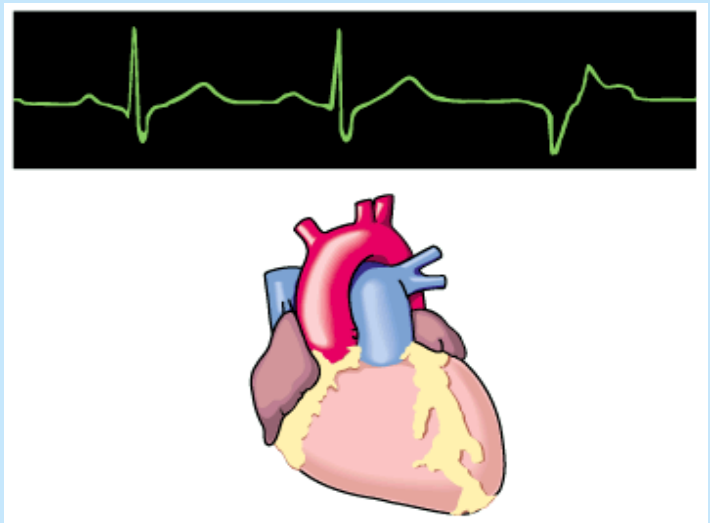
Cardiovascular Pharmacology

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

Antiarrhythmic Drugs

Dr. Aliah Alshanwani



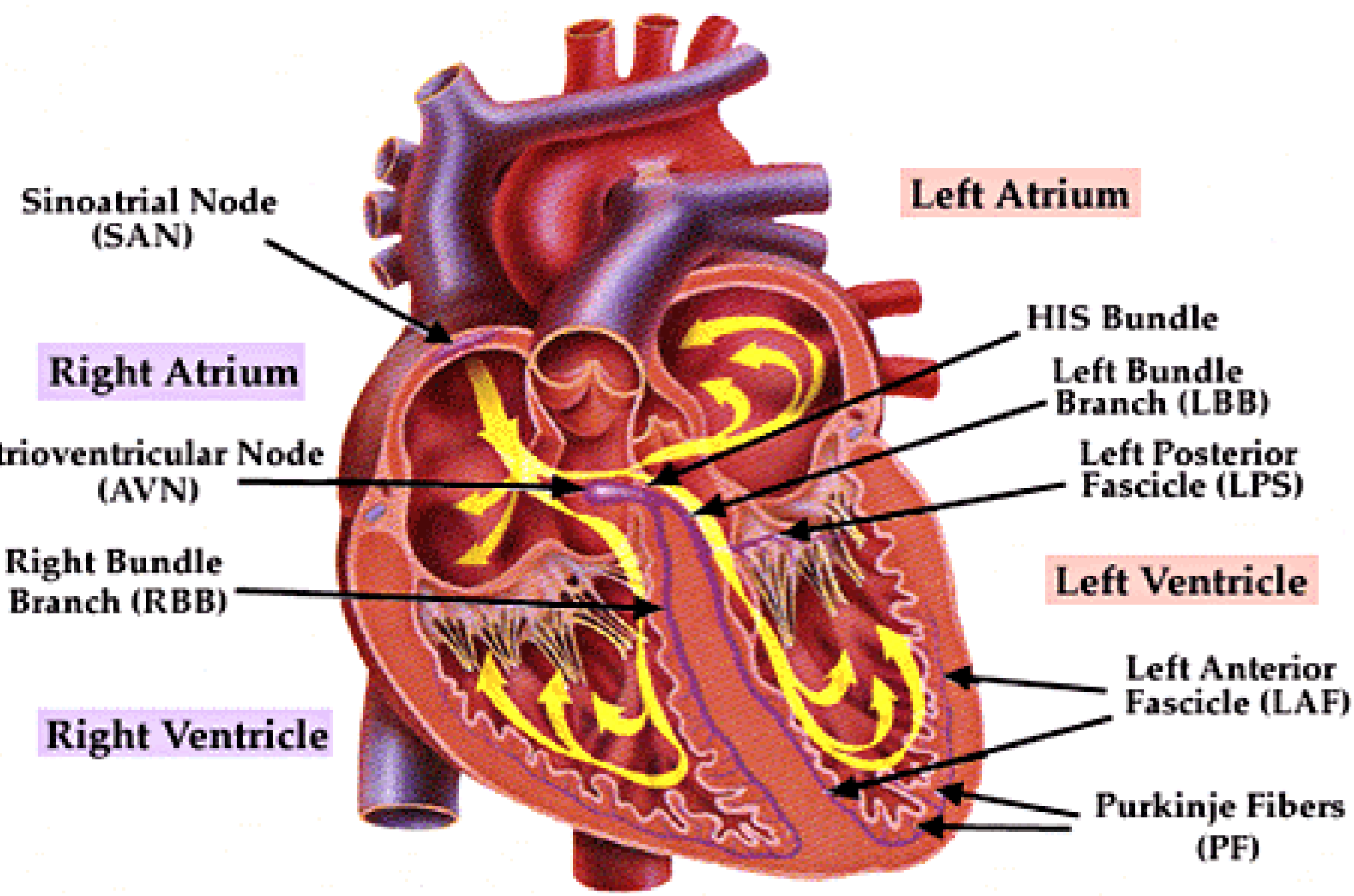
Learning objectives

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.

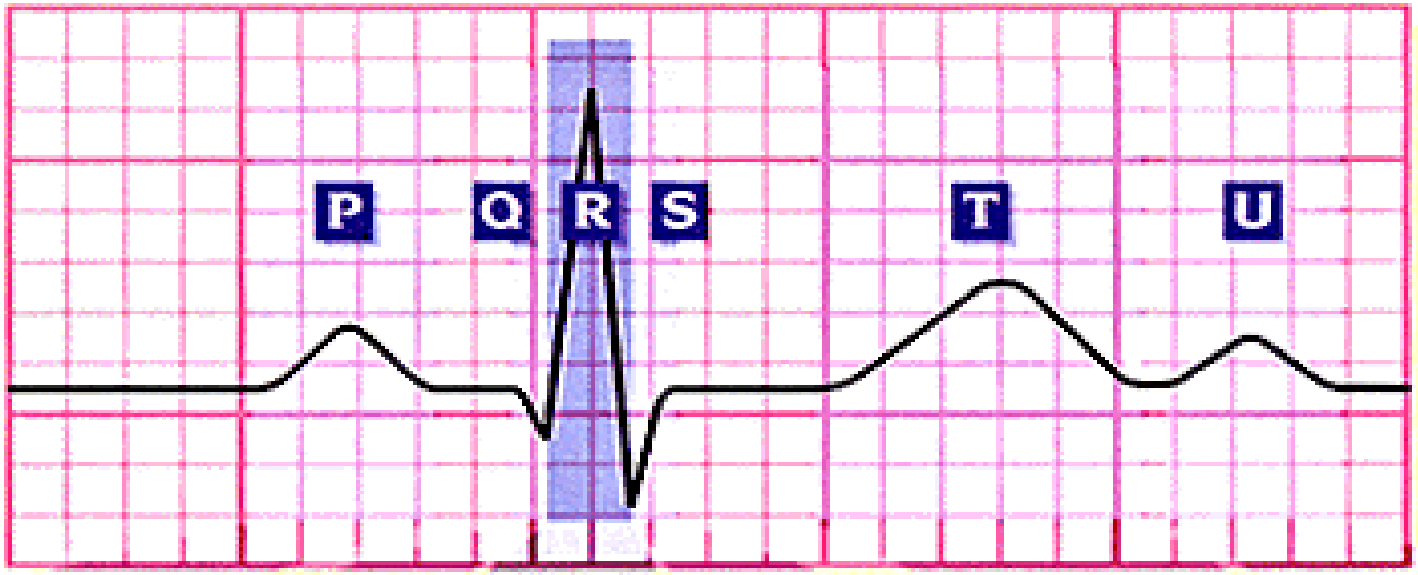


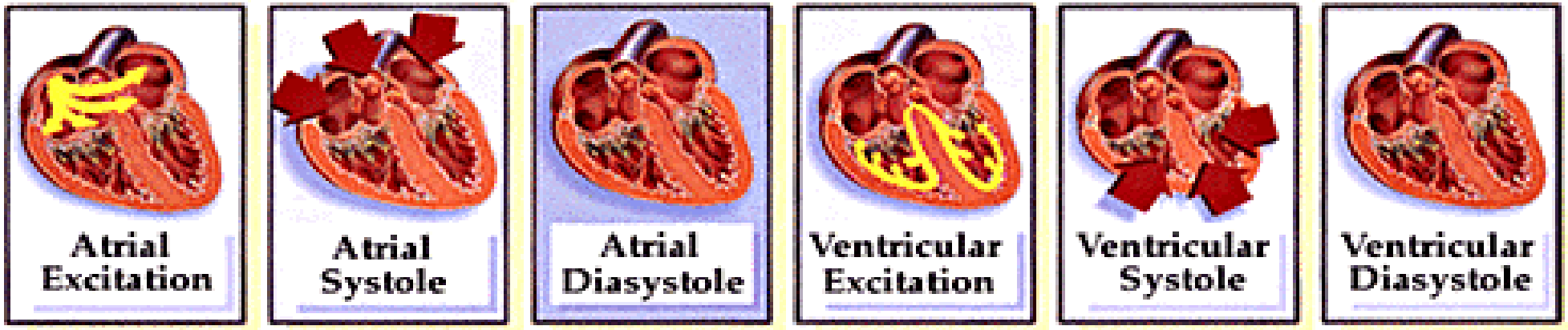
Cardiac Conduction System

CARDIAC CONDUCTION SYSTEM

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

Electrocardiogram (ECG)

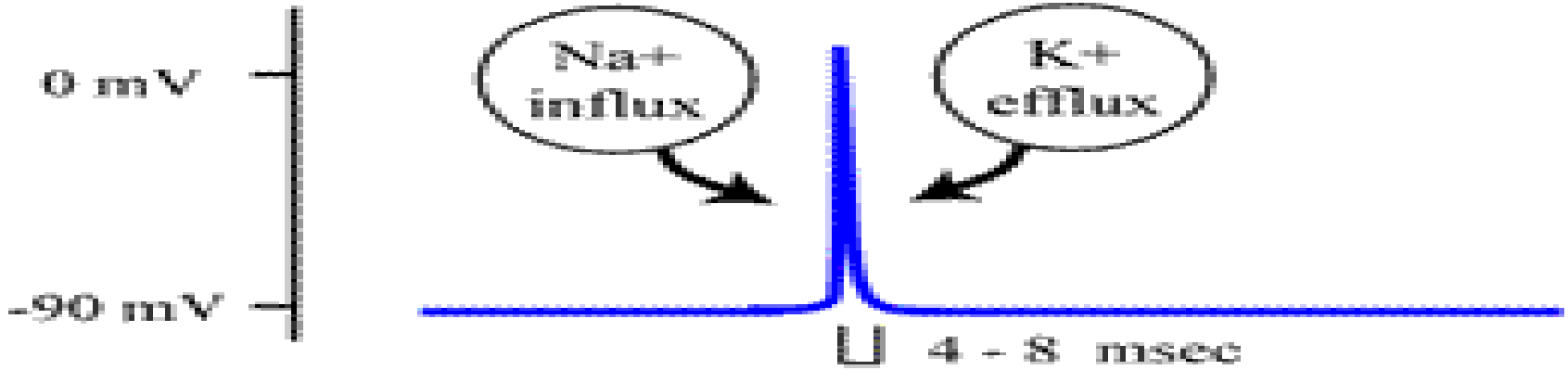




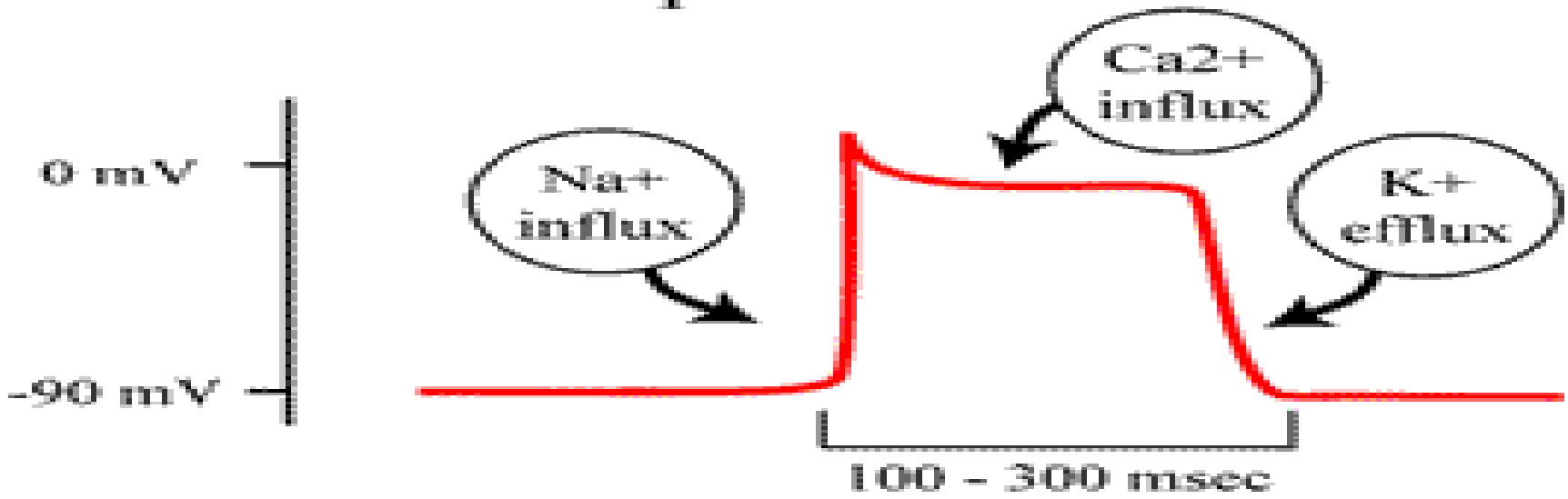
Electrical and Mechanical Events

CARDIAC ACTION POTENTIAL

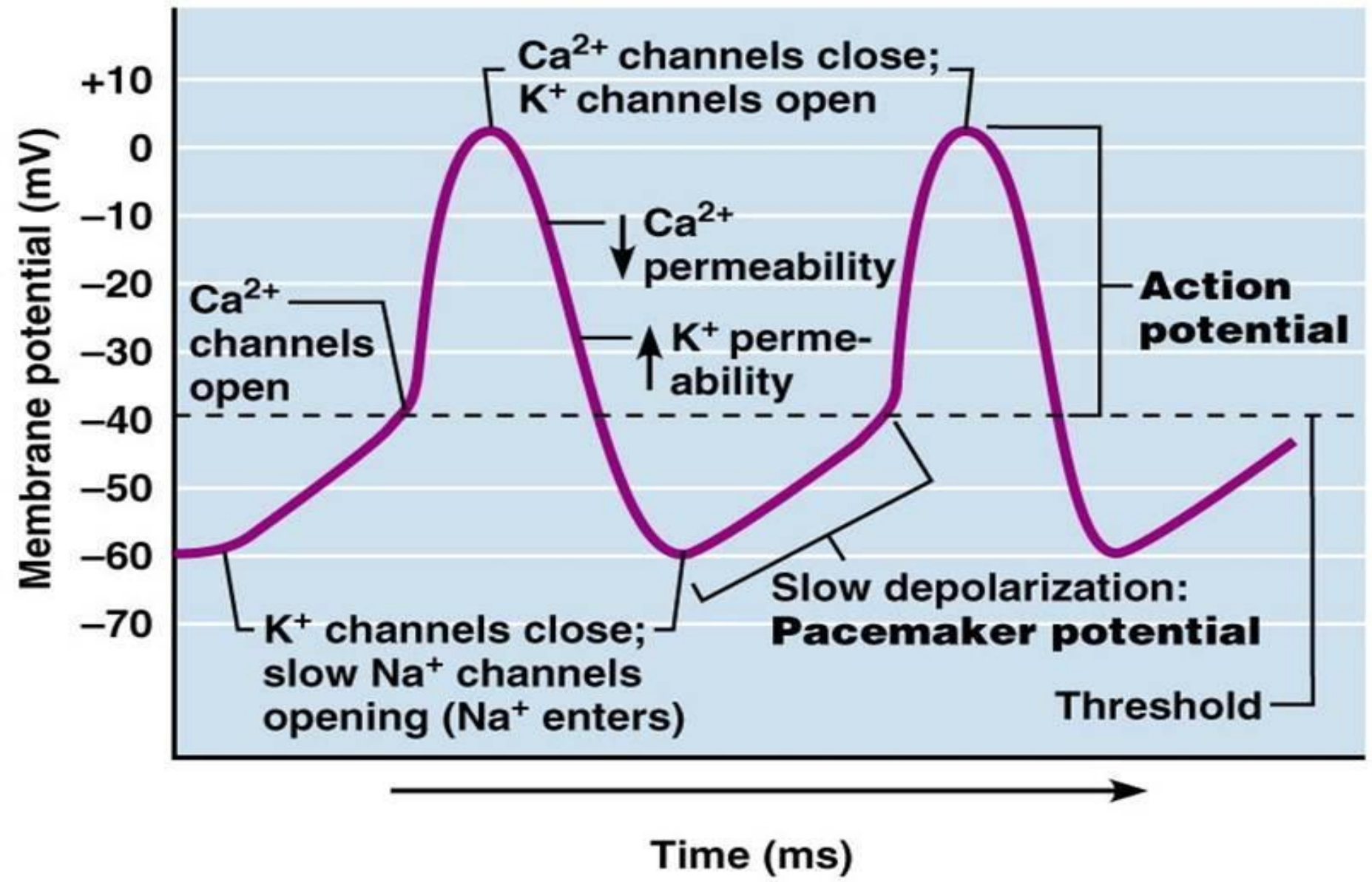
Skeletal action potential:



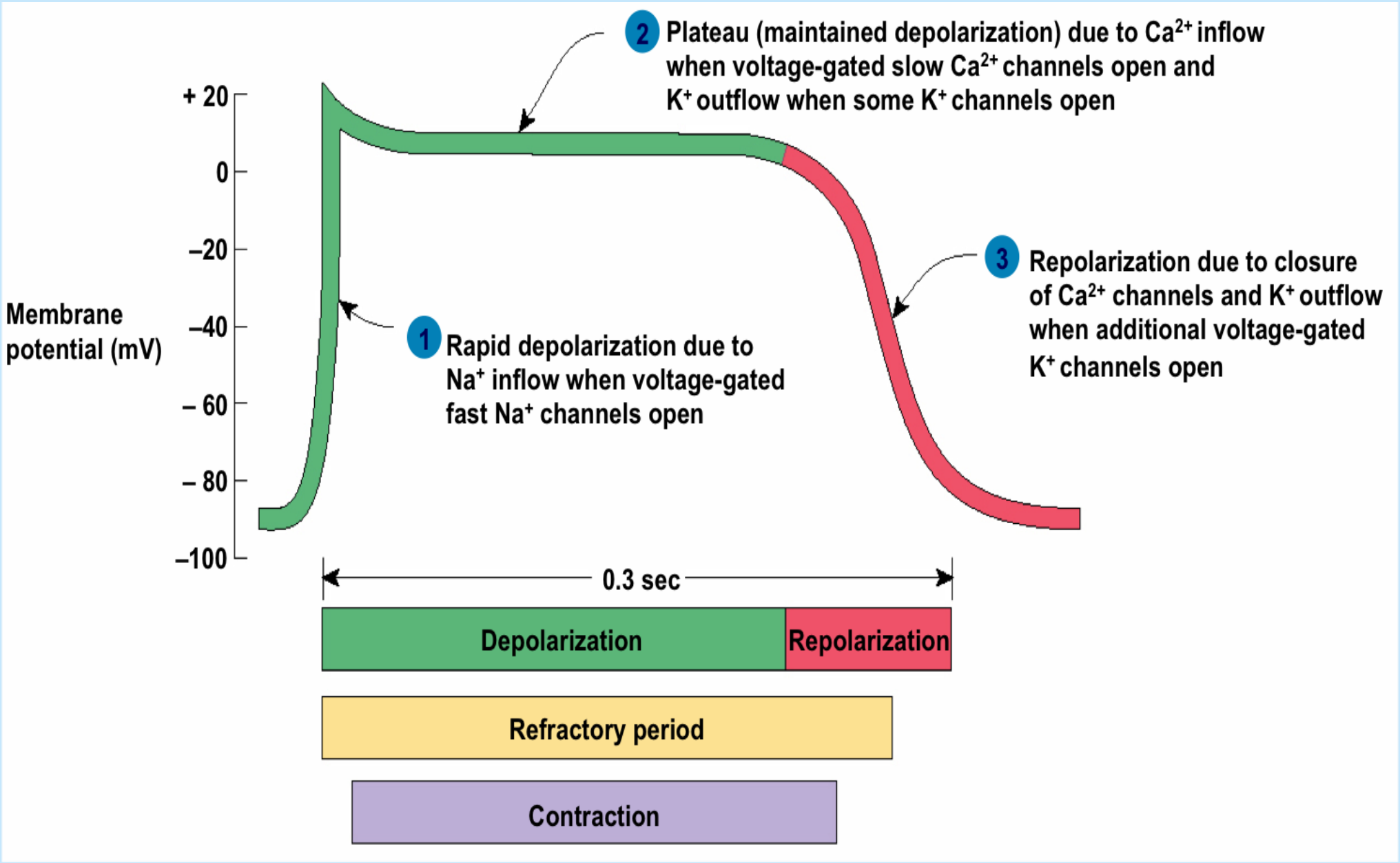
Cardiac action potential:



CARDIAC ACTION POTENTIAL
Pacemaker (SA node)

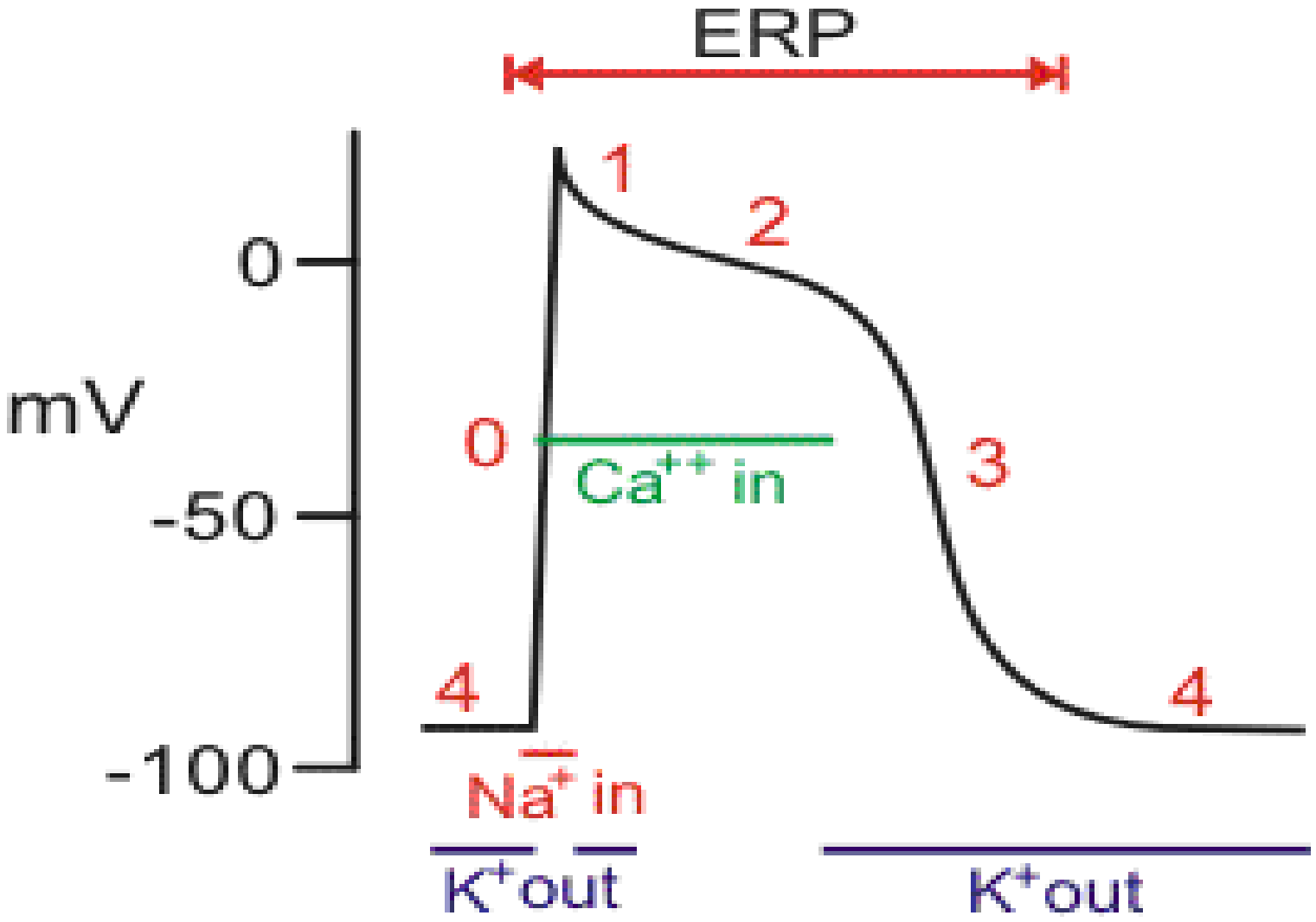


CARDIAC ACTION POTENTIAL
Non-pacemaker (ventricular muscle)

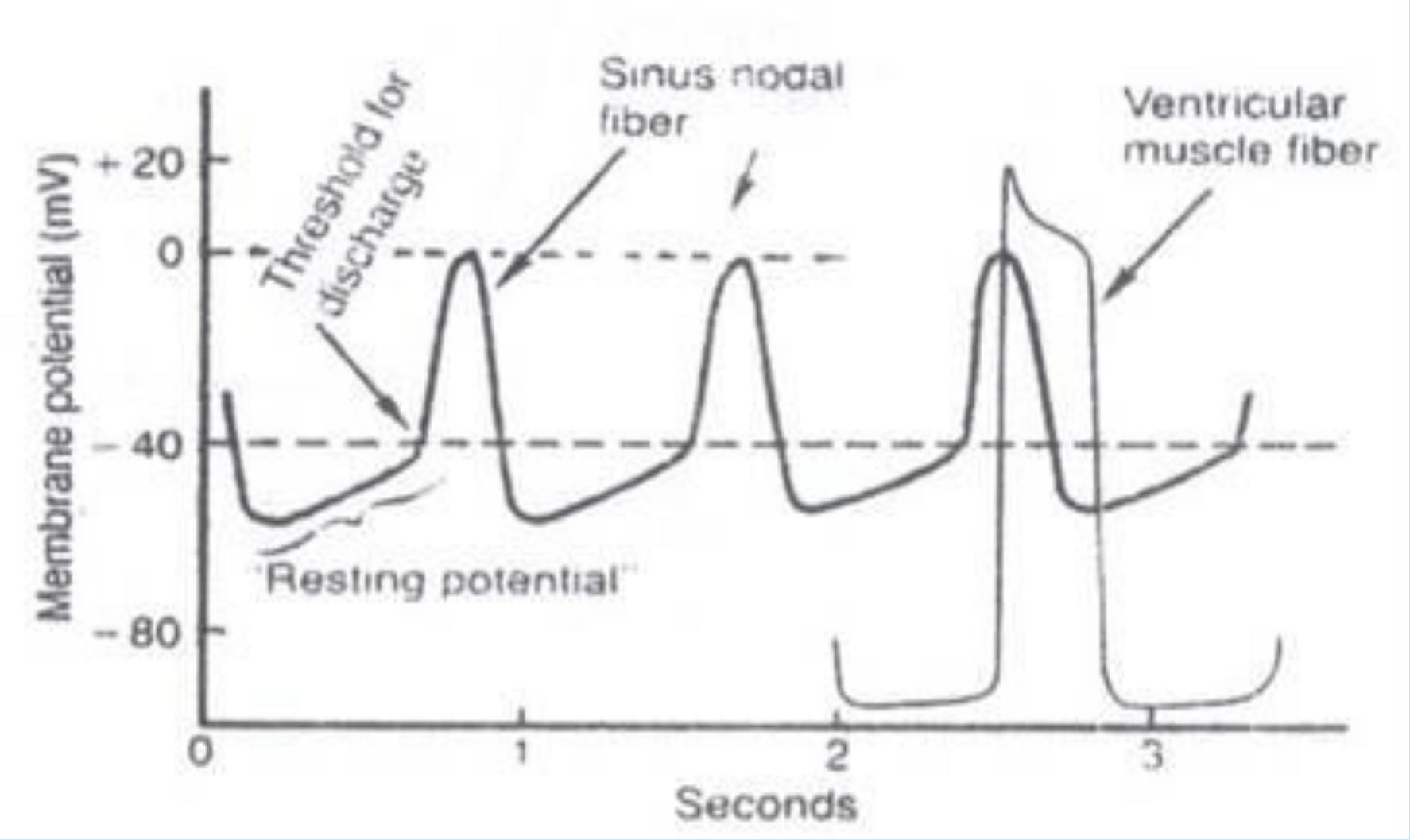


Fast-Response Action Potential

(e.g., ventricular myocyte)



Difference between pacemaker and non-pacemaker action potential



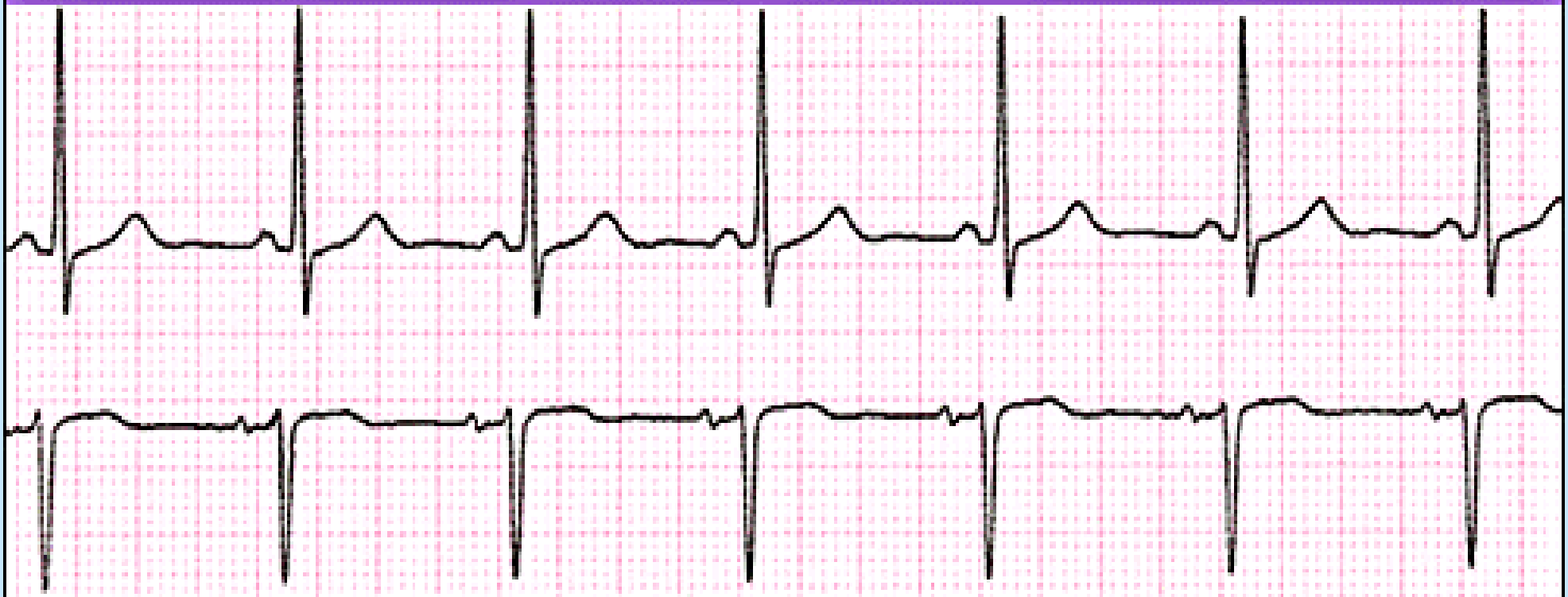
WHAT IS ARRHYTHMIA?

An abnormality in the :

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

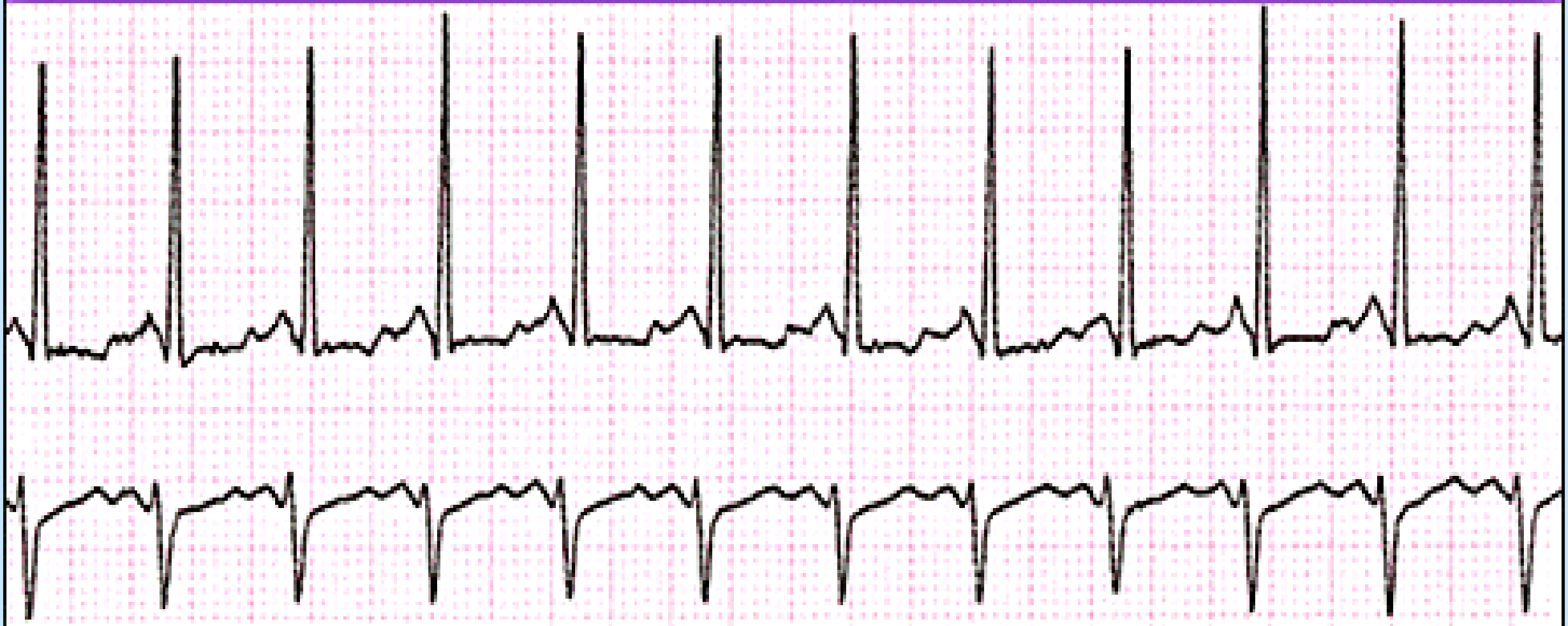
low = bradycardia

Normal Sinus Rhythm



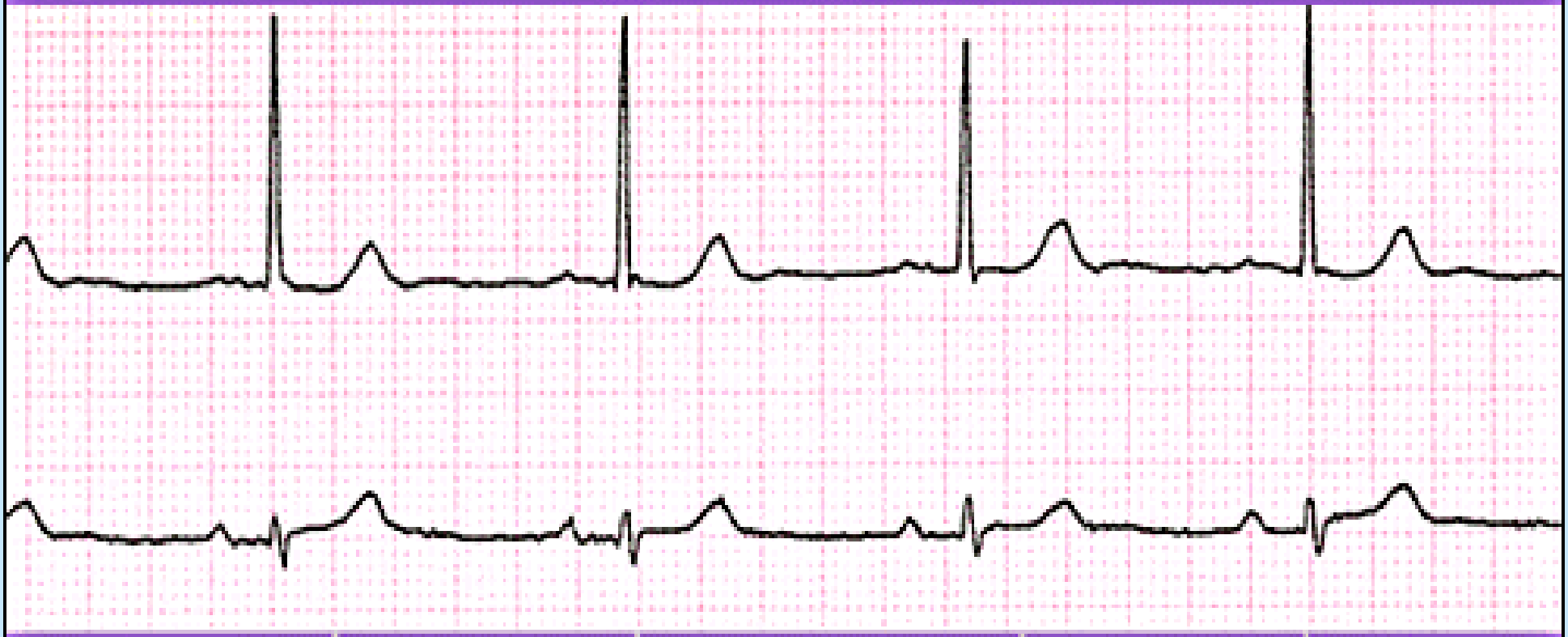
Heart Rate	Rhythm	P Wave	PR interval (in seconds)	QRS (in seconds)
60-100 bpm	Regular	Before each QRS, identical	.12 to .20	<.12

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

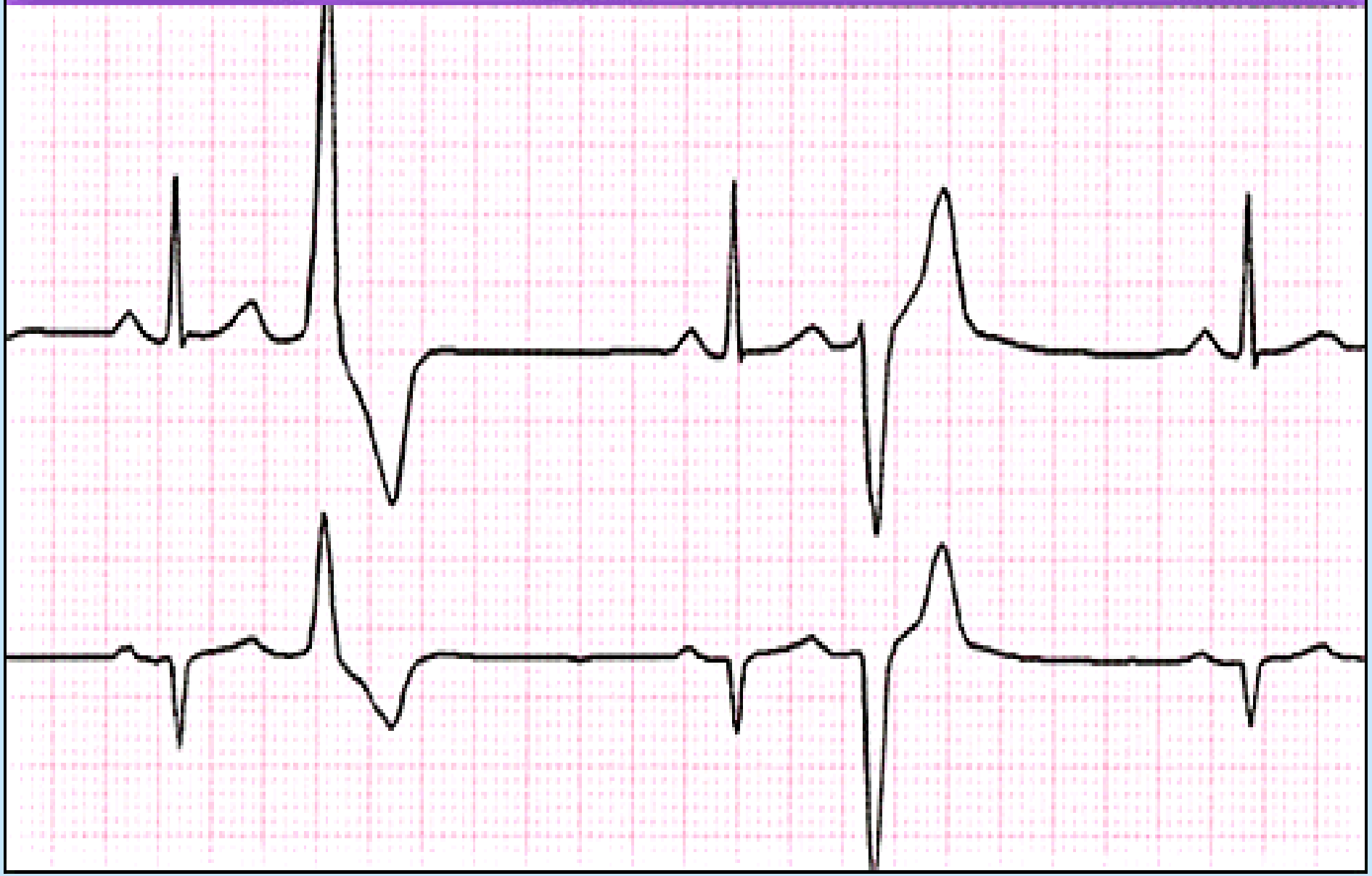
WHAT IS ARRHYTHMIA?

An abnormality in the :

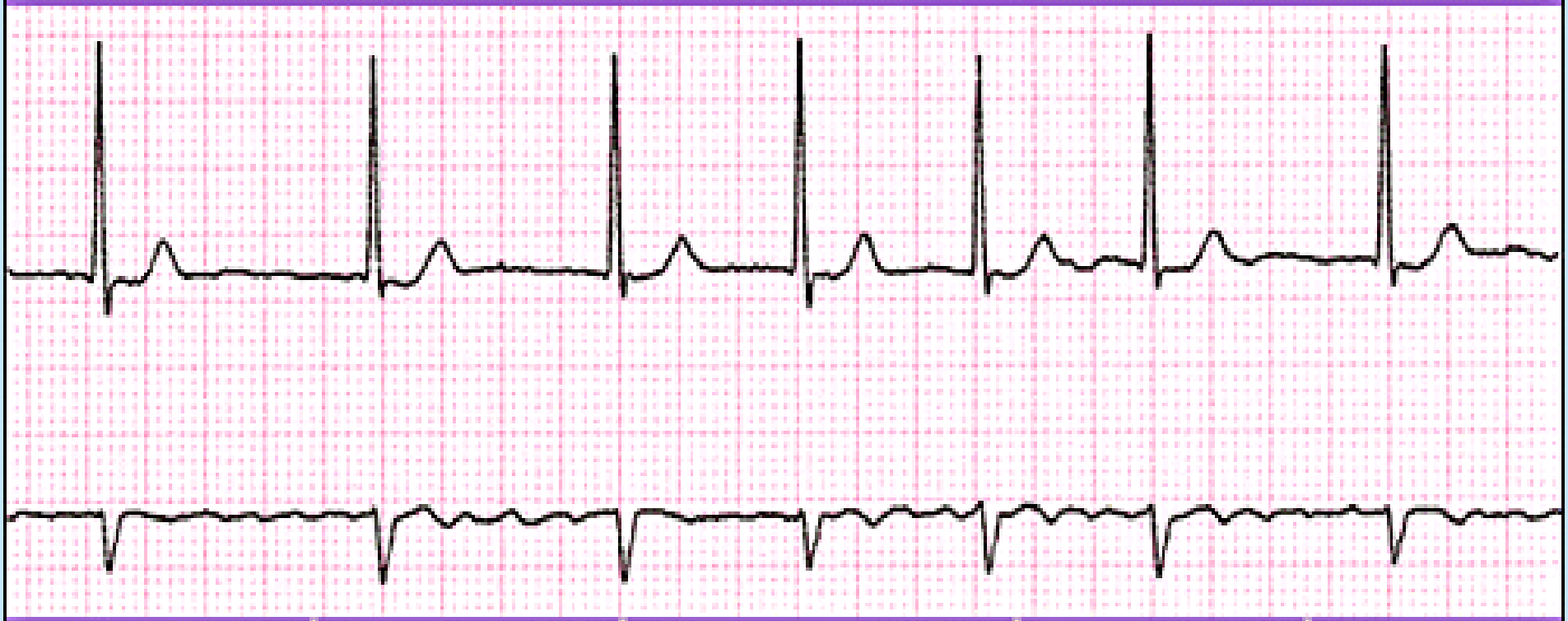
- **rate ..... high= tachycardia**
  low = bradycardia

- **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?

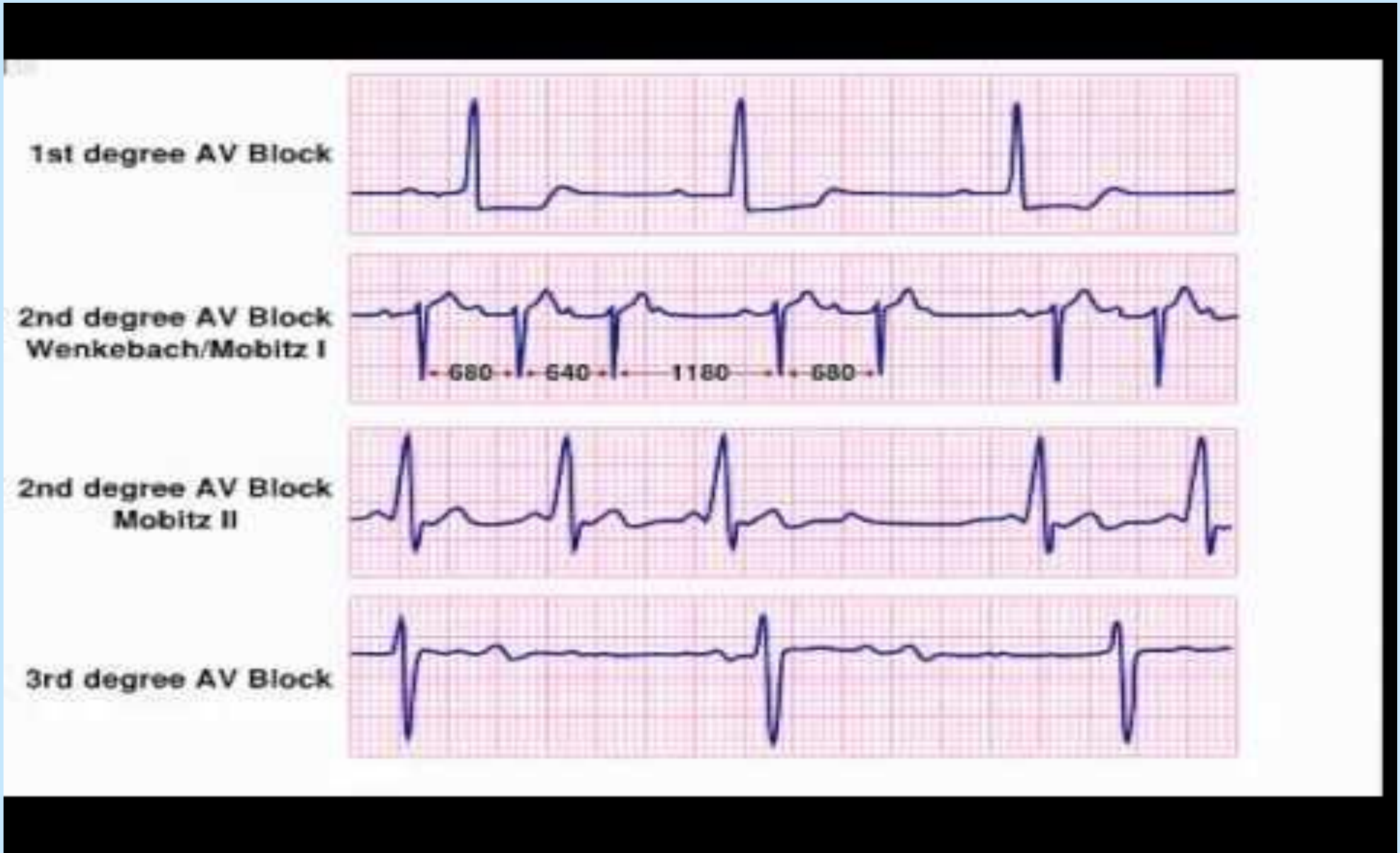
An abnormality in the :

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

  low = bradycardia

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

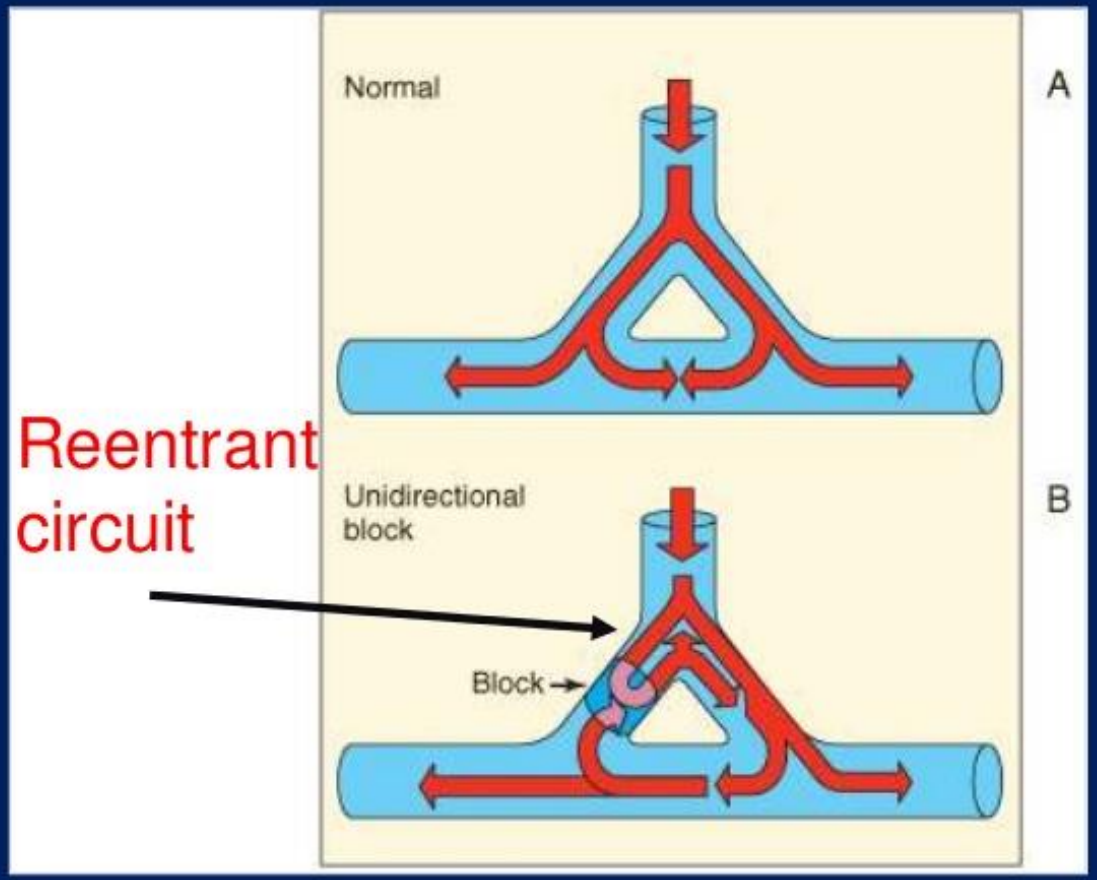
Disturbances in conduction

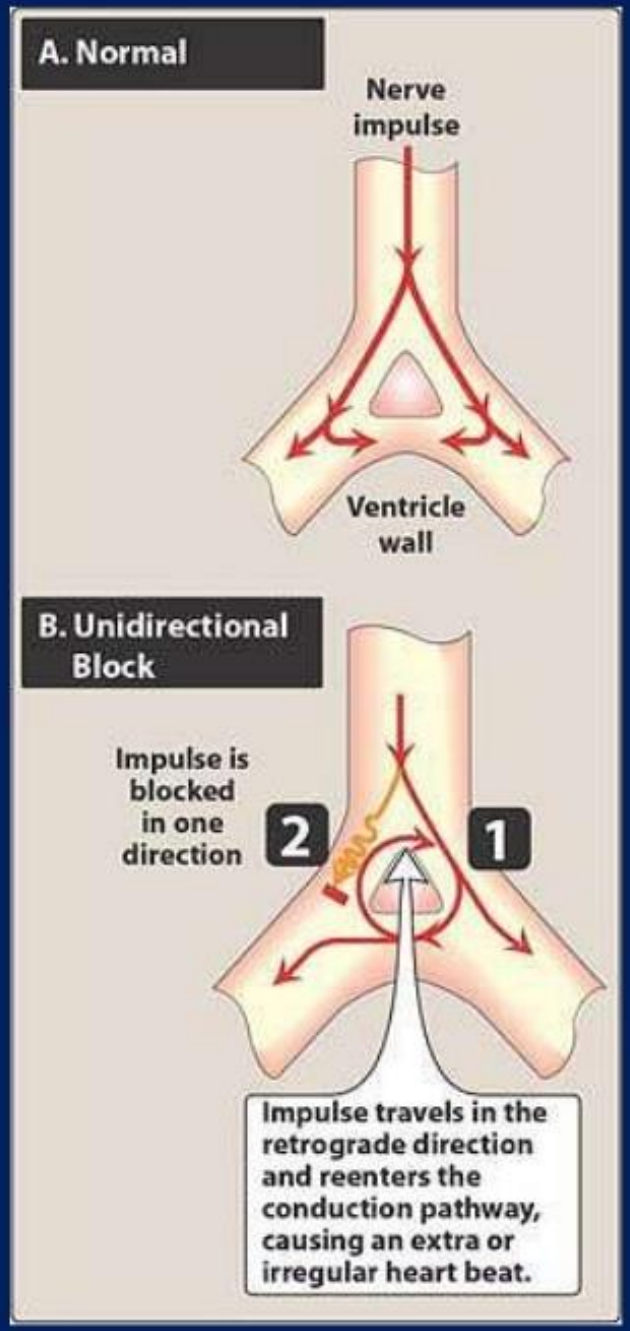


2. Disorders of impulse conduction

May result in abnormality in rate:

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





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

Na+ channel blockers

(membrane stabilizing drugs)

CLASS II:

β- adrenoceptor blockers

CLASS III:

Drugs that prolong action potential duration

CLASS IV:

Calcium channel blockers.

CLASS I

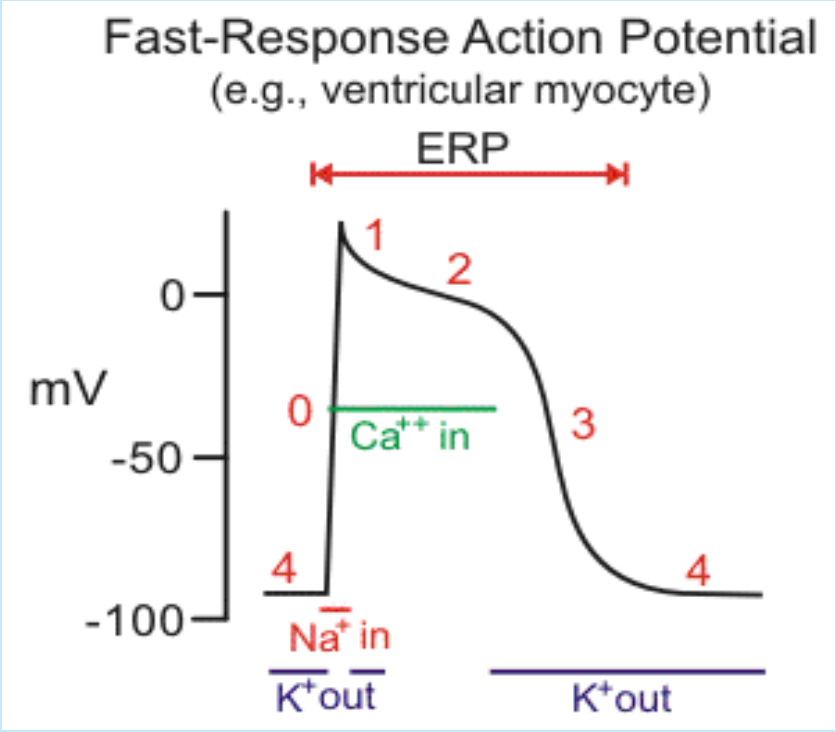
Drugs that block the influx of Na ions through Na channels

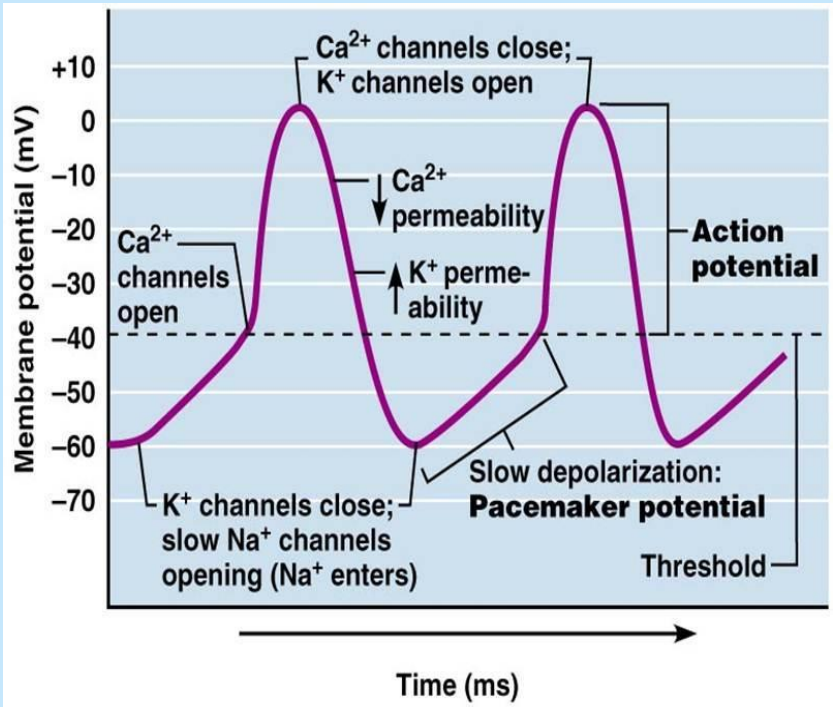
⬇

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 :**

- Ia : prolong action potential duration

- Ib : shorten action potential duration

- Ic : no effect on action potential duration

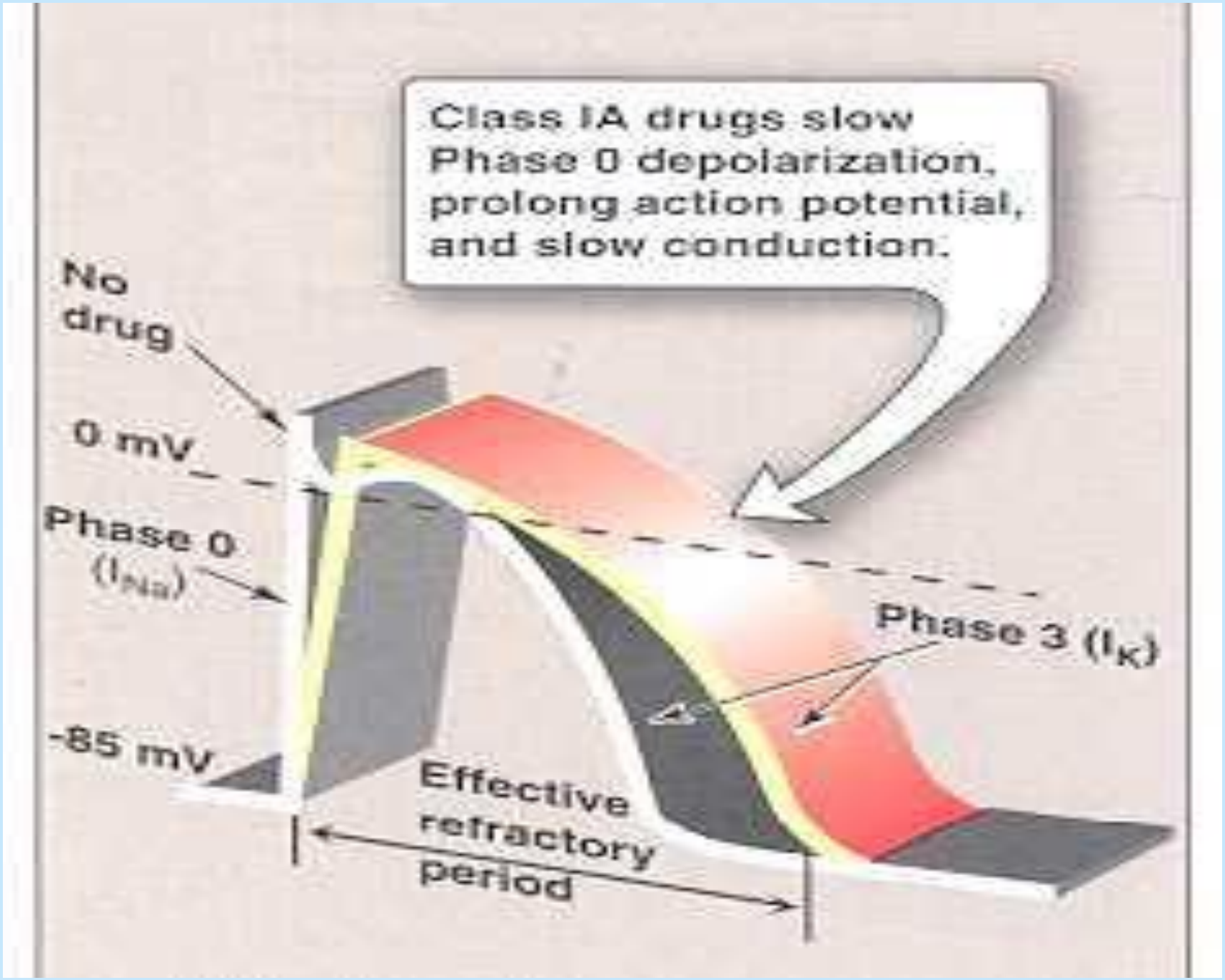
CLASS I a

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:

- **prolongs P-R and Q-T interval**
- **widens QRS complex**

CLASS I a

QUINIDINE

Therapeutic uses:

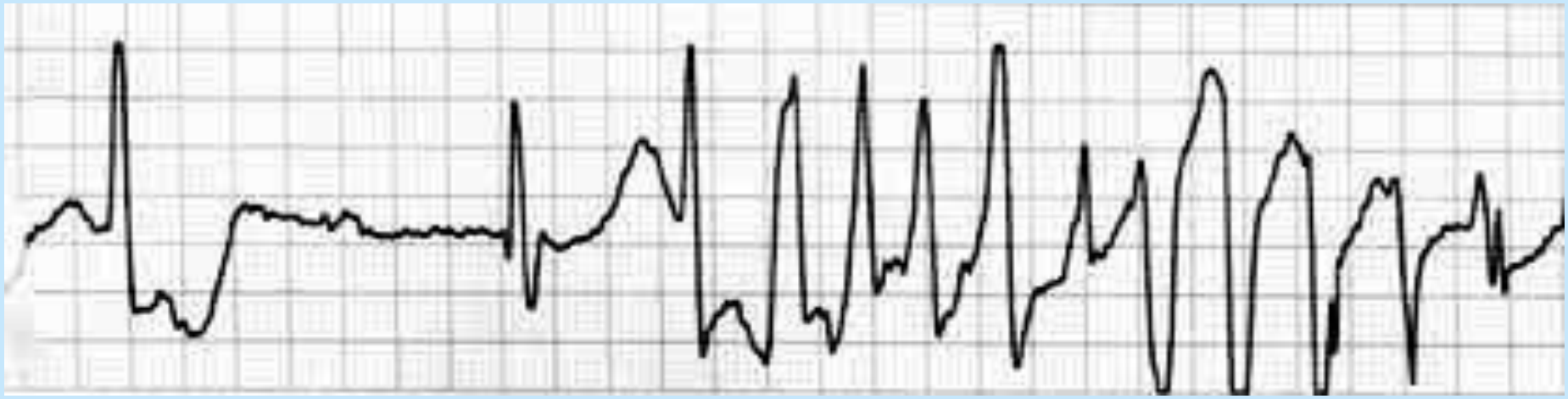
- atrial flutter & fibrillation

- 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

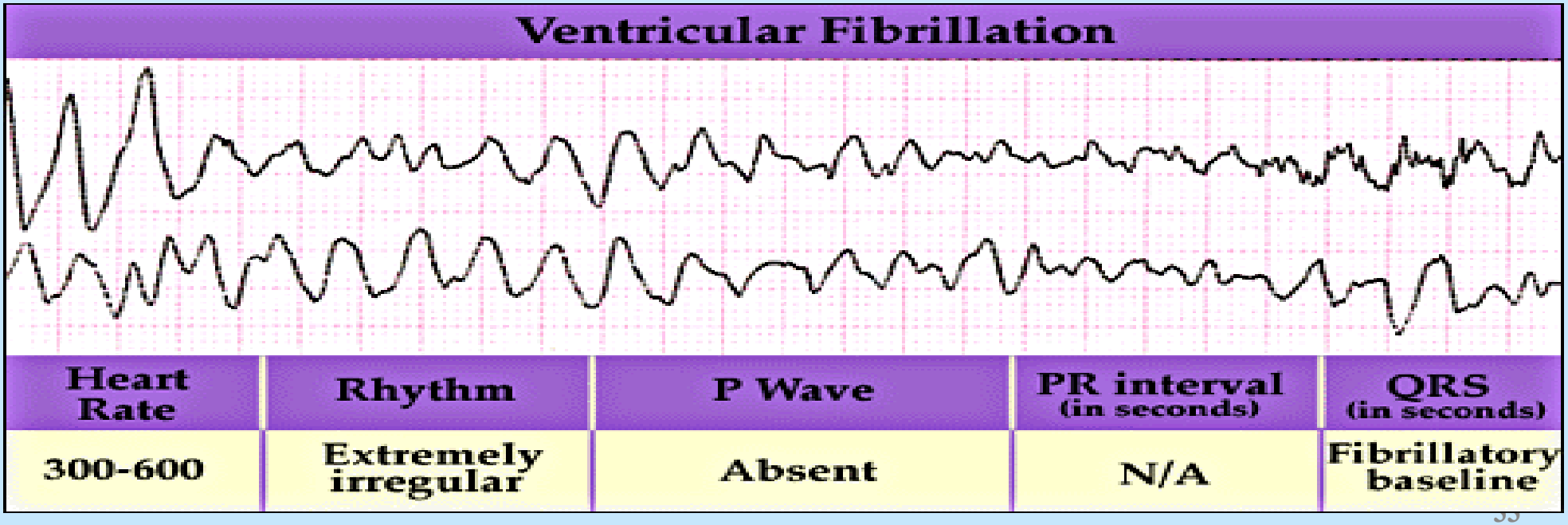


Torsades de pointes

- may terminate spontaneously or lead to

⬇

fatal ventricular fibrillation



CLASS I a

QUINIDINE

Adverse effects :

- **Anticholinergic adverse effects:**
  - Dry mouth
  - Blurred vision
  - Urinary retention
  - constipation

- **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

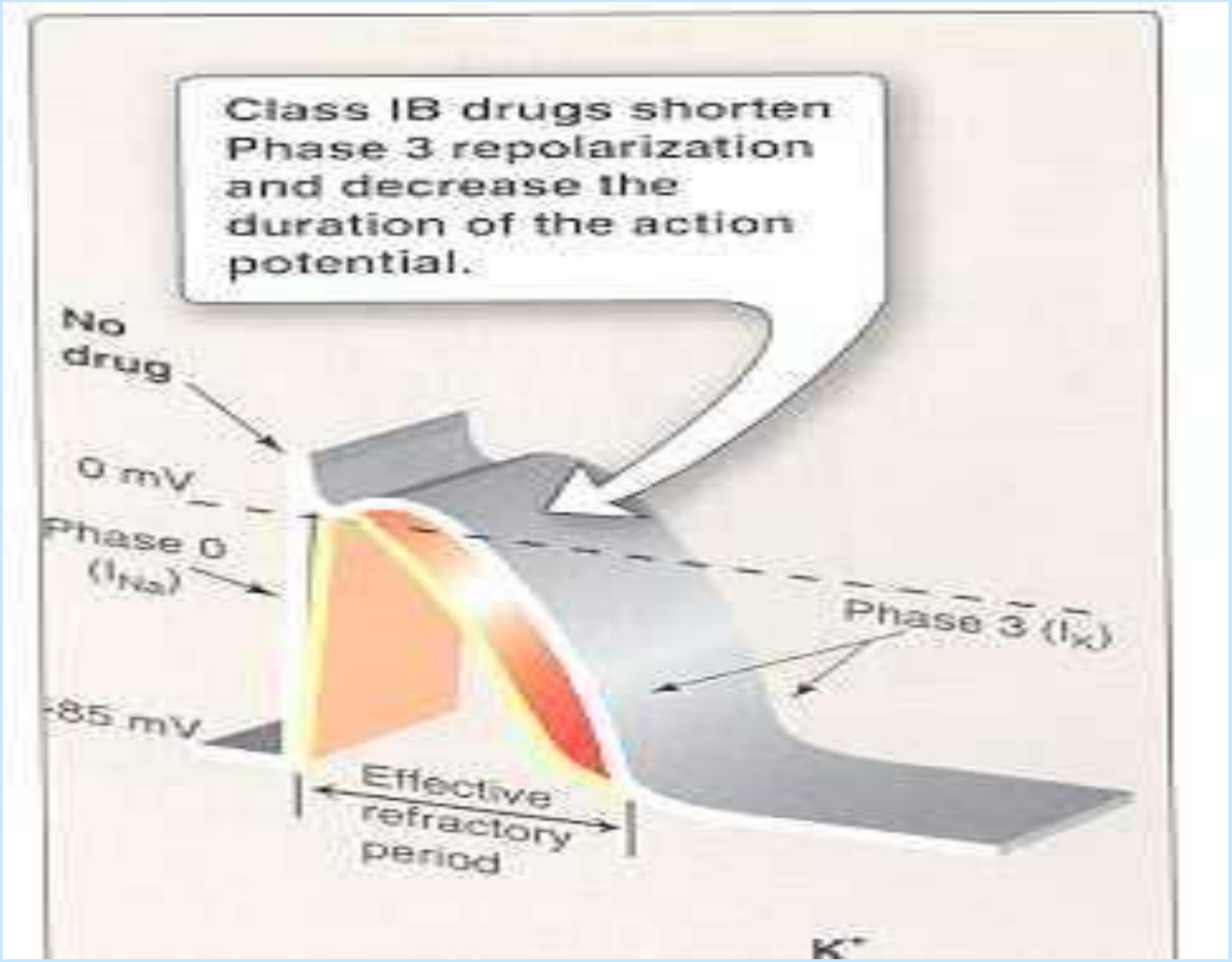
CLASS I b

- **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

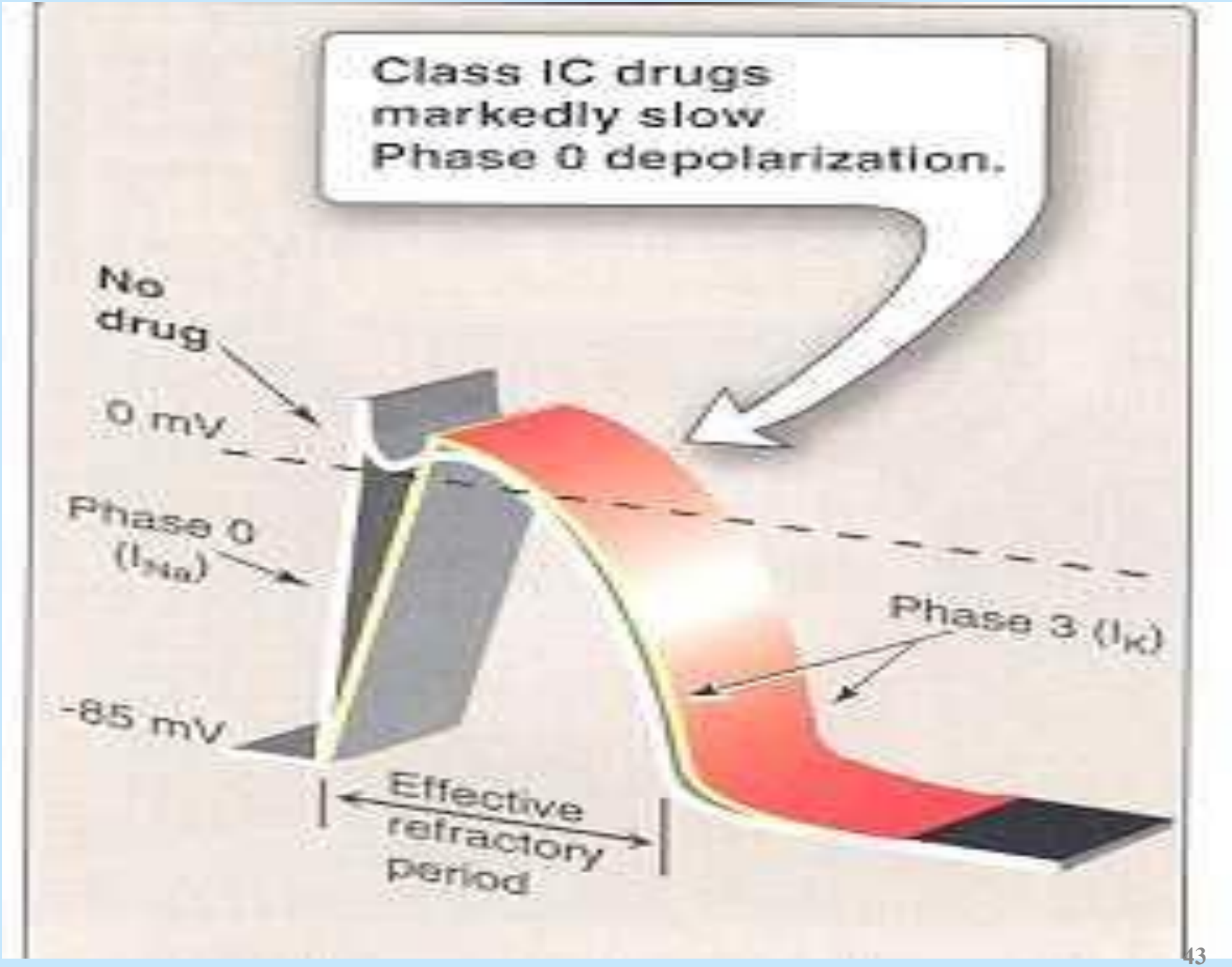
3- arrhythmias & hypotension

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

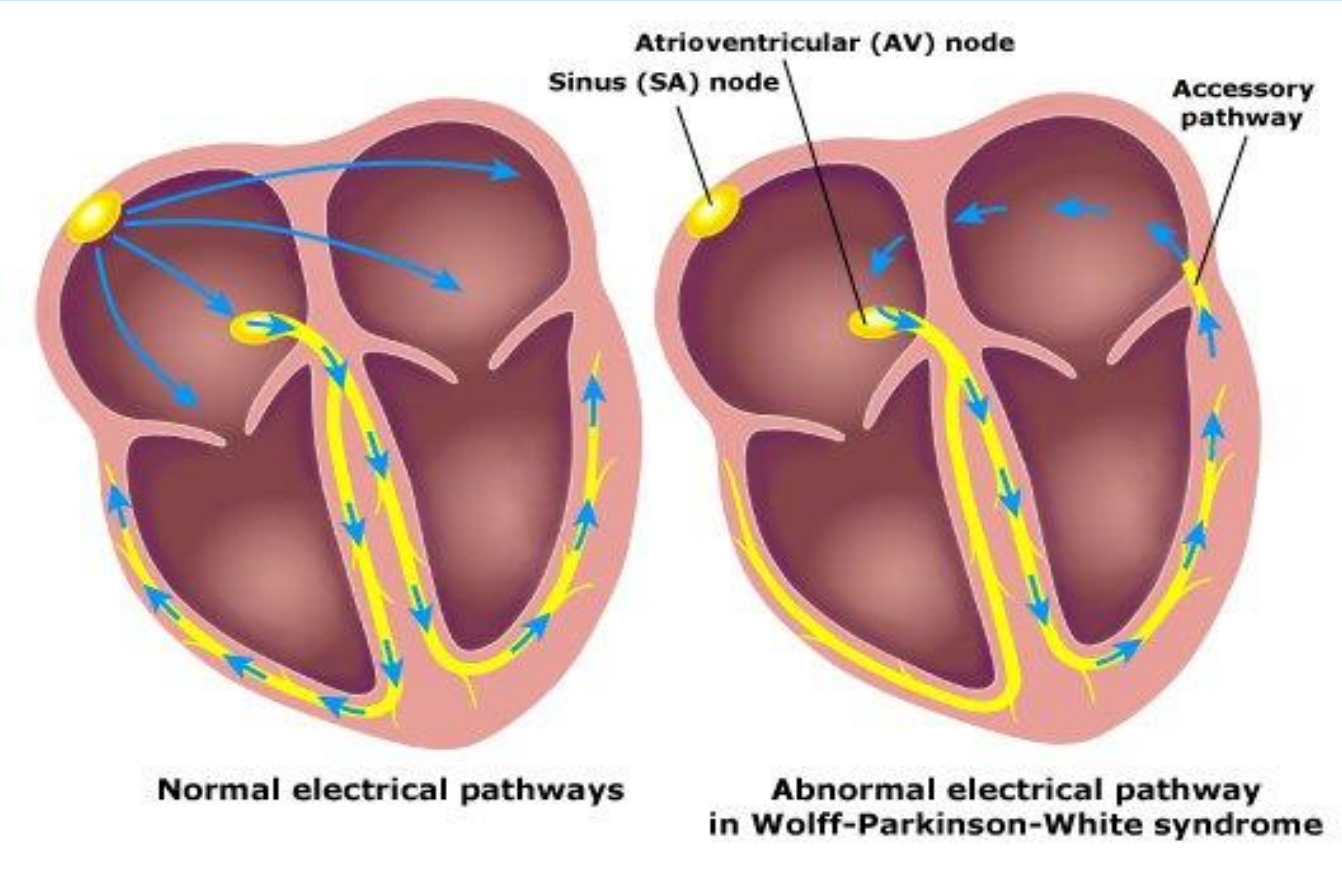
- Wolff-Parkinson-White syndrome

- 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 :

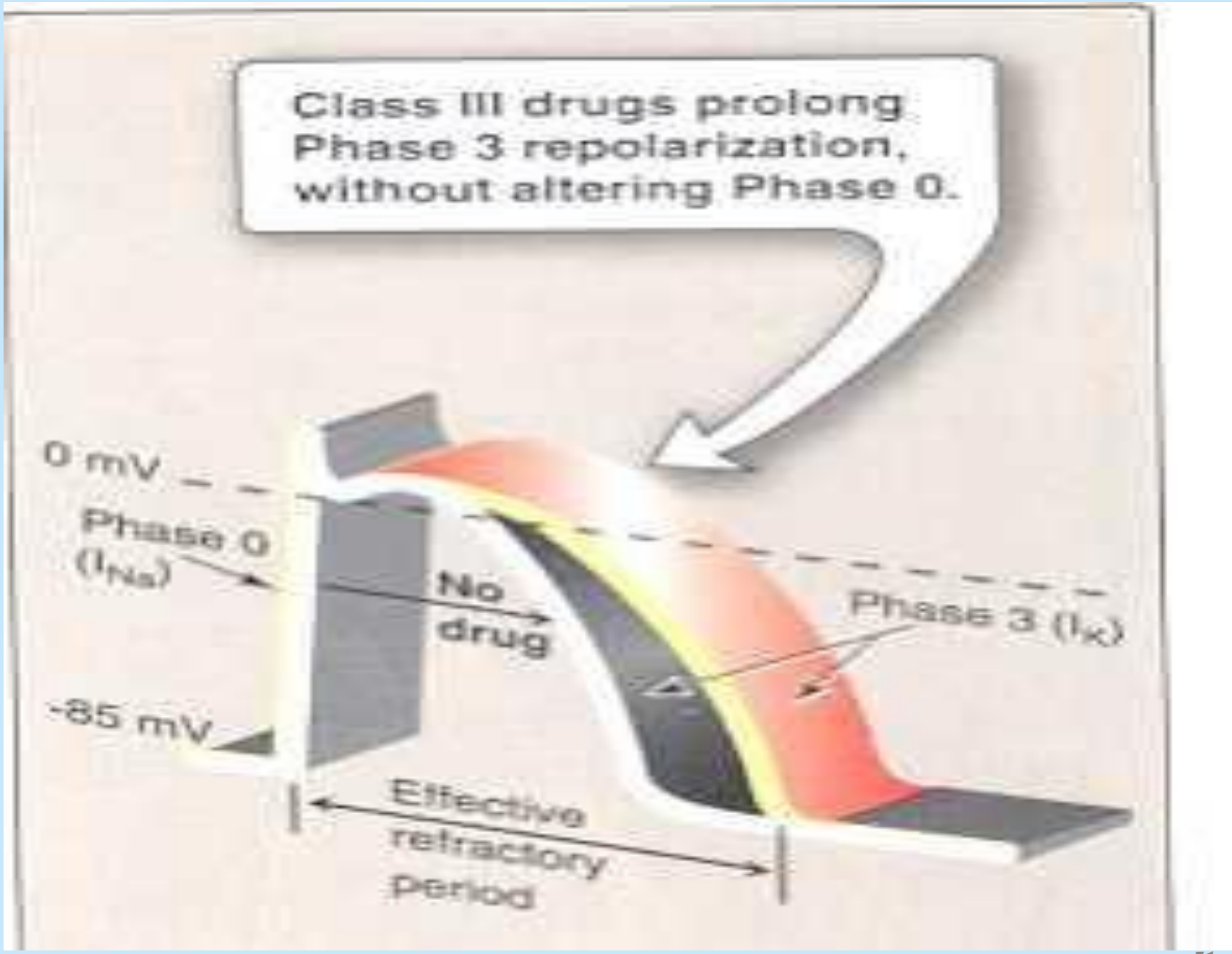
- very short acting (half-life = 9 min.)
- given I.V. for rapid control of ventricular rate in patients with atrial flutter or fibrillation

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

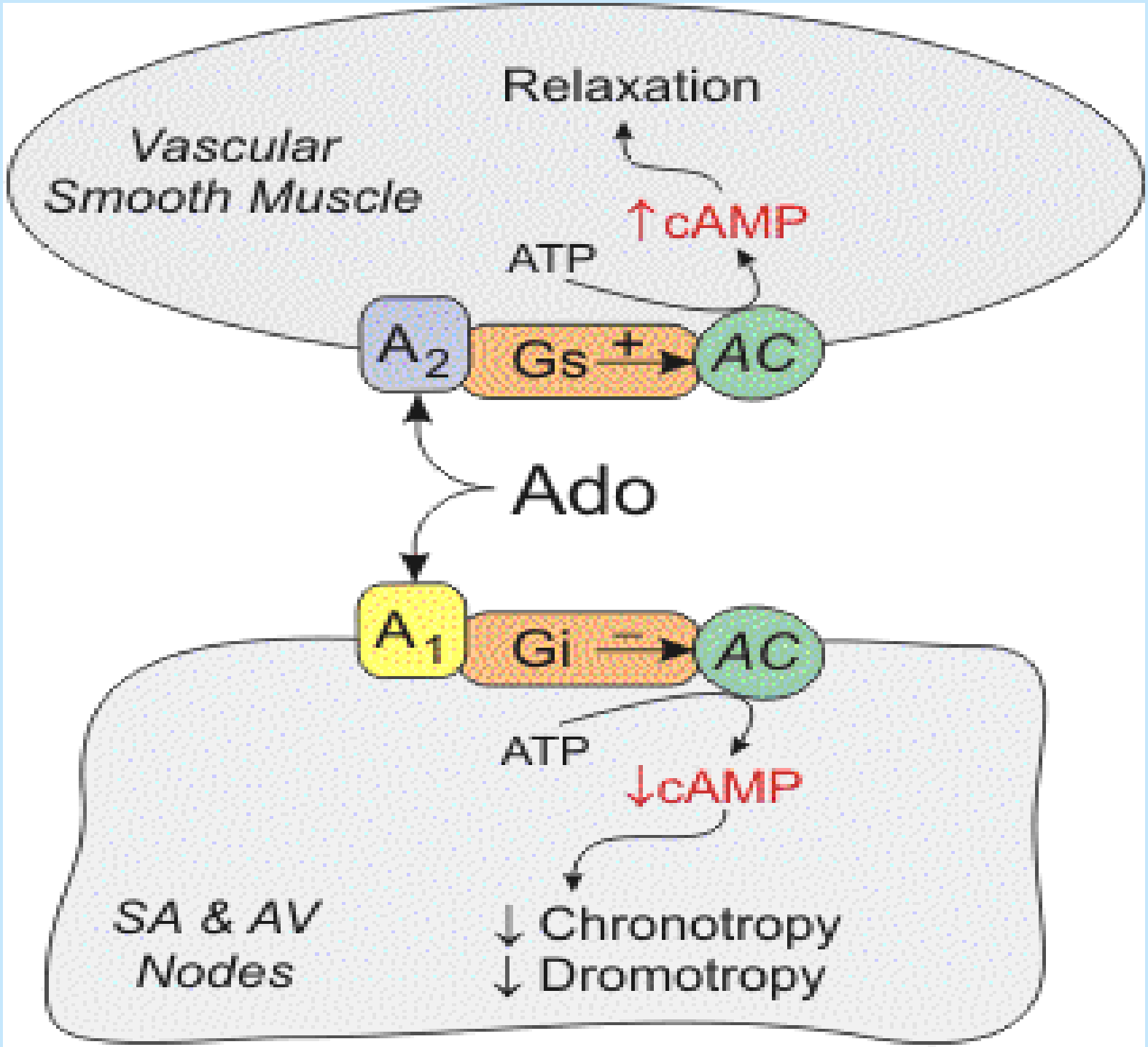
(hyperpolarization)

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

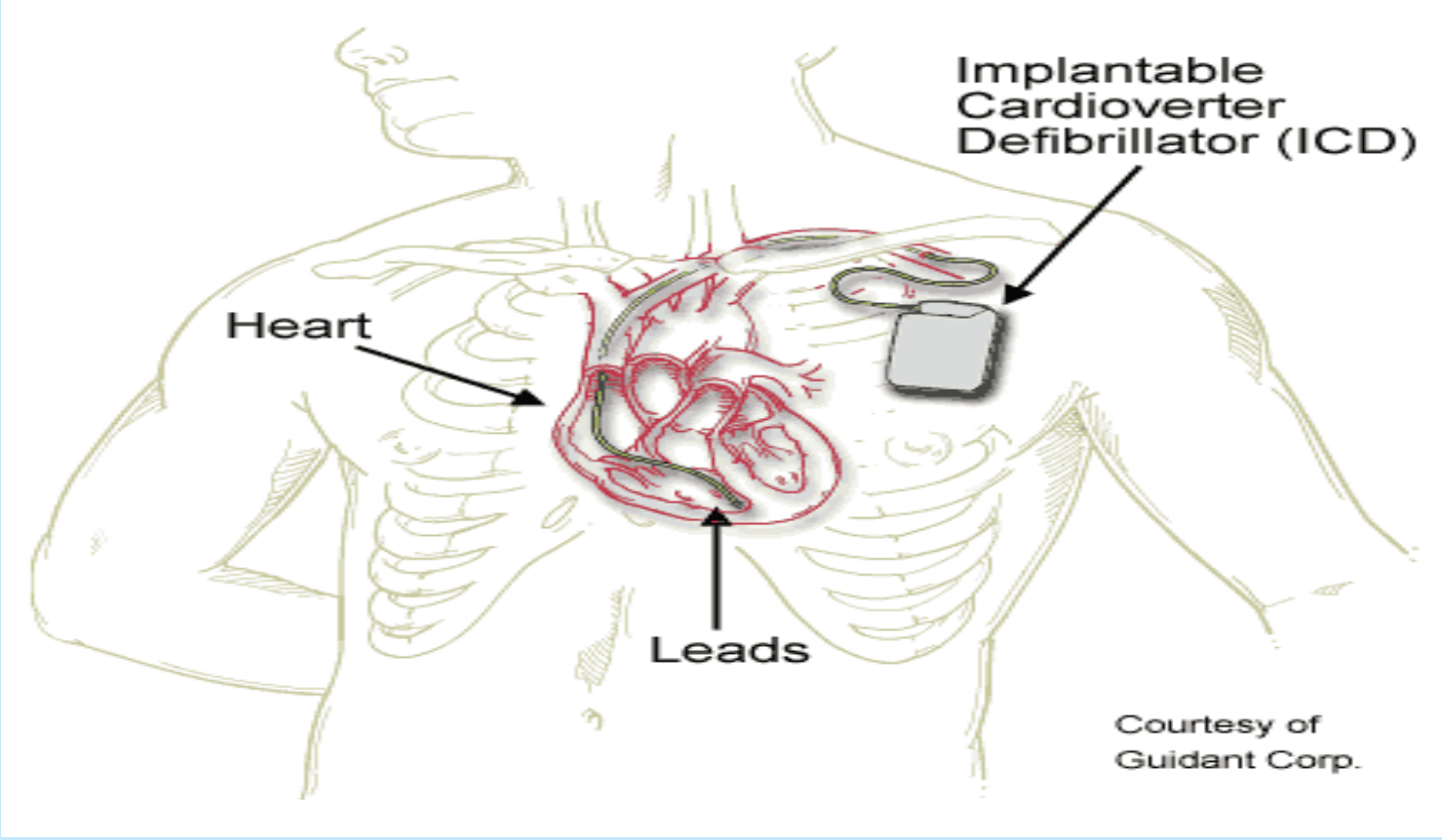
ATROPINE

- 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