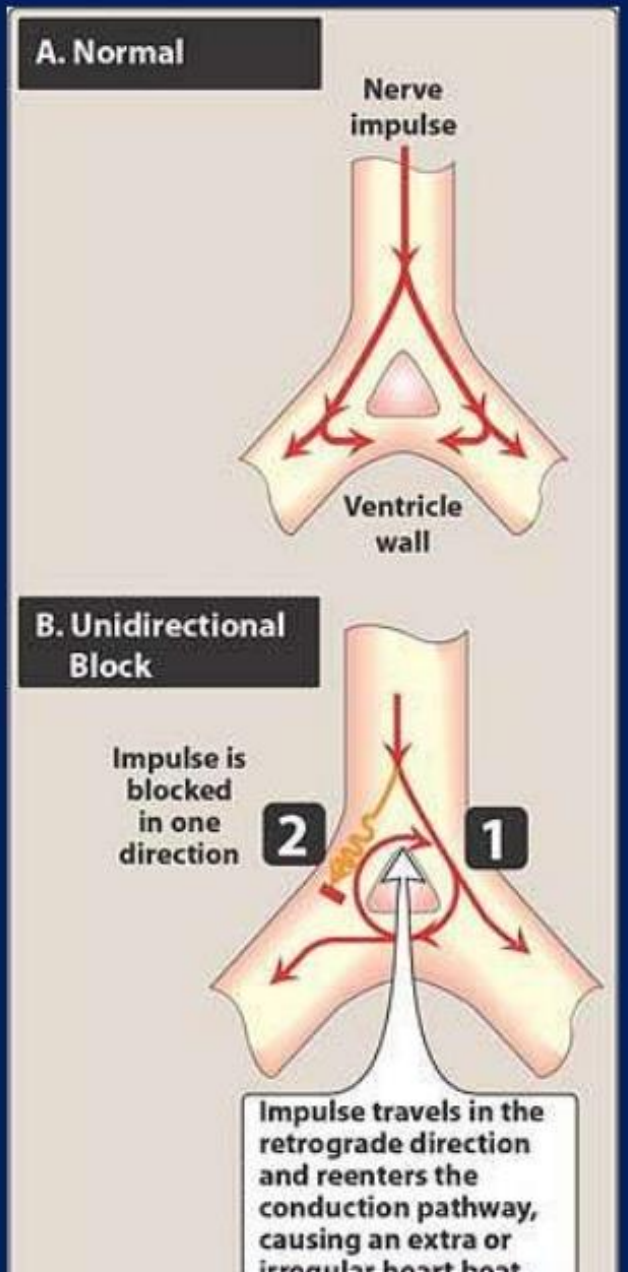
- **regularity ..... extrasystoles**
- **site of origin ... ectopic pacemakers**
- **or disturbance in conduction**

2. Disorders of impulse conduction

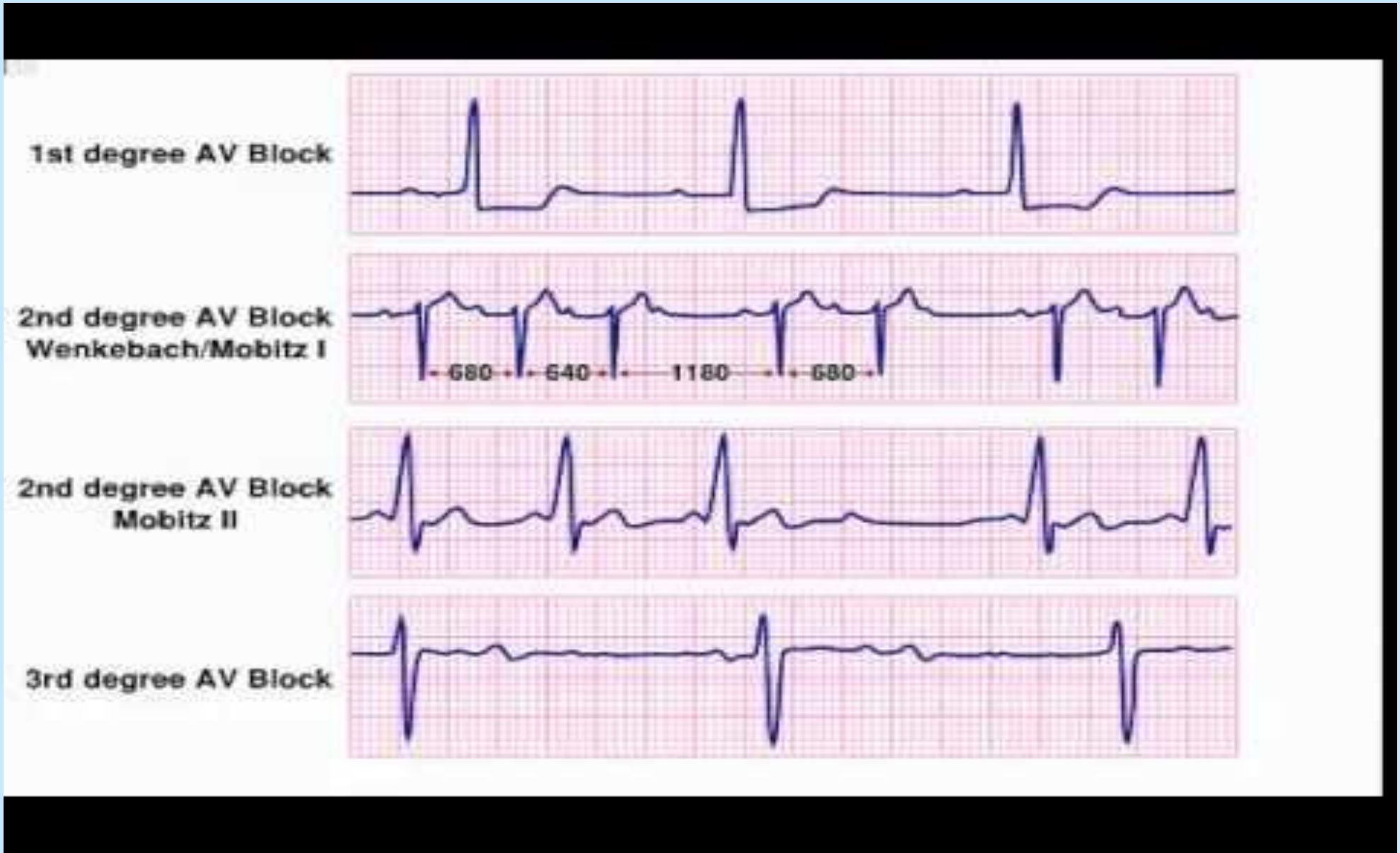
May result in abnormality in rate:

- Bradycardia (if have AV block)
- Tachycardia (if reentrant circuit occurs)





Disturbances in conduction



Therapeutic use of antiarrhythmic drugs

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 (ERP)**
- **Suppressing ectopic pacemaker activity by inhibiting phase 4 slow depolarization**

CLASSIFICATION
OF
ANTIARRHYTHMIC DRUGS

Vaughn Williams classification

CLASS I

Sodium channel blockers

CLASS II:

β- adrenoceptor blockers

CLASS III:

Potassium channel blockers

CLASS IV:

Calcium channel blockers.

CLASS I

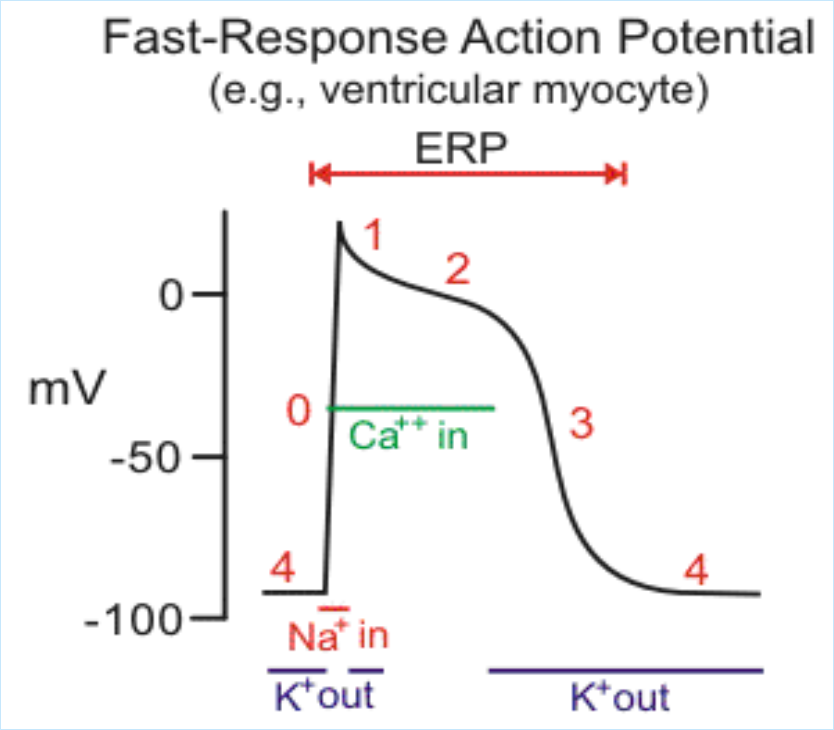
Drugs that block the influx of Na ions through Na channels

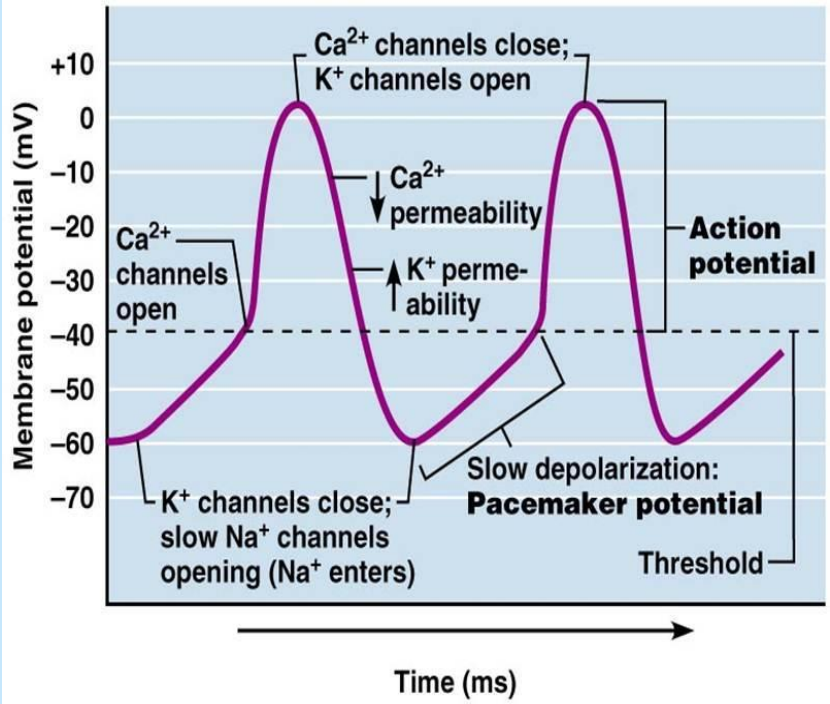
⬇

1- decrease the rate of rise of rapid depolarization (Phase O)

2- decrease phase 4 slow depolarization (suppress pacemaker activity)

(membrane stabilizing effect)





CLASS I

- **Sub classified according to their effect on action potential duration (APD) :**

- Ia : prolong APD

- Ib : shorten APD

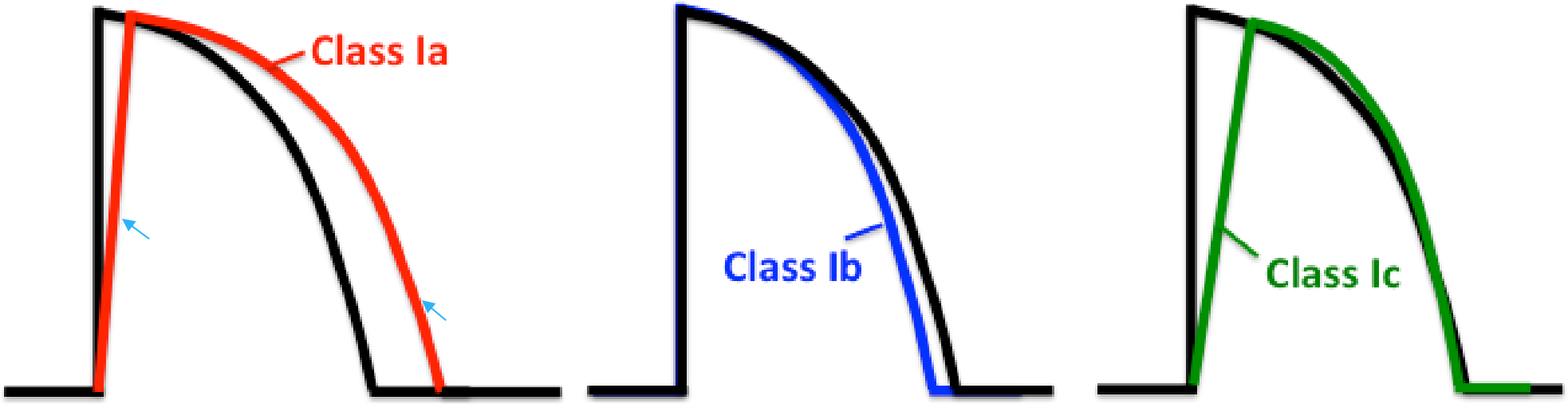
- Ic : Minimal effects on APD

Type I - Na Channel Blockers

Class I Antiarrhythmic Drug Effects

Increasing AP increases the QT interval

On the Ventricular Action Potential:



On the ECG:

↑QRS & ↑QT	↓QT	↑↑QRS
Blocks Na (I) and K (III) channels Slow rate of rise Increase ERP Increase AP	Short Repolarization Decrease in AP Decrease ERP	Pure Na channel blockers Depress rate of rise Slows conduction velocity No change in AP

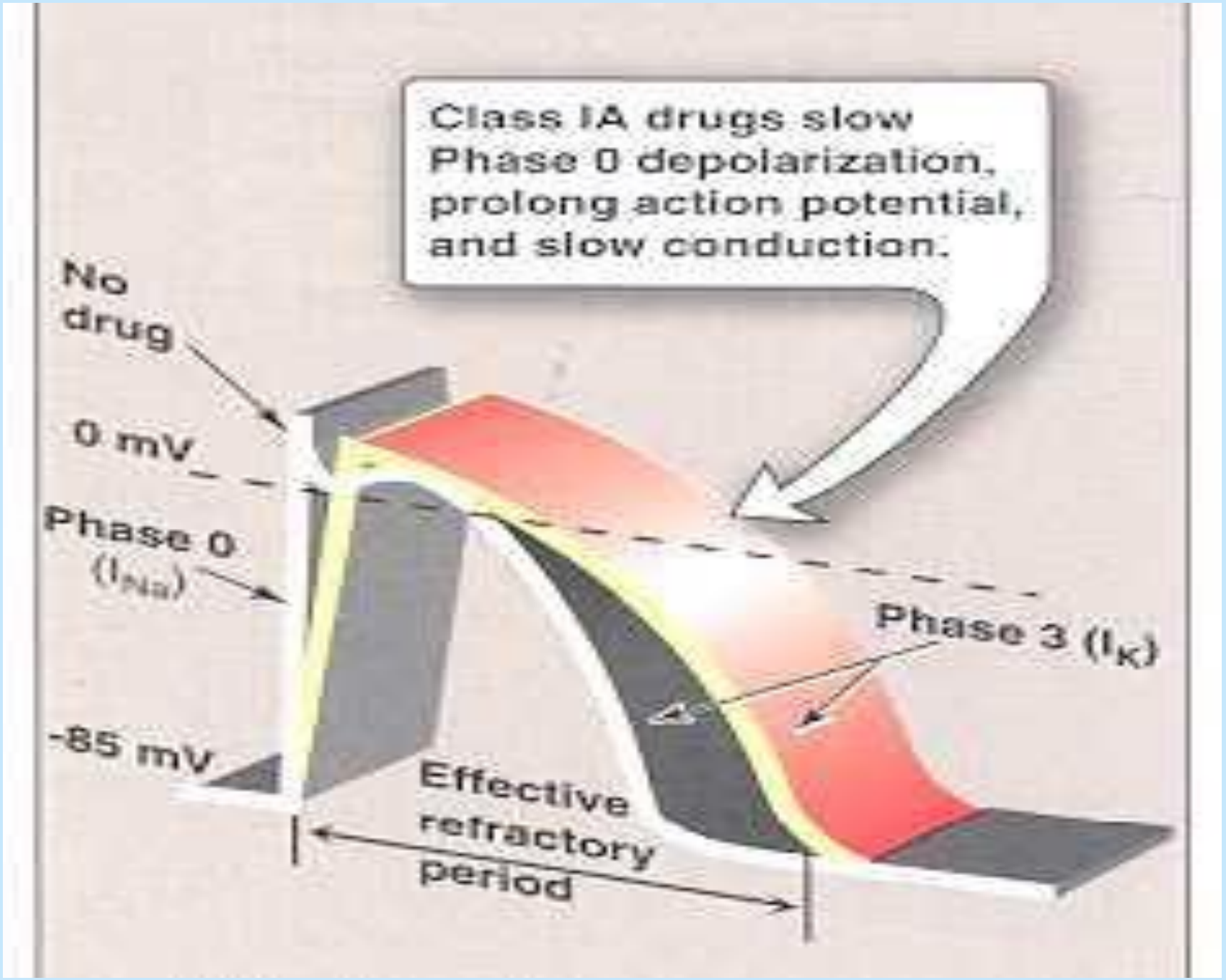
CLASS I a

Ia : prolong action potential duration

e.g.

Quinidine

Procainamide


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

CLASS I a

QUINIDINE

Other pharmacological actions :

1- Anticholinergic effect:

⬇

Increase conduction through the A.V. node

(risk of ventricular tachycardia)

2- α-adrenergic blocking effect:

⬇

may cause vasodilatation & reflex sinus tachycardia

(seen more after I.V. dose)

3- ECG changes:

- **P-R and Q-T prolongation**
- **widens QRS complex**

CLASS I a

QUINIDINE

Therapeutic uses:

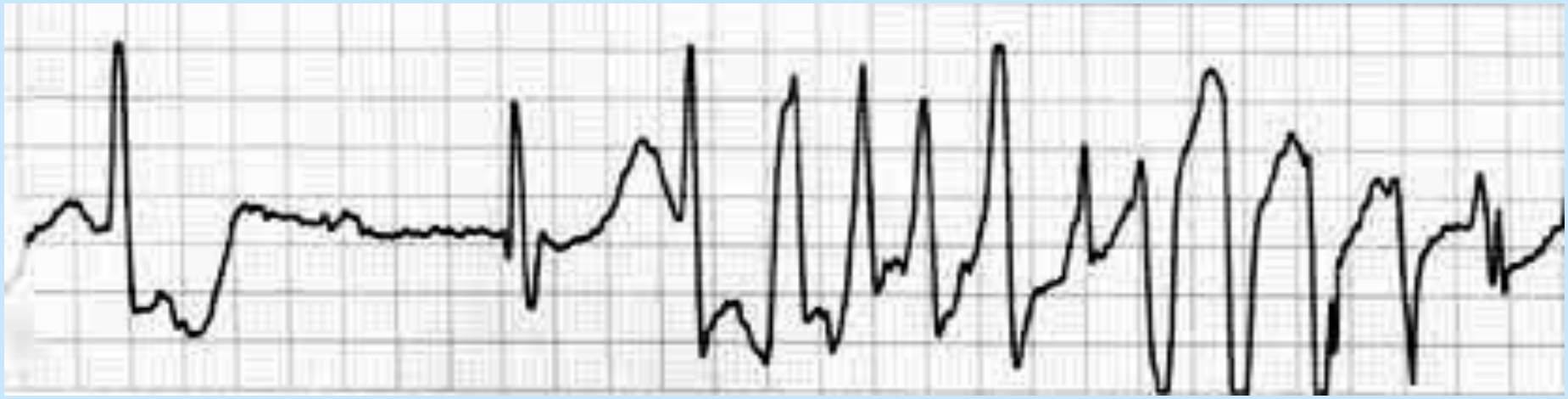
- atrial flutter & fibrillation

- maintaining sinus rhythm after cardioversion

CLASS Ia
QUINIDINE

Adverse effects :

quinidine syncope: episodes of fainting
due to torsades de pointes (twisting of the spikes)
developing at therapeutic plasma levels

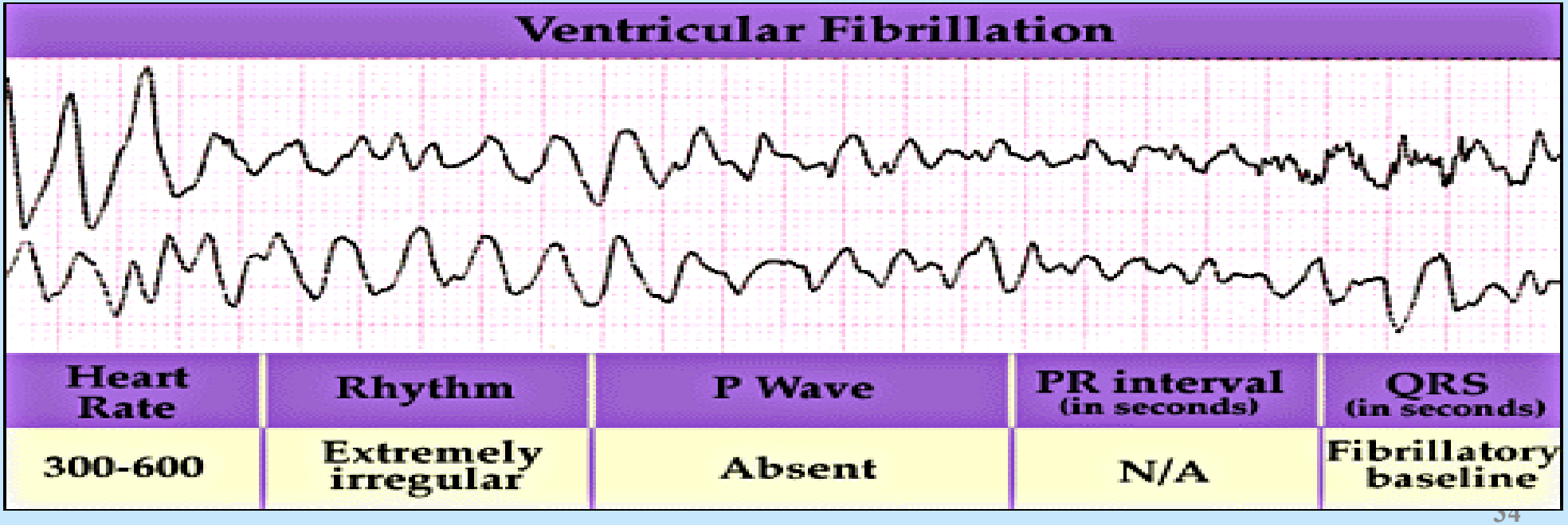


Torsades de pointes

- may terminate spontaneously or lead to

⬇

fatal ventricular fibrillation



CLASS I a

QUINIDINE

Adverse effects :

- **Anticholinergic adverse effects:**
  - Dry mouth
  - Blurred vision
  - Urinary retention
  - N/V/D

- **Hypotension**
  - due to depressing contractility & vasodilatation

GIVEN ORALLY (Rarely given I.V.)

CLASS I a

PROCAINAMIDE

Similar to quinidine except :

1- less toxic on the heart...

can be given I.V.

2- more effective in ventricular than in

atrial arrhythmias

3 – Less anticholinergic or α-blocking actions

CLASS I a

PROCAINAMIDE

Adverse effects:

- In *long term* therapy it causes reversible lupus erythematosus-like syndrome

- Hypotension

- **Torsades de pointes** (at toxic dose)

- Hallucination & psychosis

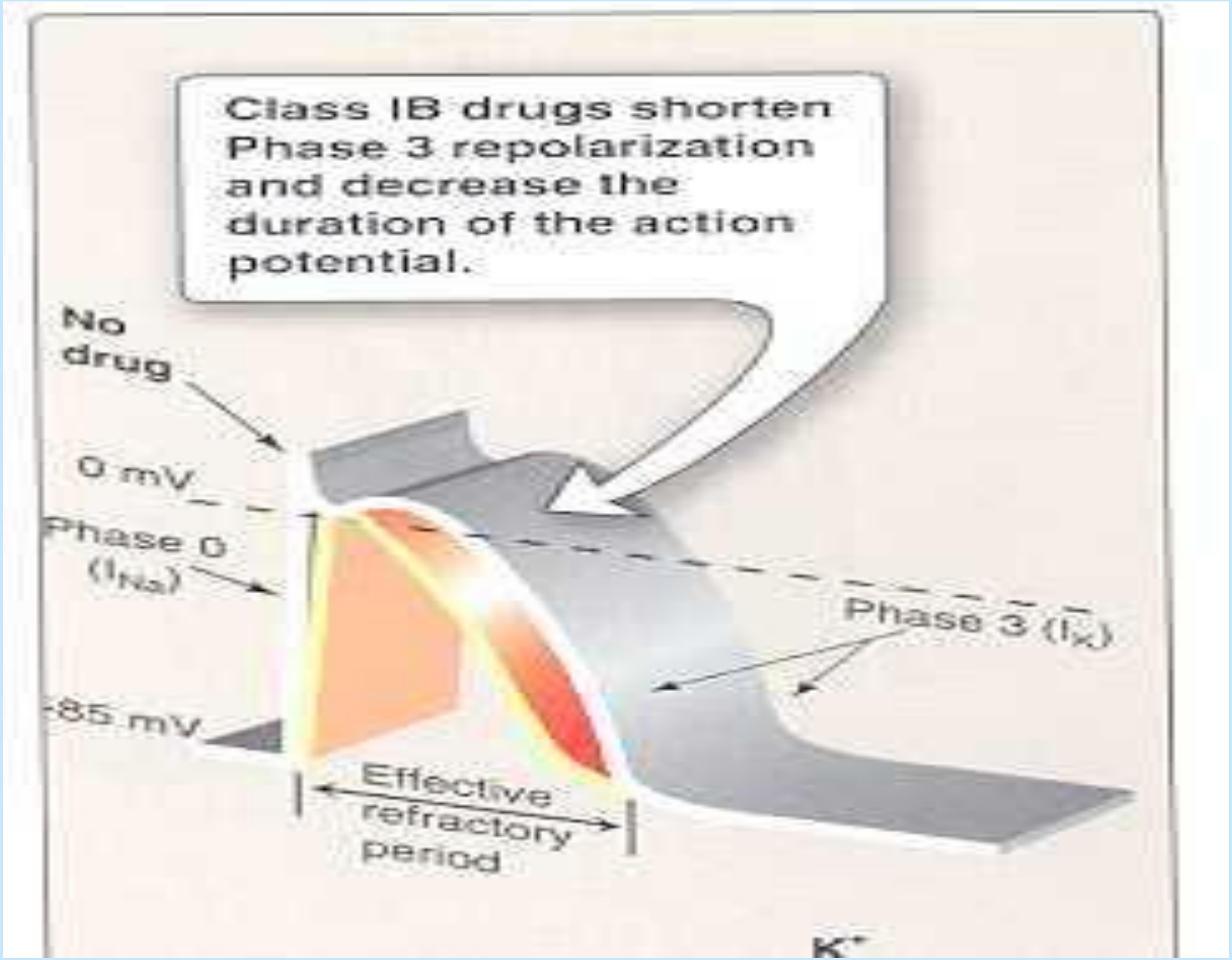
CLASS I b

- **Shorten action potential duration**

  e.g.

  Lidocaine

  Mexiletine


Class IB drugs shorten Phase 3 repolarization and decrease the duration of the action potential.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period
K^+

CLASS Ib

LIDOCAINE

Therapeutic uses :

treatment of emergency ventricular arrhythmias

e.g. :

1 - during surgery

2 - following acute myocardial infarction

- **NOT effective in atrial arrhythmias**
- **NOT effective orally (3% bioavailability)**
- **Only given I.V. bolus or slow infusion**
- **$t_{1/2}$ = 2 hours**

CLASS Ib

LIDOCAINE

Adverse effects:

- hypotension
- similar to other local anesthetics, causes CNS adverse effects such as:
  - paresthesia
  - tremor
  - dysarthria (slurred speech)
  - tinnitus
  - confusion
  - convulsions

CLASS Ib

MEXILETINE

- **EFFECTIVE ORALLY**

Therapeutic uses :

1- ventricular arrhythmia

2- digitalis-induced arrhythmias

$t_{1/2}$ = 10 hours

ADVERSE EFFECTS :

1- nausea, vomiting

2- tremor, drowsiness, diplopia

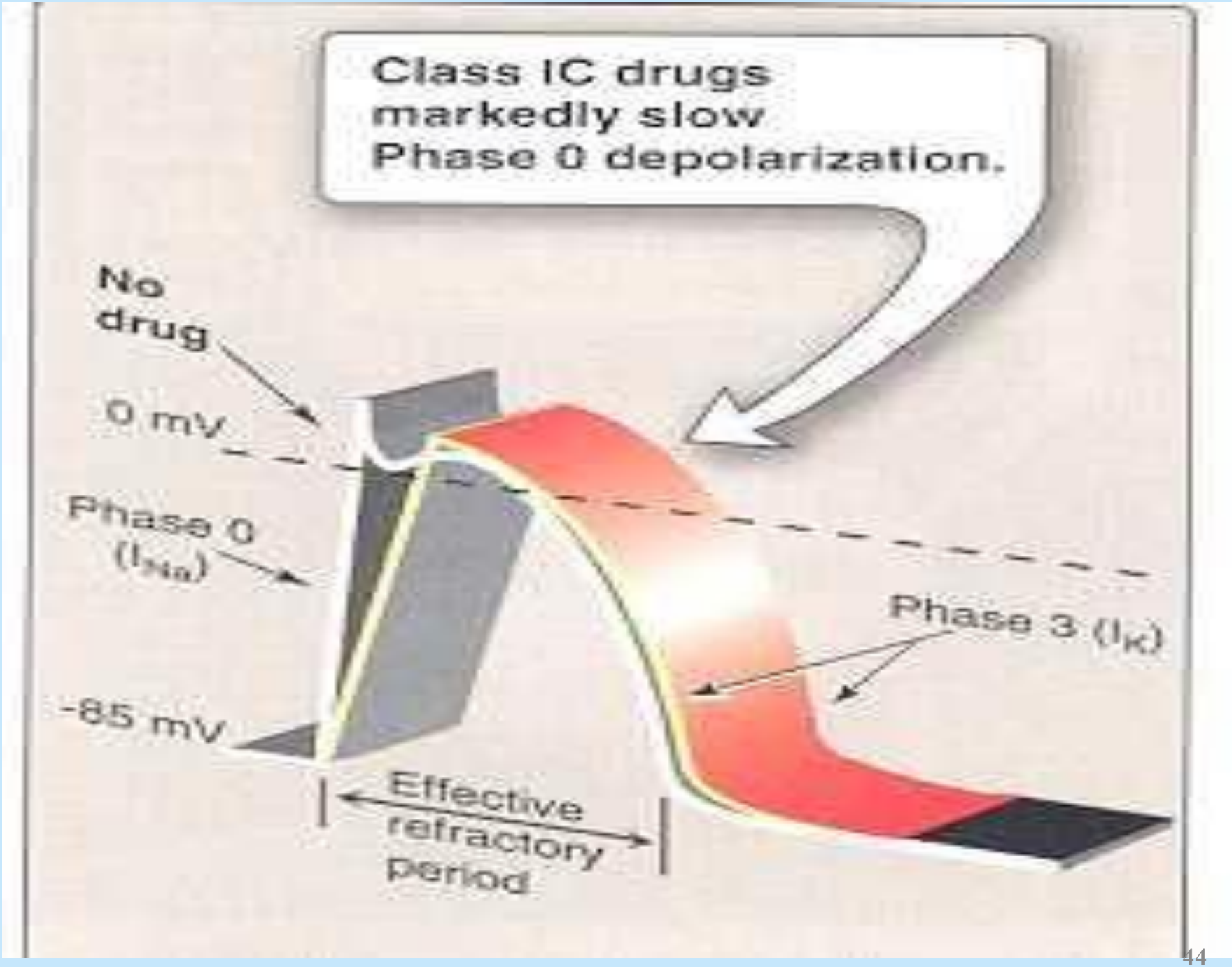
3- arrhythmias & hypotension

CLASS Ic

- have no effect on action potential duration

e.g.

Flecainide


Class IC drugs
markedly slow
Phase 0 depolarization.
No
drug
0 mV
Phase 0
(I_{Na})
Phase 3 (I_K)
-85 mV
Effective
refractory
period

CLASS Ic

FLECAINIDE

Therapeutic uses :

- supraventricular arrhythmias

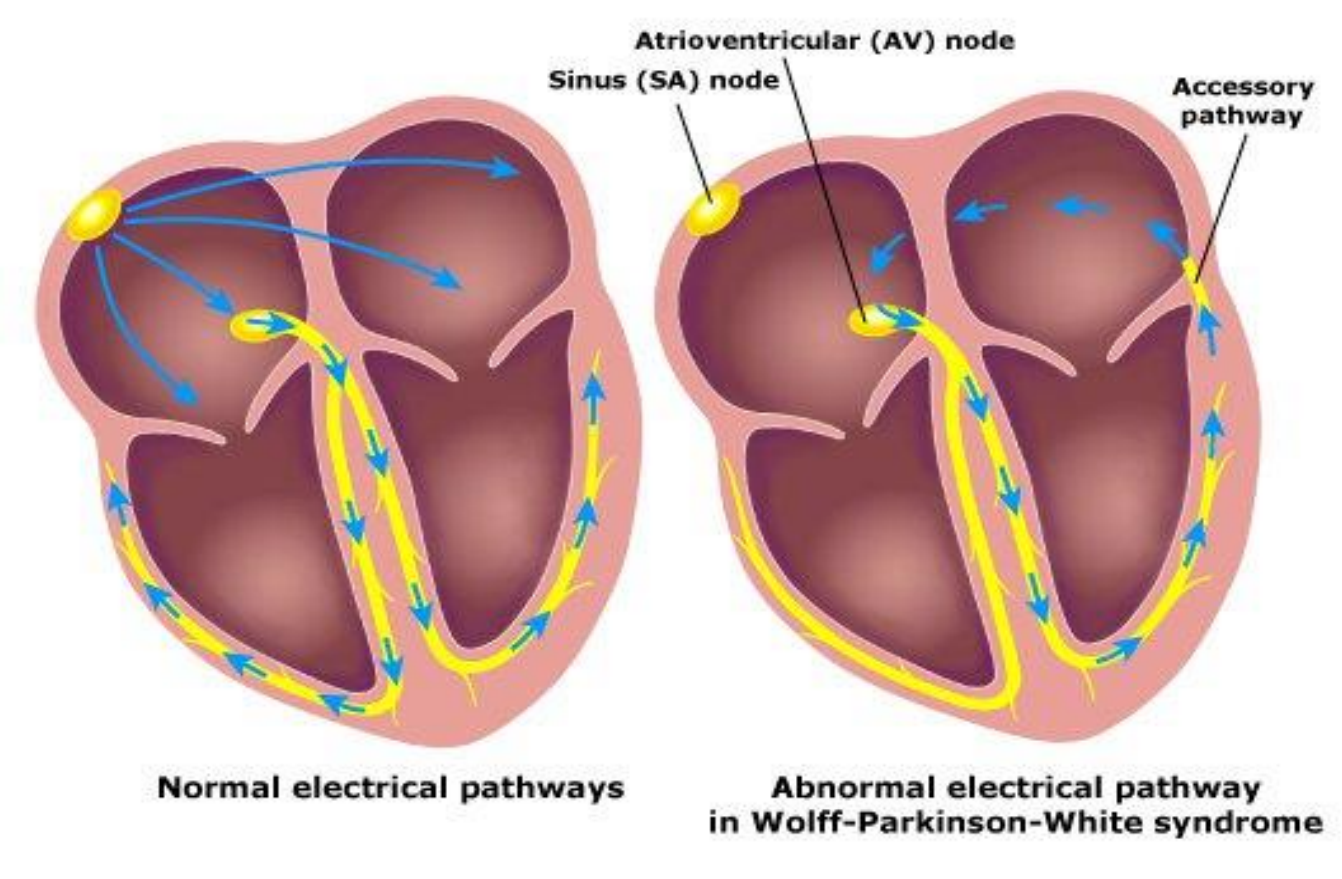
- Wolff-Parkinson-White syndrome

- very effective in ventricular arrhythmias, but very high risk of proarrhythmia

- should be reserved for resistant arrhythmias

Wolff-Parkinson-White syndrome

- **Pre-excitation of the ventricles due to an accessory pathway known as the Bundle of Kent.**



CLASS Ic
FLECAINIDE

Adverse effects:

1- proarrhythmia

2- CNS :
dizziness, tremor, blurred vision,
abnormal taste sensations, paraesthesia

3- heart failure due to -ve inotropic effect.

CLASS II DRUGS

β- ADRENOCEPTOR BLOCKERS

pharmacological actions :

block β_1- receptors in the heart

↓

reduce the sympathetic effect on the heart

↓

1 - decrease automaticity of S.A. node &

ectopic pacemakers

2 - prolong RP (slow conduction) of the A.V node

CLASS II DRUGS

β- ADRENOCEPTOR BLOCKERS

Therapeutic uses :

1- atrial arrhythmias associated with emotion:

e.g. : - after exercise

- thyrotoxicosis

2- WPW

3- digitalis-induced arrhythmias.

CLASS II DRUGS
β- ADRENOCEPTOR BLOCKERS

Therapeutic uses :

Esmolol :

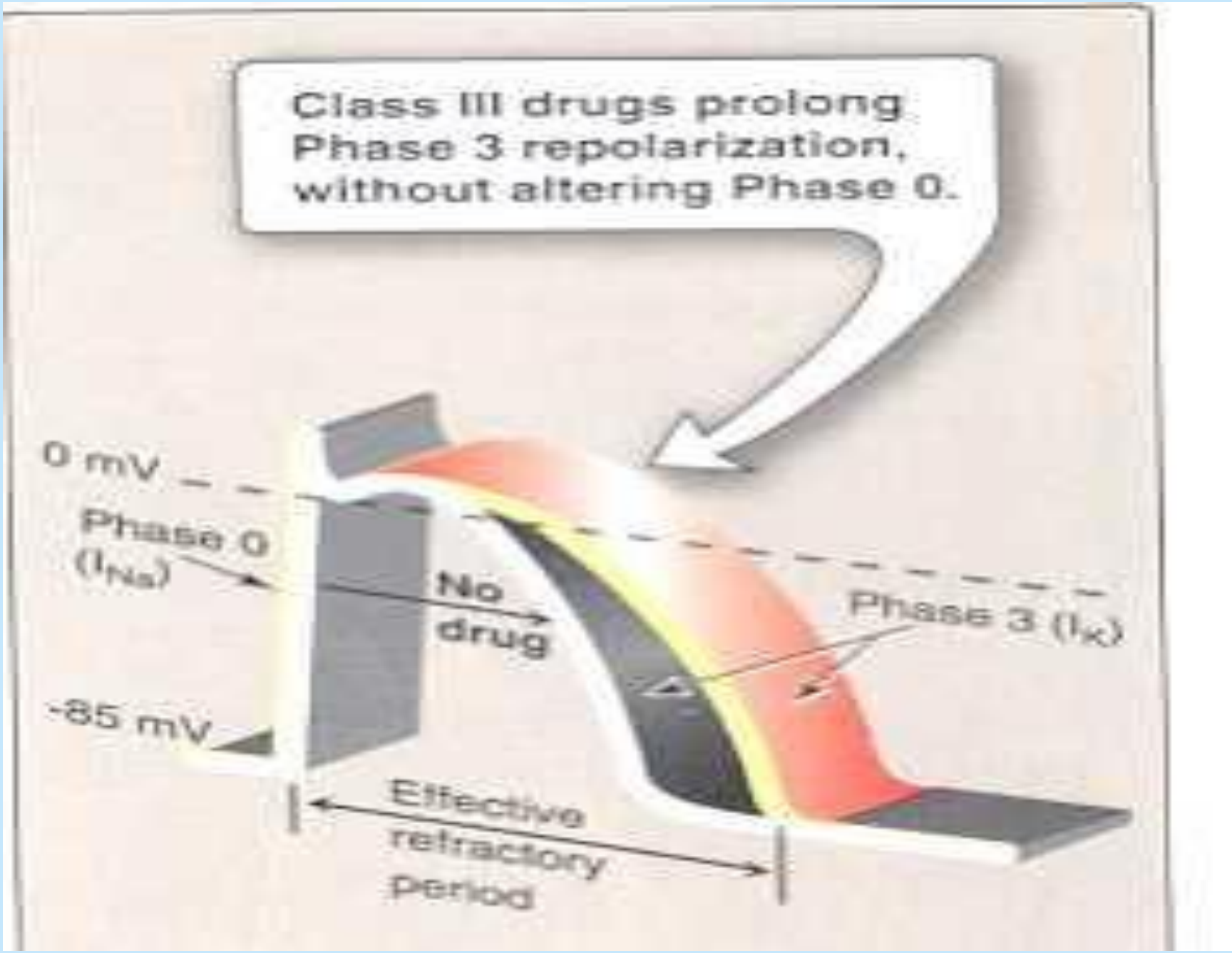
- very short acting (half-life = 9 min.)
- given I.V. for rapid control of ventricular rate in patients with atrial flutter or fibrillation

Propranolol, Atenolol, Metoprolol :

- 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 & RP**
- **Prolong phase 3 repolarization**


Class III drugs prolong Phase 3 repolarization, without altering Phase 0.
0 mV
Phase 0 (I_{Na})
No drug
Phase 3 (I_K)
-85 mV
Effective refractory period

CLASS III DRUGS

AMIODARONE

pharmacological actions :

- prolongs action potential duration & therefore prolongs RP (Main effect)
- additional class Ia, II & IV effects
- vasodilating effects

(due to its α- & β-adrenoceptor blocking effects & its calcium channel blocking effects)

CLASS III DRUGS

AMIODARONE

Therapeutic uses :

1- main use : serious resistant ventricular arrhythmias

2- maintenance of sinus rhythm after cardioversion

3- resistant supraventricular arrhythmias (e.g. WPW)

CLASS III DRUGS

AMIODARONE

Adverse effects:

- exacerbation of ventricular arrhythmias (high dose)
- bradycardia & heart failure
- pulmonary fibrosis
- hyper- or hypothyroidism
- photodermatitis & skin deposits (avoid exposure to the sun).

CLASS III DRUGS

AMIODARONE

Adverse effects:

- Neurological:

  e.g. tremors & peripheral neuropathy

- nausea, vomiting & constipation

- corneal micro deposits

- hepatocellular necrosis

CLASS III DRUGS

AMIODARONE

Pharmacokinetics:

- extremely long $t_{1/2}$ = 13 - 103 DAYS
- metabolized by CYP3A4 and CYP2C8 to its major active metabolite: N-desethylamiodarone
- eliminated primarily by hepatic metabolism
- cross placenta & appear in breast milk.

CLASS III DRUGS

AMIODARONE

Drug Interactions:

1 - Co-administration of amiodarone with drugs that prolong the QT interval increases the risk of Torsades de Pointes

e.g. :

macrolide antibiotics (Clarithromycin, Erythromycin)

azole antifungals (Ketoconazole)

CLASS III DRUGS

AMIODARONE

Drug Interactions:

2- Drugs (or substances) that inhibit CYP3A4 & CYP2C8 enzymes cause increase in serum concentration of amiodarone

e.g. : Loratadine, Ritonavir, Trazodone

Cimetidine, Grapefruit juice

3- Drugs that induce these enzymes

Cause decrease in serum concentration of amiodarone

e.g. : Rifampin

PURE CLASS III
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).

Class 1V
Calcium channel blockers

Verapamil, Diltiazem

- **main site of action is A.V.N & S.A.N**

  cause:

  - slowing of conduction

  - prolongation of ERP

Class 1V
Calcium channel blockers

Therapeutic uses :

1- atrial arrhythmias

2- re-entry supraventricular arrhythmias
e.g. WPW

3- NOT effective in ventricular arrhythmias.

ADENOSINE

Mechanism of action :

- inhibits c.AMP by binding to adenosine A1 receptors causing the following actions:

1 - opening of potassium channels

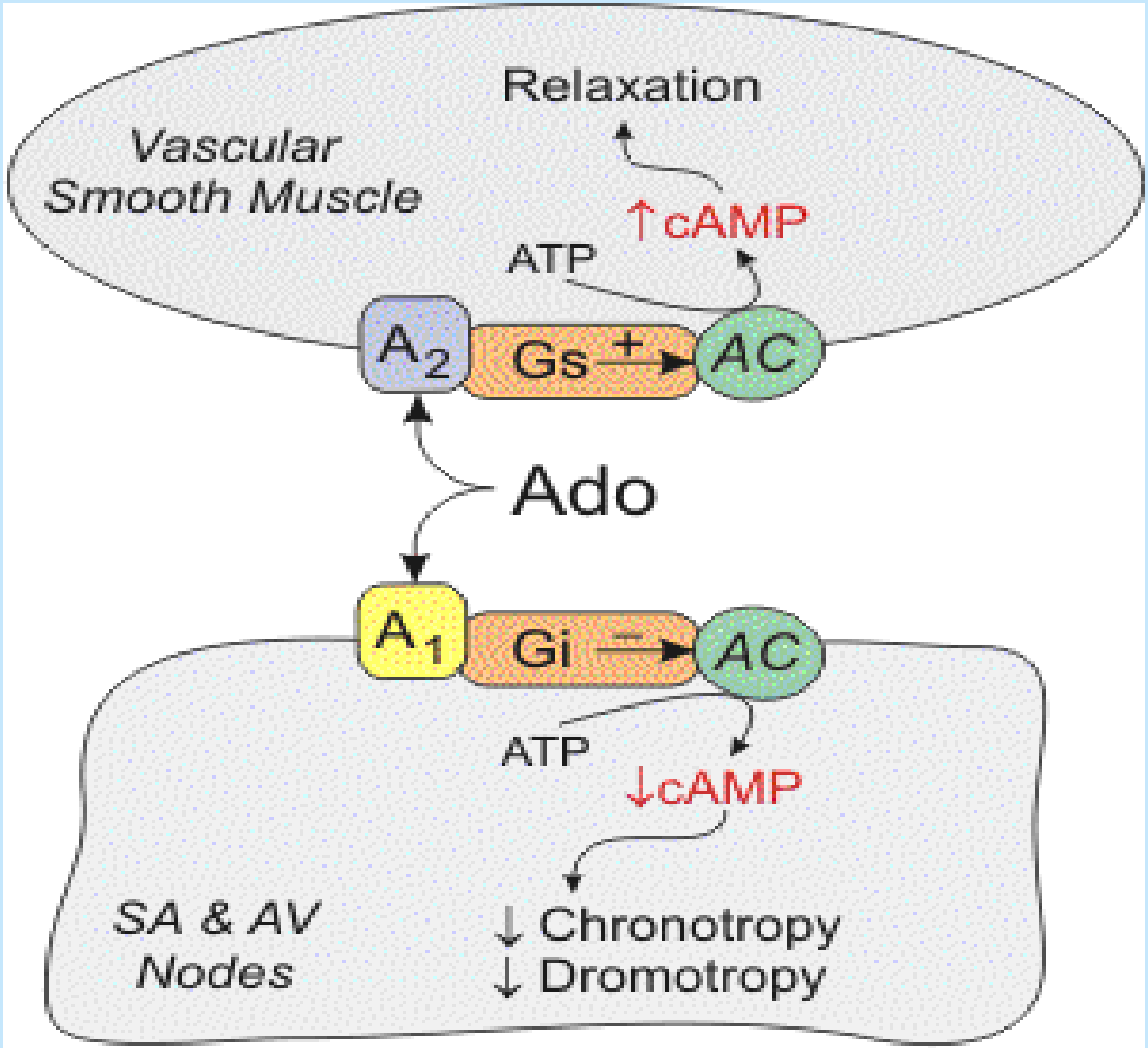
(hyperpolarization)

2 - decreasing conduction velocity mainly at AV node

(negative dromotropic effect)

3- inhibiting phase 4 pacemaker action potential at SA node

(negative chronotropic effect)


Relaxation
Vascular
Smooth Muscle
↑cAMP
ATP
A2
Gs
+
AC
Ado
A1
Gi
−
AC
ATP
↓cAMP
SA & AV
Nodes
↓ Chronotropy
↓ Dromotropy

ADENOSINE

Therapeutic uses :

- drug of choice for acute management of paroxysmal supraventricular tachycardia

- preferred over verapamil

  (safer & does not depress contractility)

  half-life = less than 10 sec

ADENOSINE

Adverse effects:

- flushing in about 20% of patients
- shortness of breath & chest burning in 10% of patients (due to bronchospasm)
- brief AV block (contraindicated in heart block)

New Antiarrhythmic Drugs

Dronedarone

- a noniodinated congener of amiodarone
- has antiarrhythmic properties belonging to all four classes
- Used for maintenance of sinus rhythm following cardioversion in patients with atrial flutter or fibrillation.

New Antiarrhythmic Drugs

Dronedarone

WARNINGS

- **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 & stroke, may be increased in these patients.**

BRADYARRHYTHMIAS

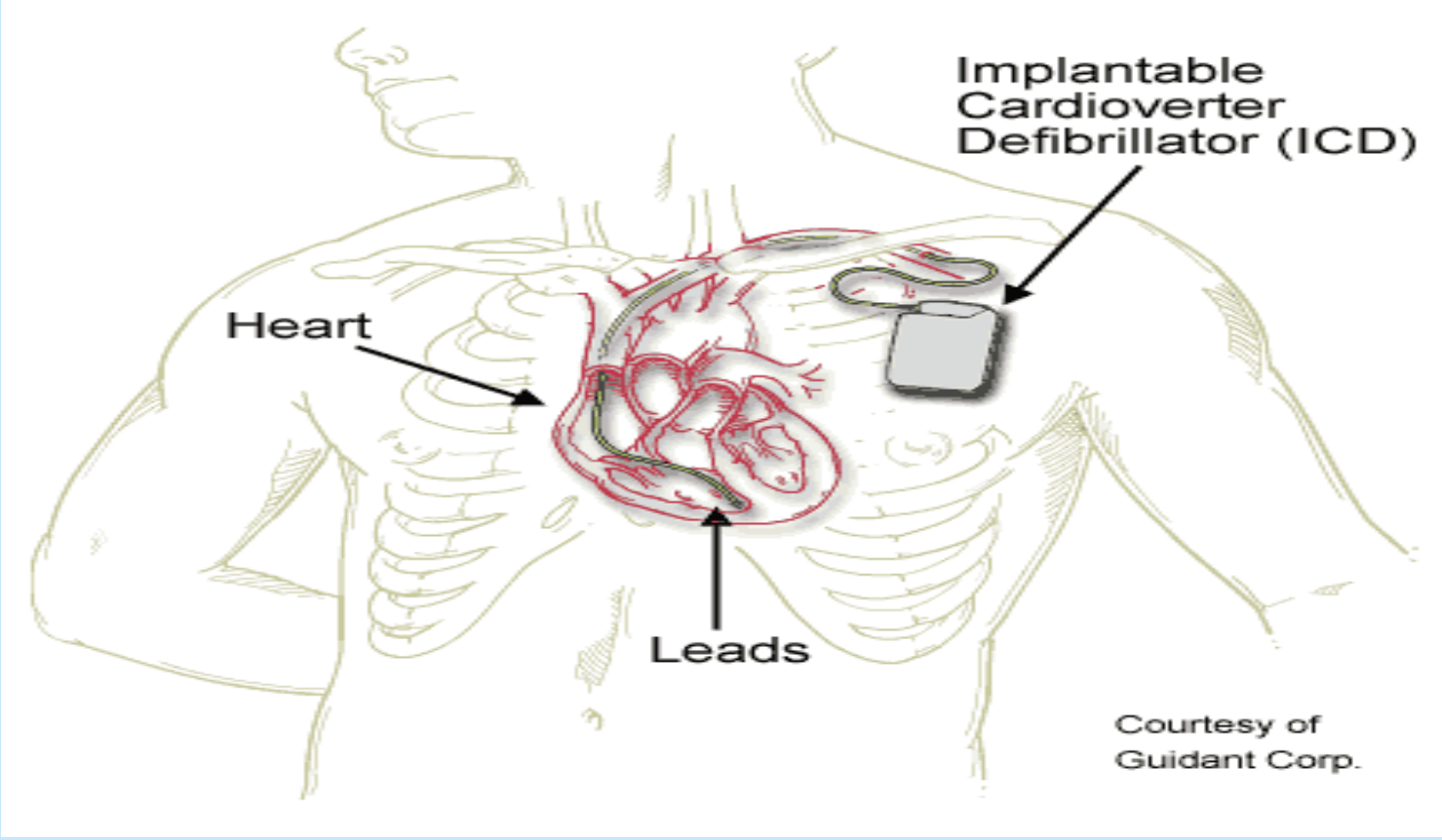
ATROPINE

- used in sinus bradycardia after myocardial infarction & in heart block
- in emergency heart block isoprenaline may be combined with atropine (caution)

NONPHARMACOLOGIC THERAPY OF ARRHYTHMIAS

Implantable Cardiac Defibrillator (ICD)

- can automatically detect & treat fatal arrhythmias such as ventricular fibrillation




Thank you