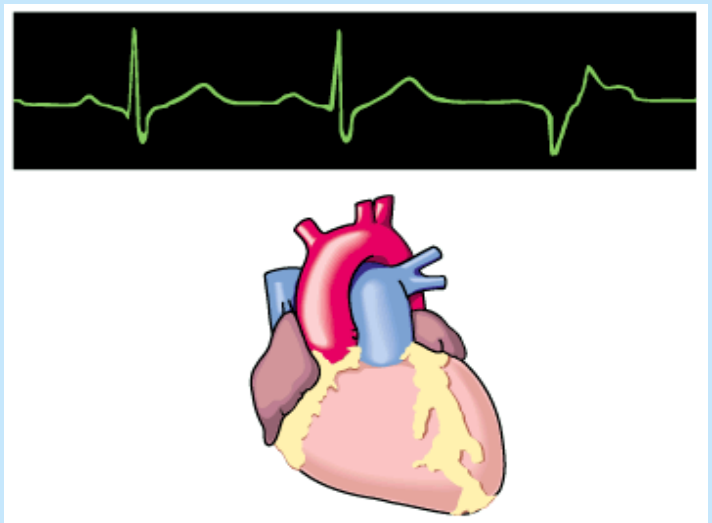
# Antiarrhythmic Drugs

**Prof. Abdulrahman Almotrefi**



# Cardiovascular Pharmacology

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

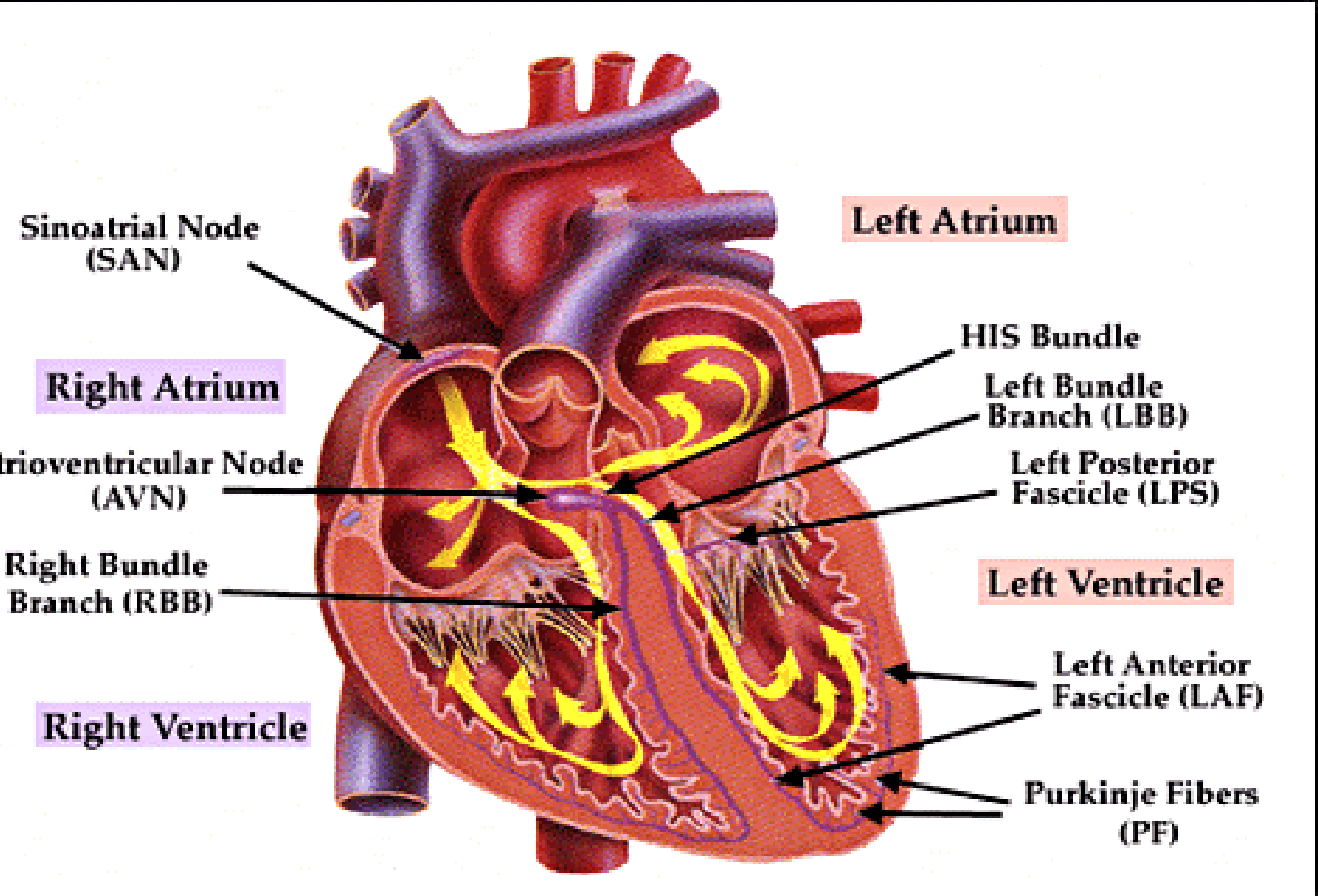
# Learning objectives

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

- Understand definition of arrhythmias and their different types

- describe different classes of Antiarrhythmic drugs and their mechanism of action

- understand their pharmacological actions, clinical uses, adverse effects and their interactions with other drugs.

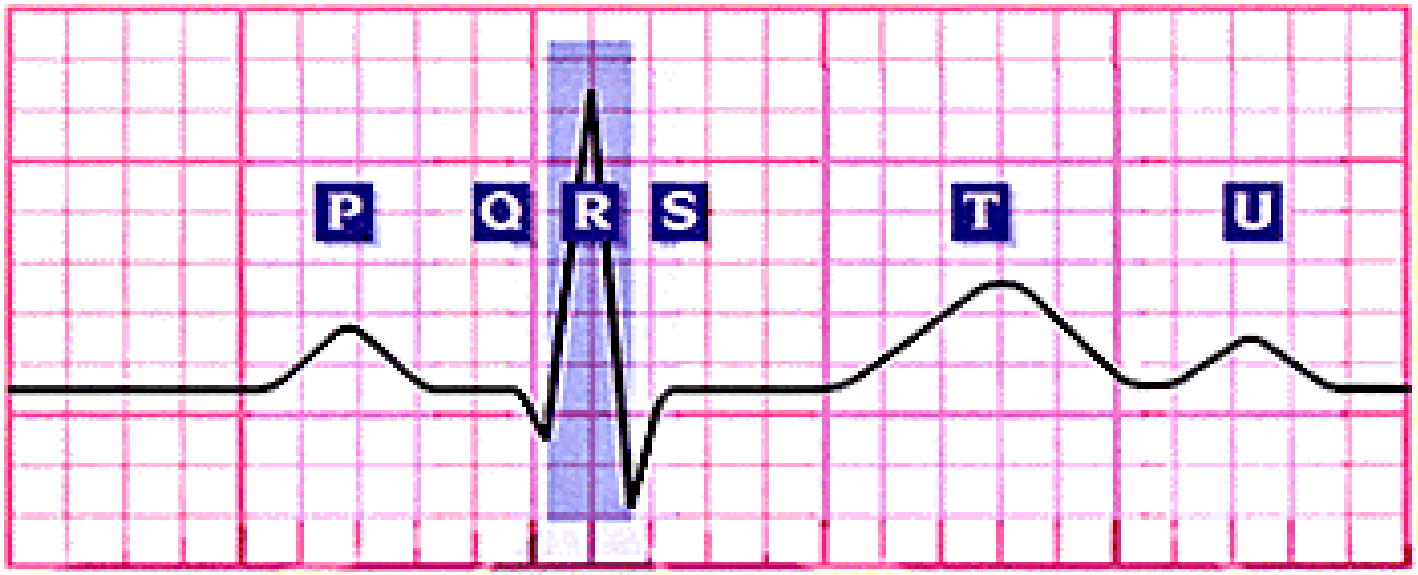


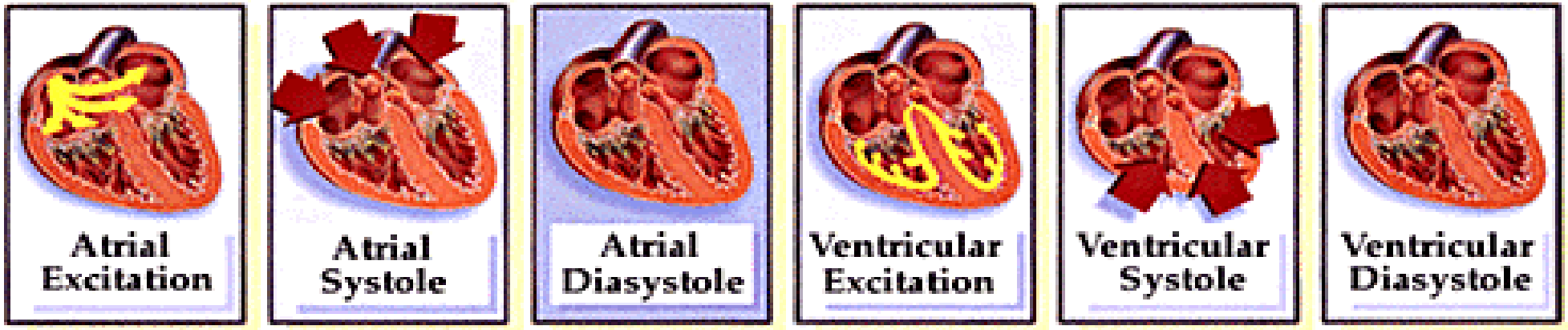

# Cardiac Conduction System

# CARDIAC CONDUCTION SYSTEM

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

# Electrocardiogram (ECG)

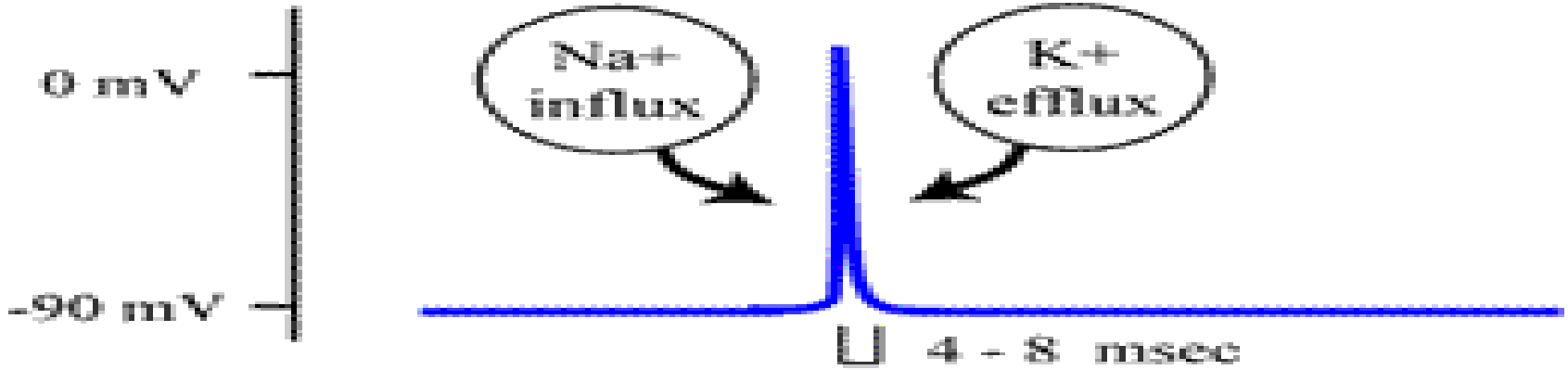


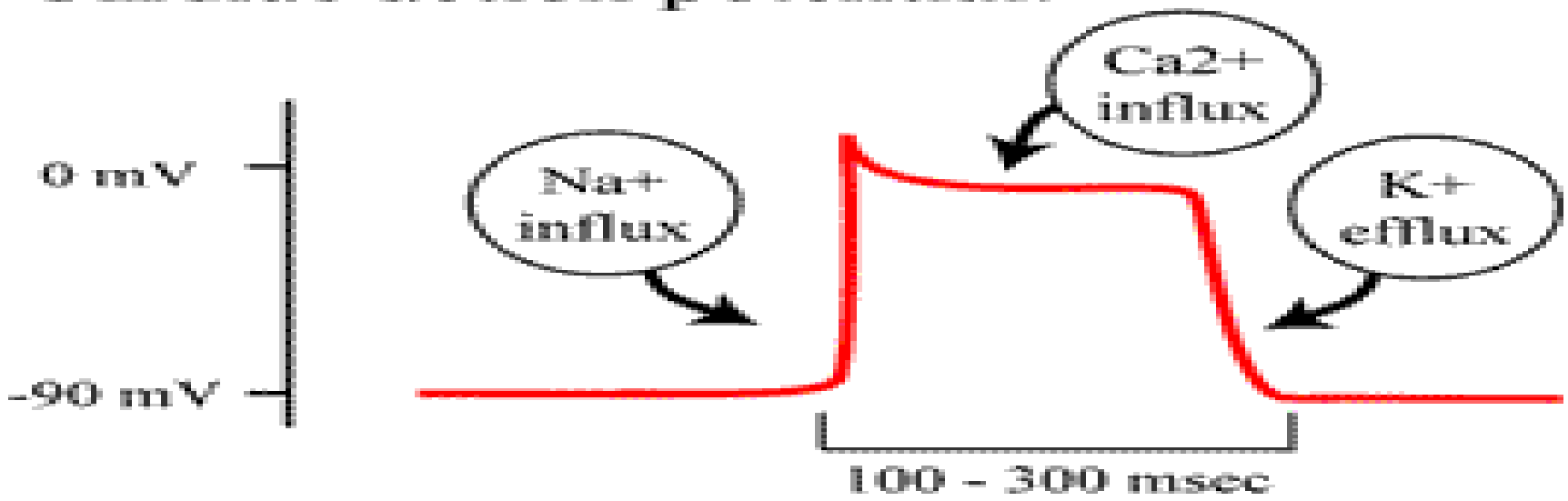

**Electrical and Mechanical Events**

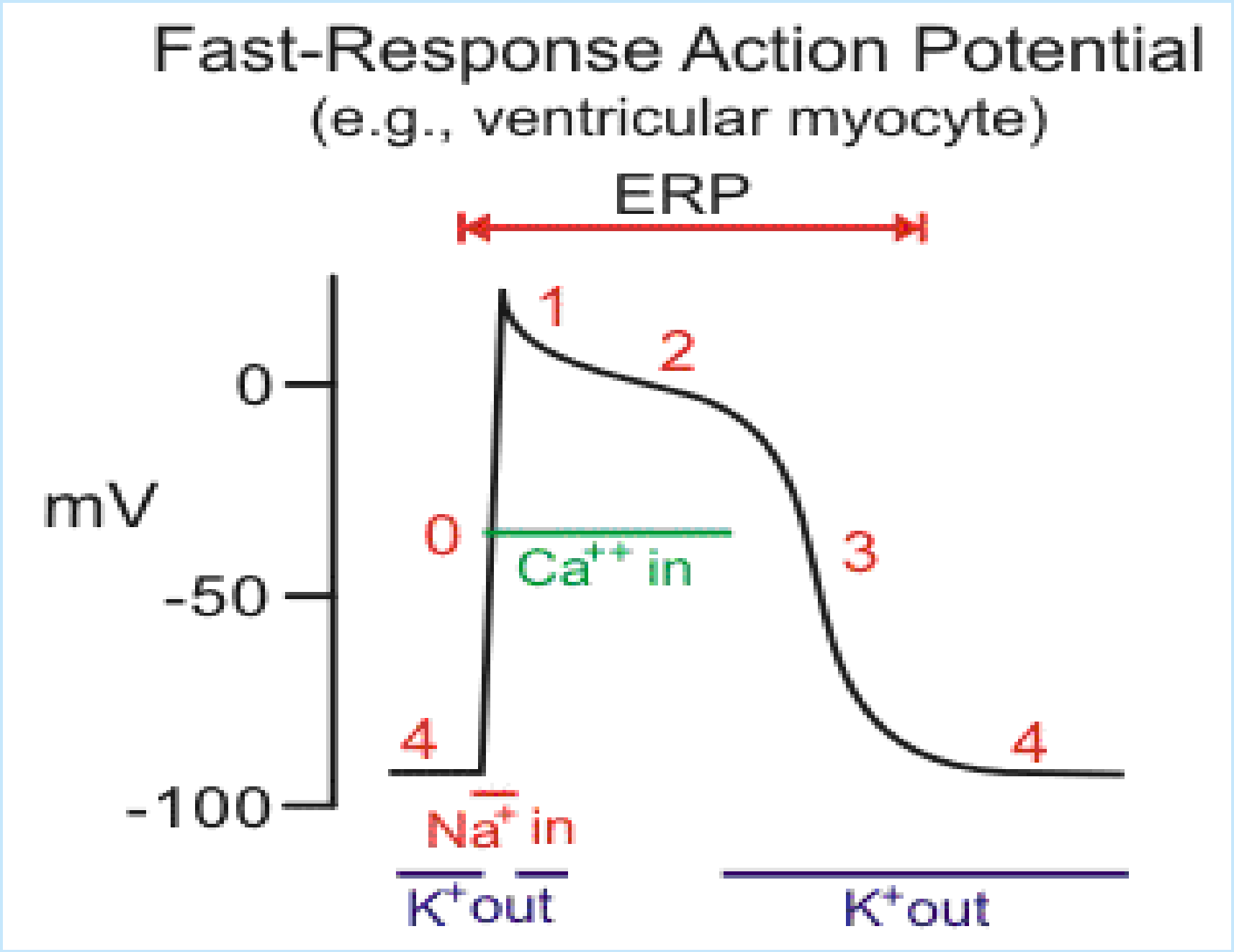
# CARDIAC ACTION POTENTIAL

Skeletal action potential:

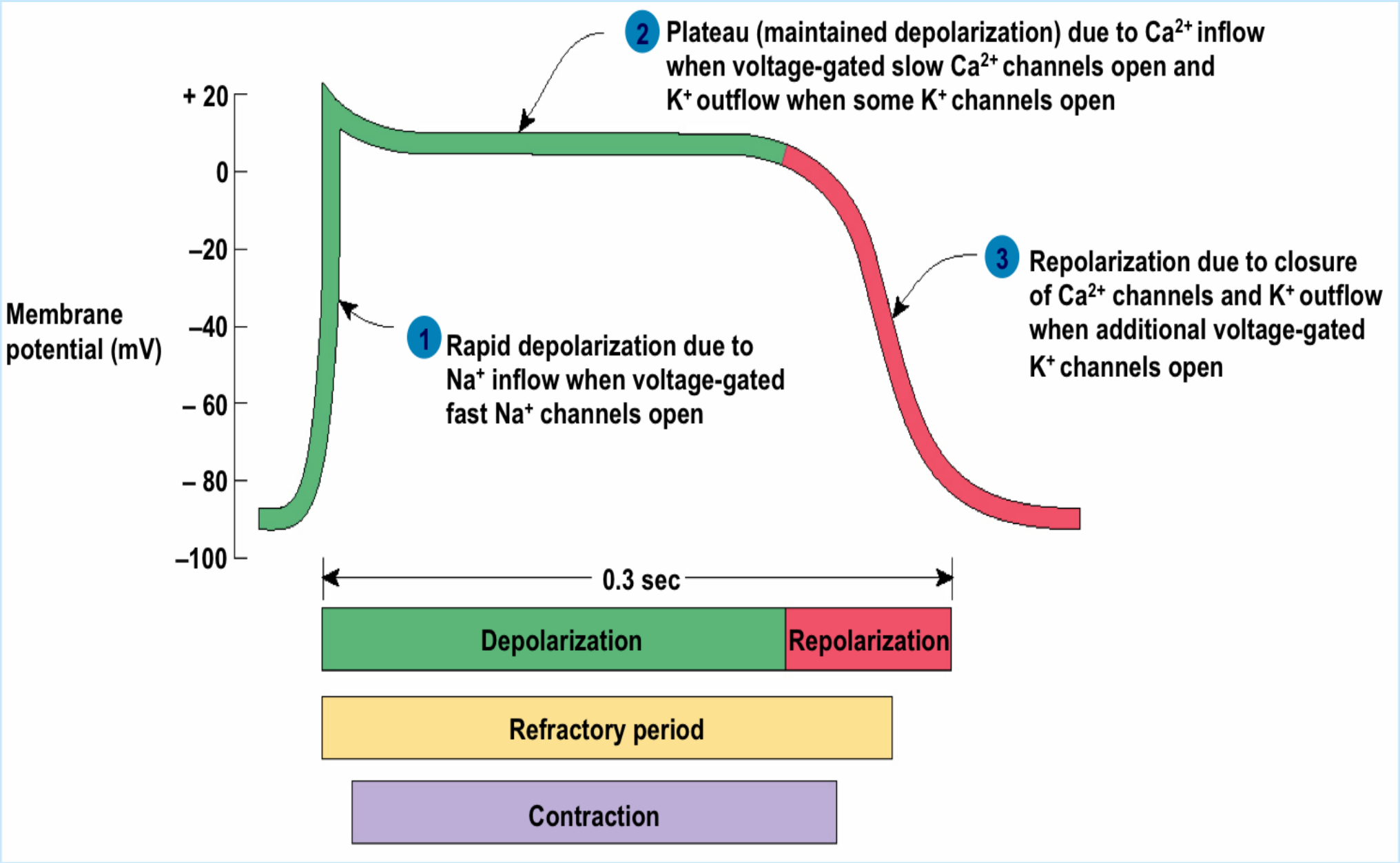



Cardiac action potential:

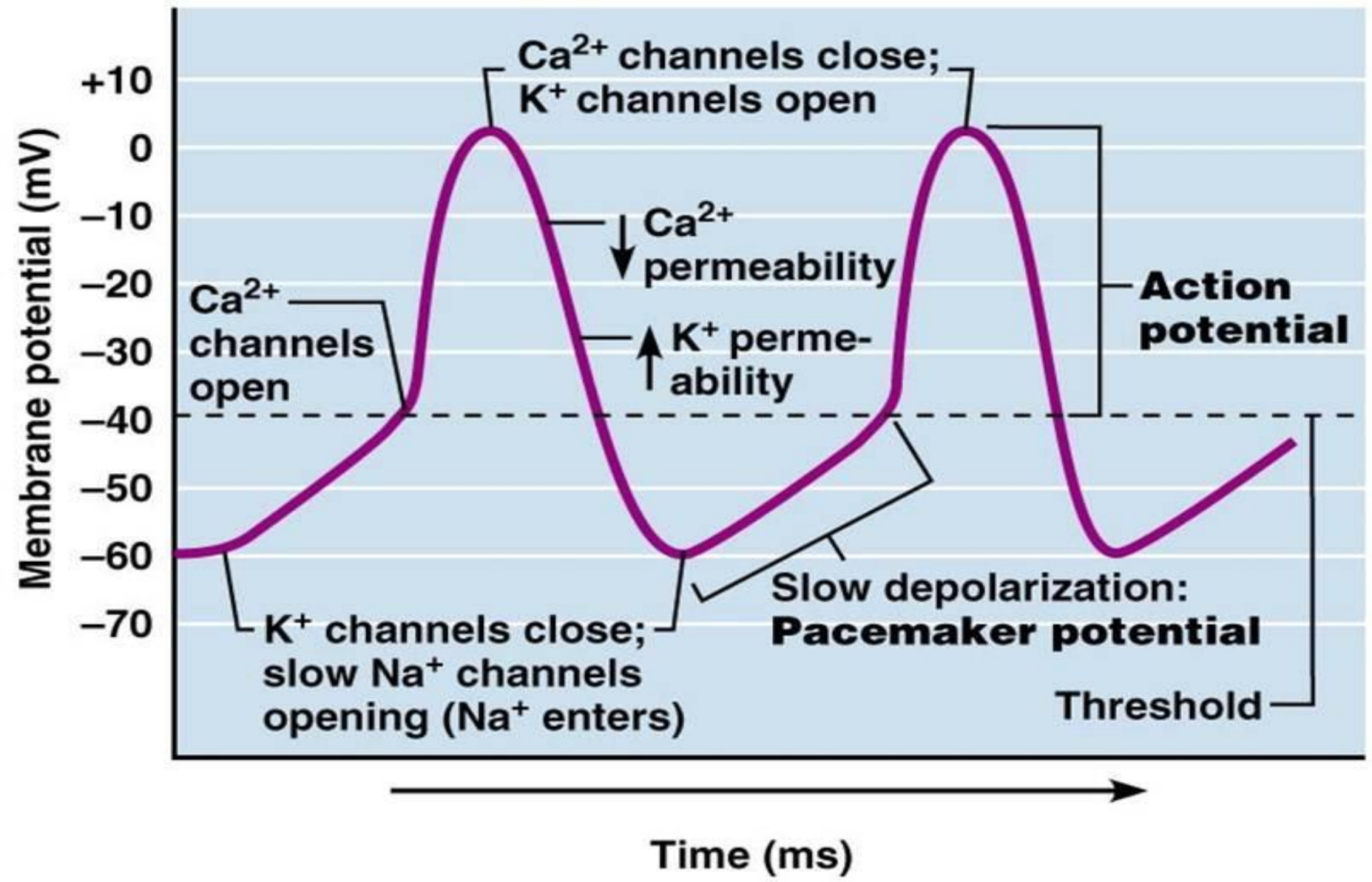



Fast-Response Action Potential
(e.g., ventricular myocyte)
ERP
mV
0
-50
-100
1
2
3
4
4
0
Ca++ in
Na+ in
K+out
K+out

# CARDIAC ACTION POTENTIAL
# Non-pacemaker (ventricular muscle)



# CARDIAC ACTION POTENTIAL
## Pacemaker (SA node)



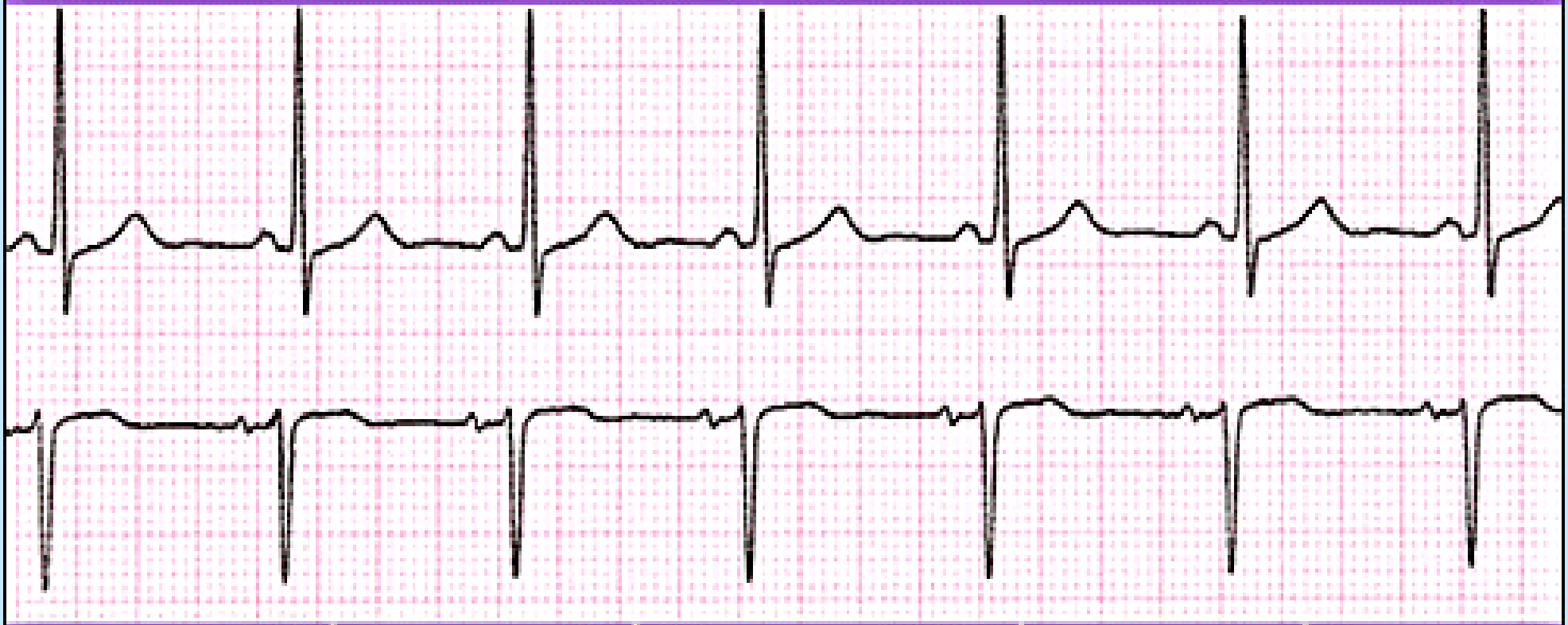
# WHAT IS ARRHYTHMIA?

**An abnormality in the :**

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

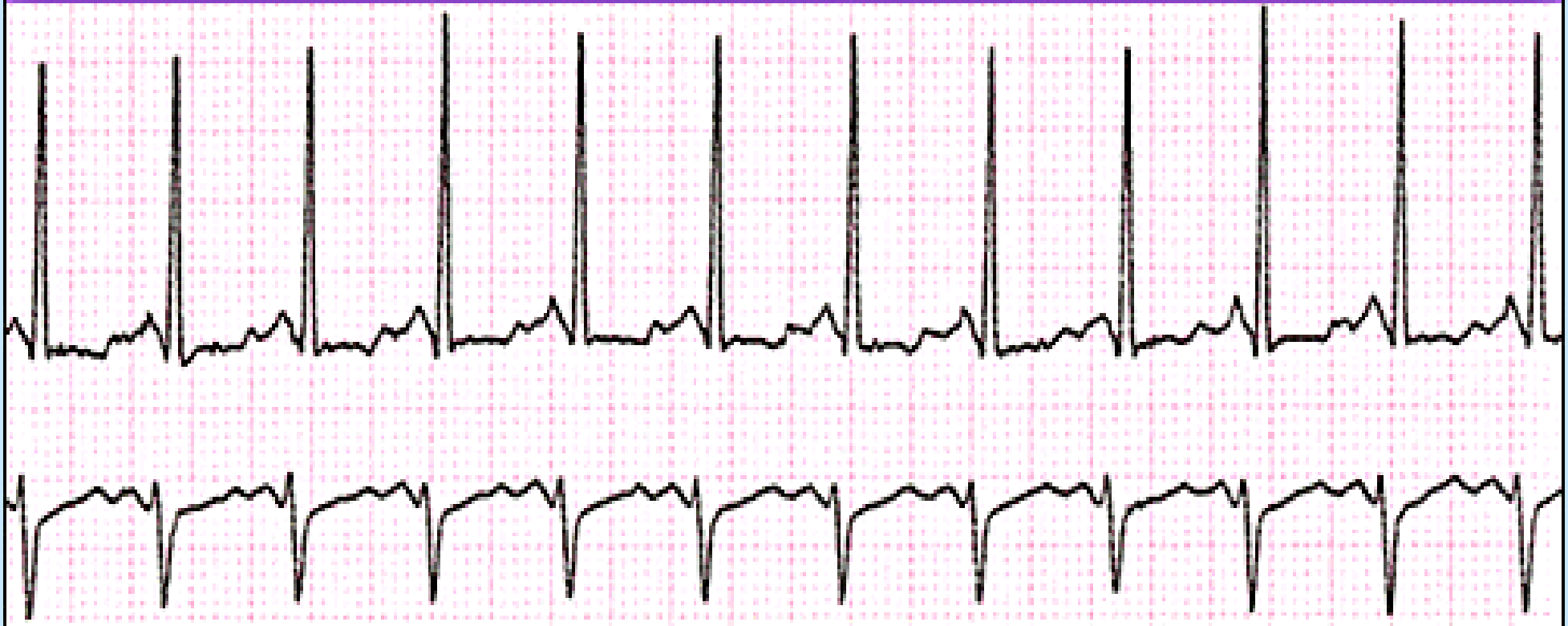
  **low = bradycardia**

# Normal Sinus Rhythm



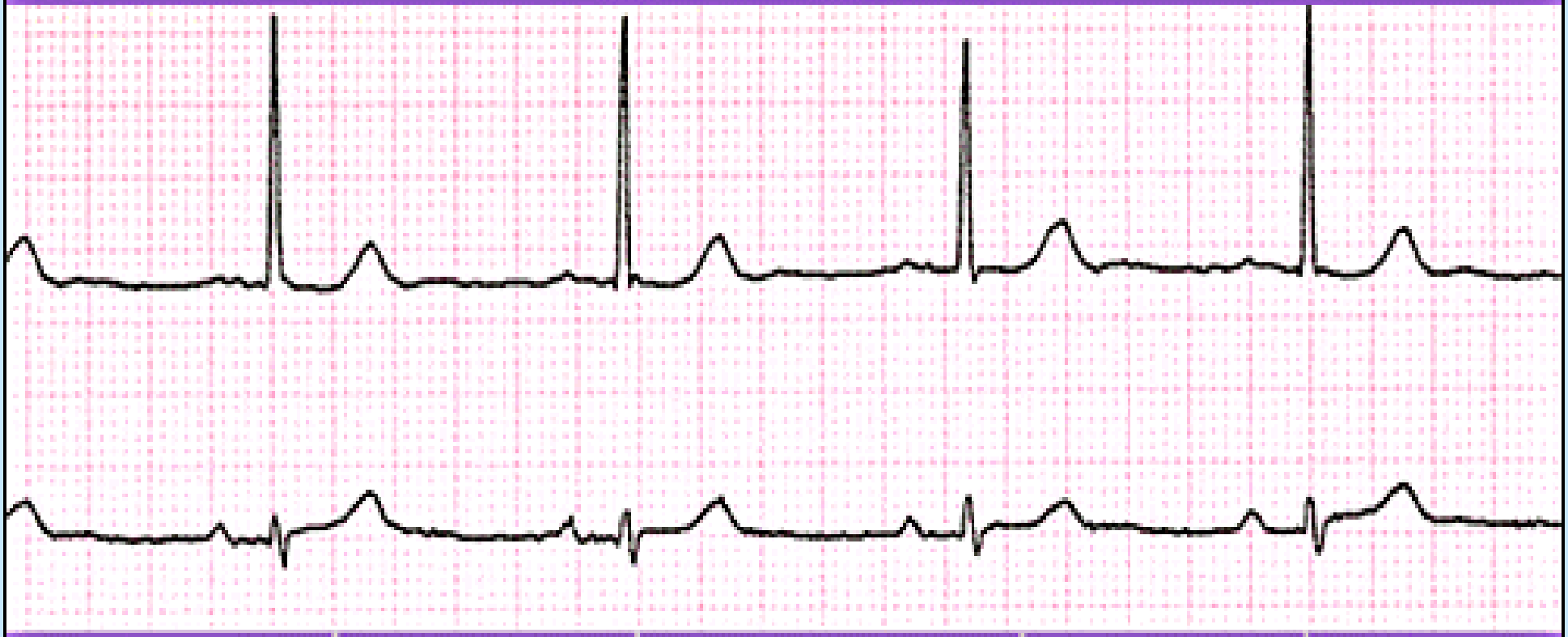
| Heart Rate | Rhythm | P Wave | PR interval (in seconds) | QRS (in seconds) |
|---|---|---|---|---|
| 60-100 bpm | Regular | Before each QRS, identical | .12 to .20 | <.12 |

# 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 |

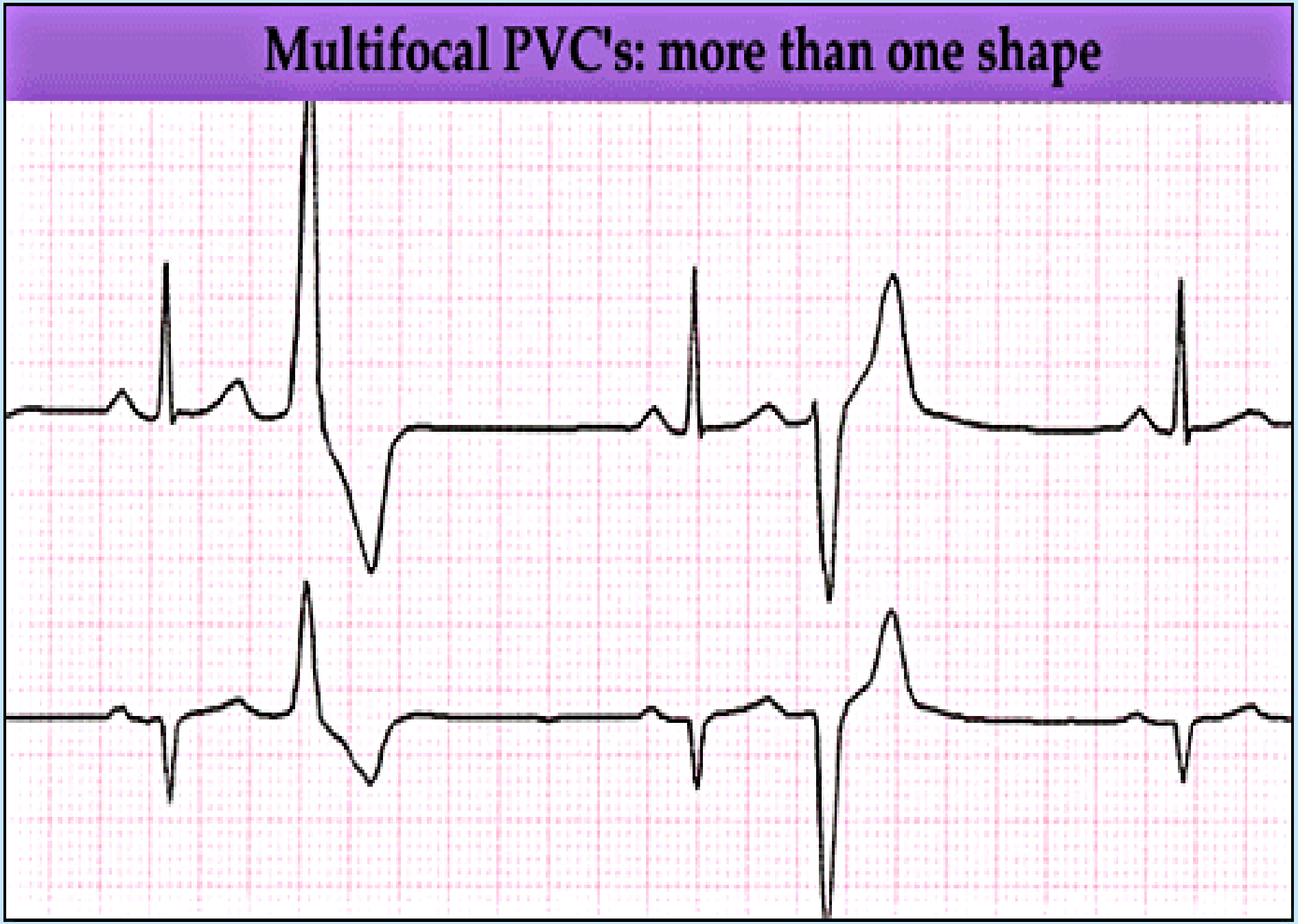
# WHAT IS ARRHYTHMIA?

**An abnormality in the :**

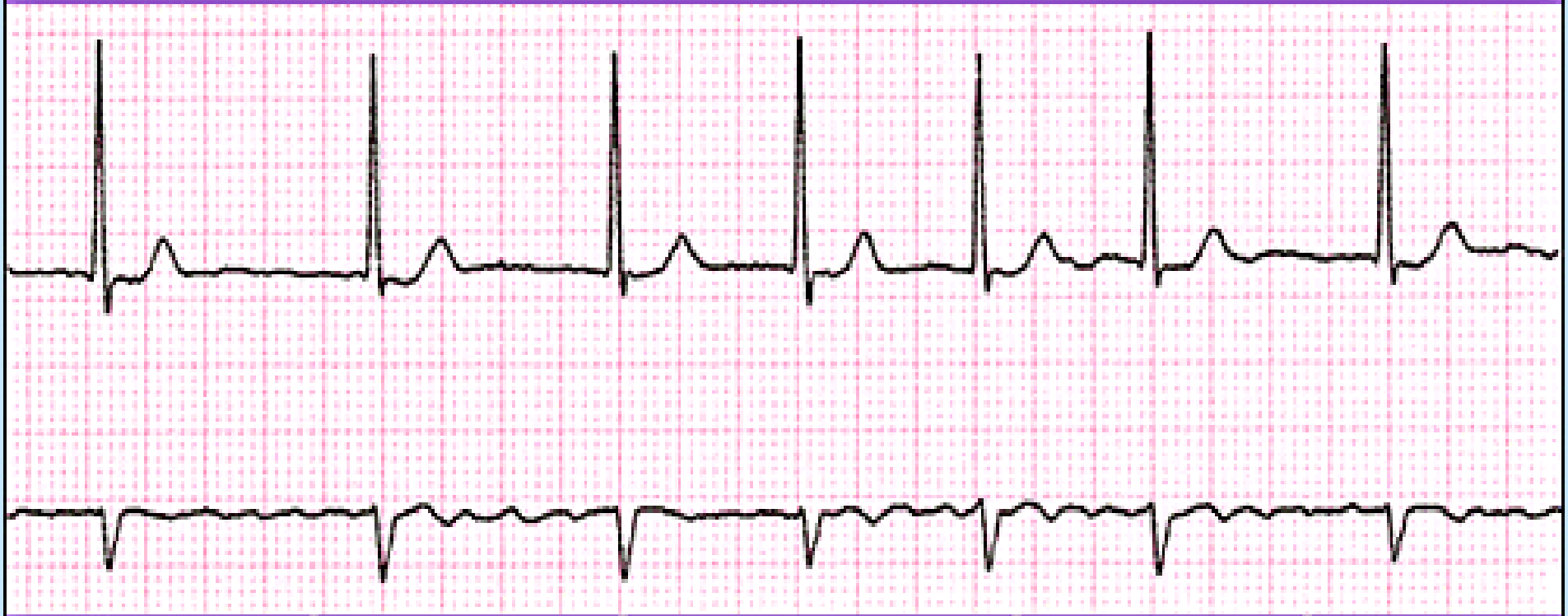
- **rate ..... high= tachycardia**
  **low = bradycardia**

- **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<br>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**

# 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**
- **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

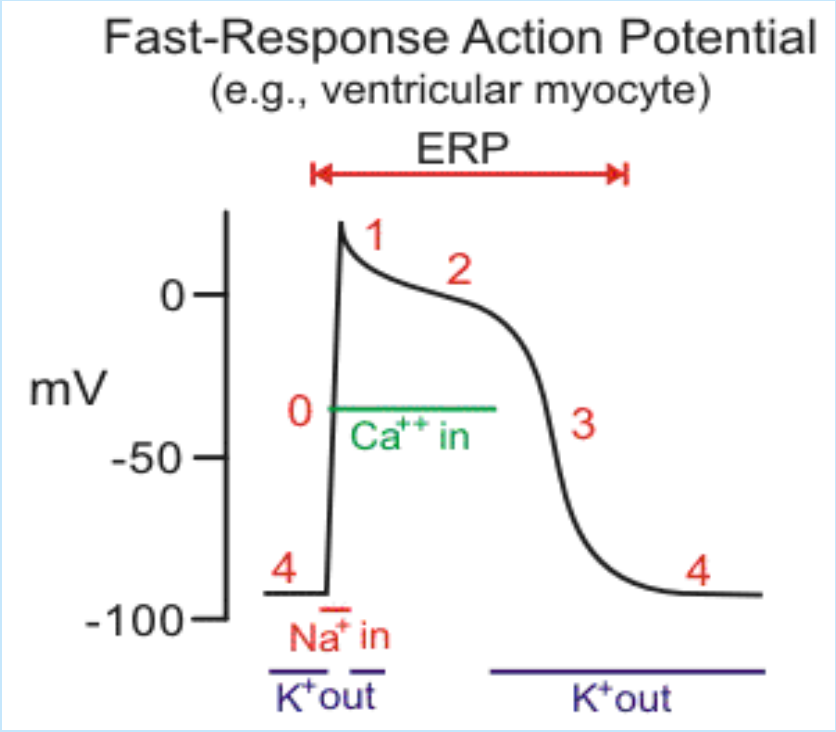
**Drugs that block the influx of Na ions through Na channels**

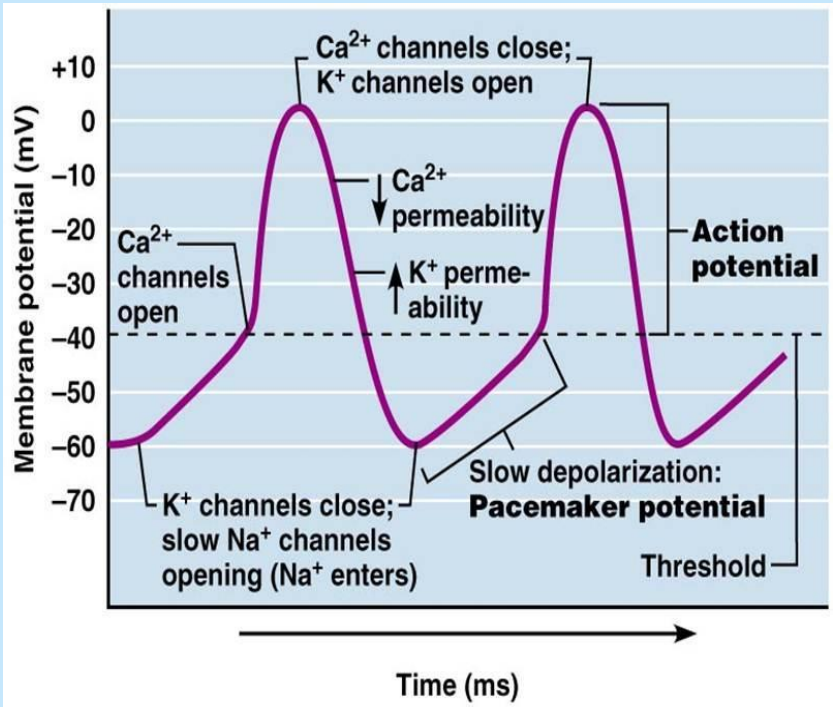
**⬇**

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

**2- decrease phase 4 slow diastolic 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**

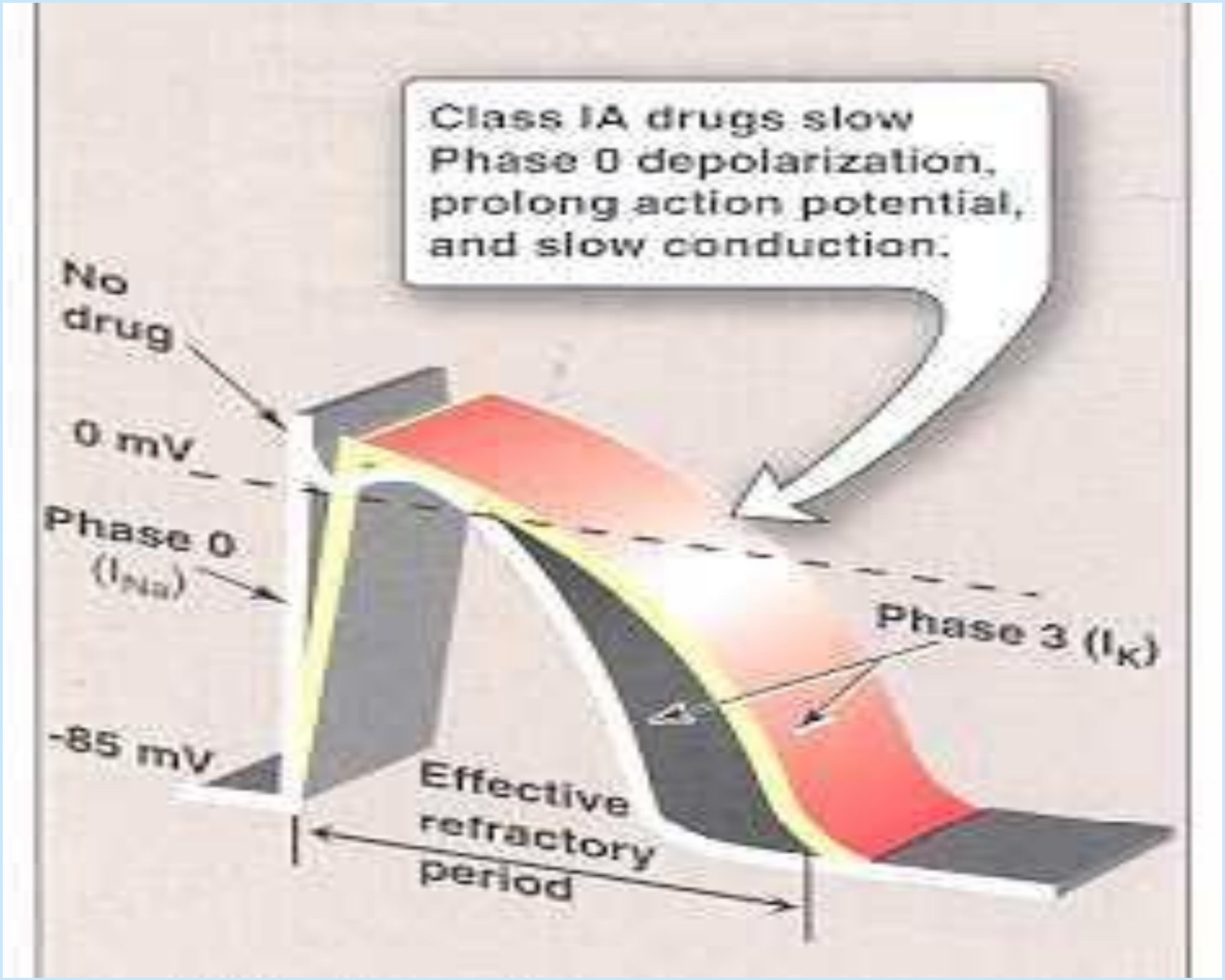
# CLASS I a

**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

## pharmacological actions :

## Cardiac (direct) :

1- Membrane stabilizing effect

2- Blocking of K channels

↓

prolongation of action potential duration

( refractory period )

3- ECG changes:

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

# CLASS I a

# QUINIDINE

## pharmacological actions :

### Actions on A.N.S. (indirect) :

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 )

# CLASS I a

## QUINIDINE

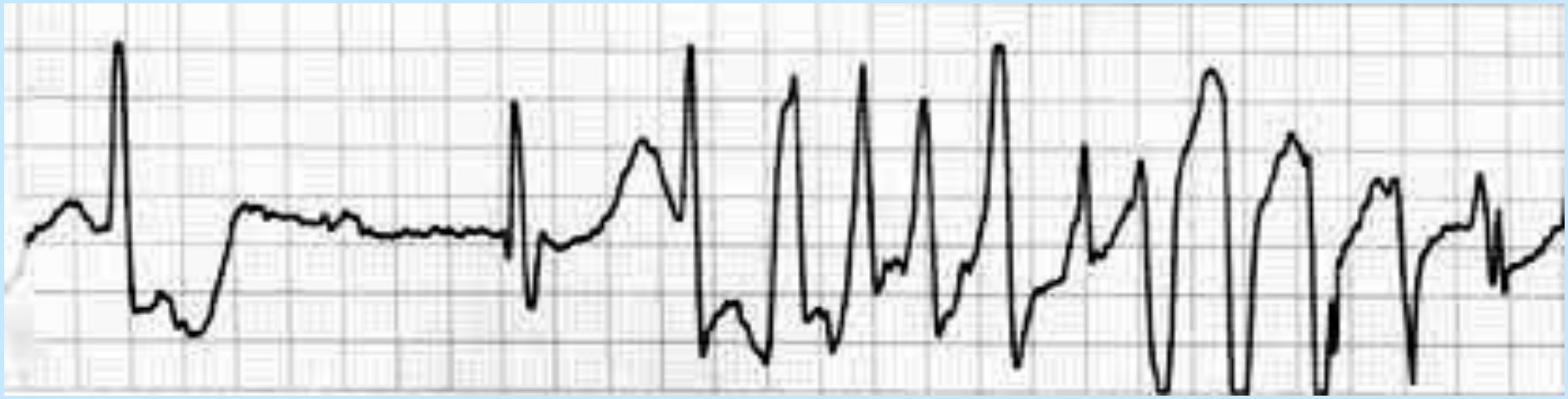
## Therapeutic uses:

- common uses: atrial flutter & fibrillation
- can be used for ventricular tachycardia
- maintaining sinus rhythm after D.C. cardio version

# CLASS Ia
# QUINIDINE

## Adverse effects :

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

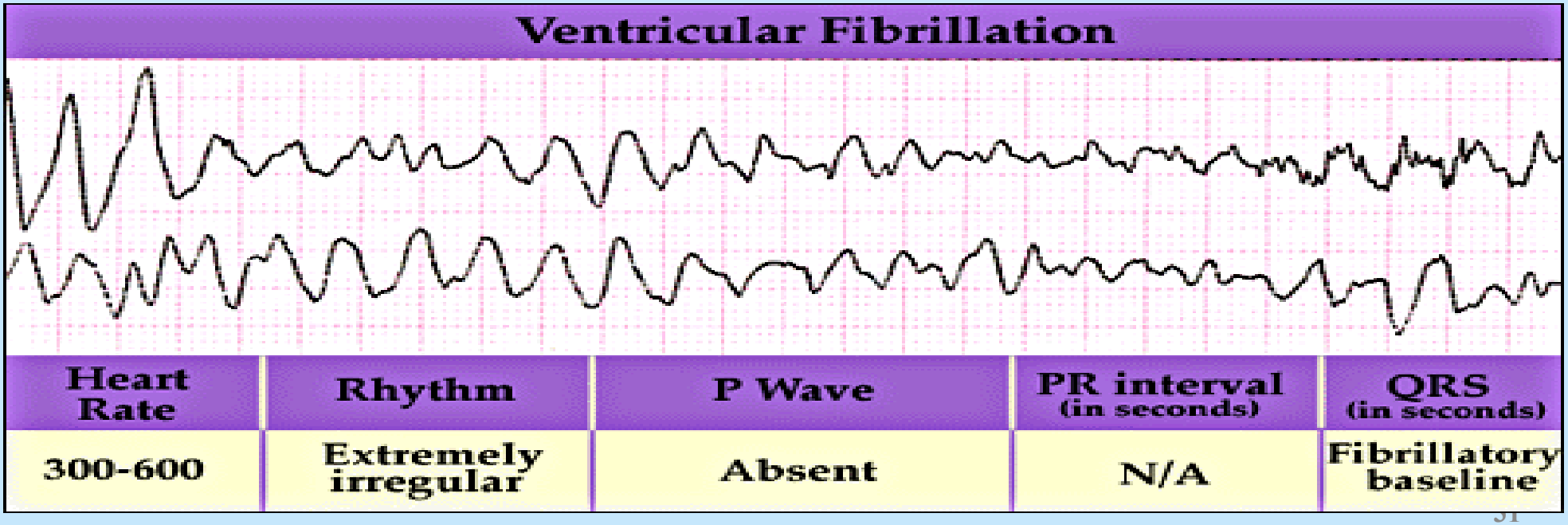


# Torsades de pointes

- 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 - No 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

- Hallucination & psychosis

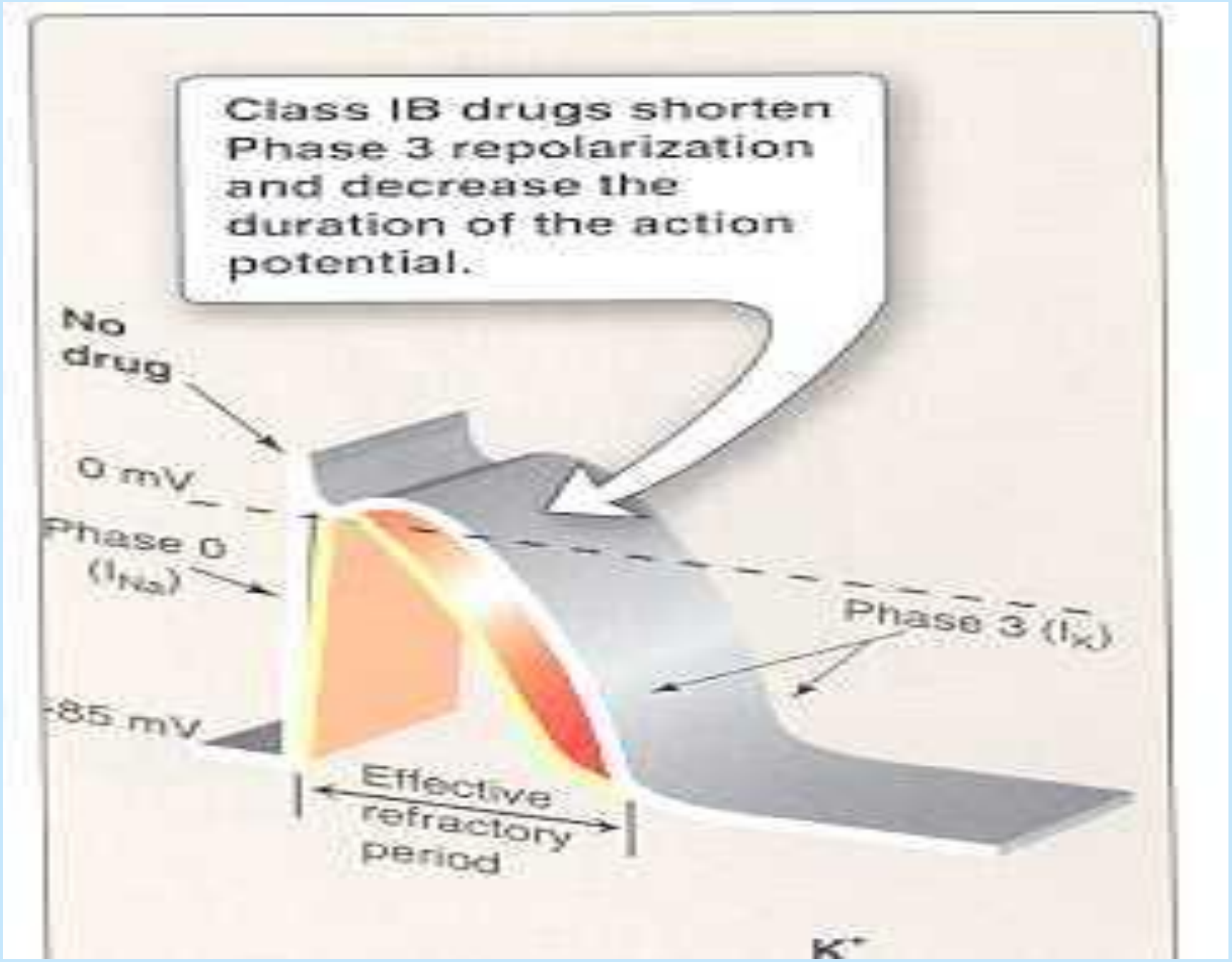
# CLASS I b

- **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)**

- **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**

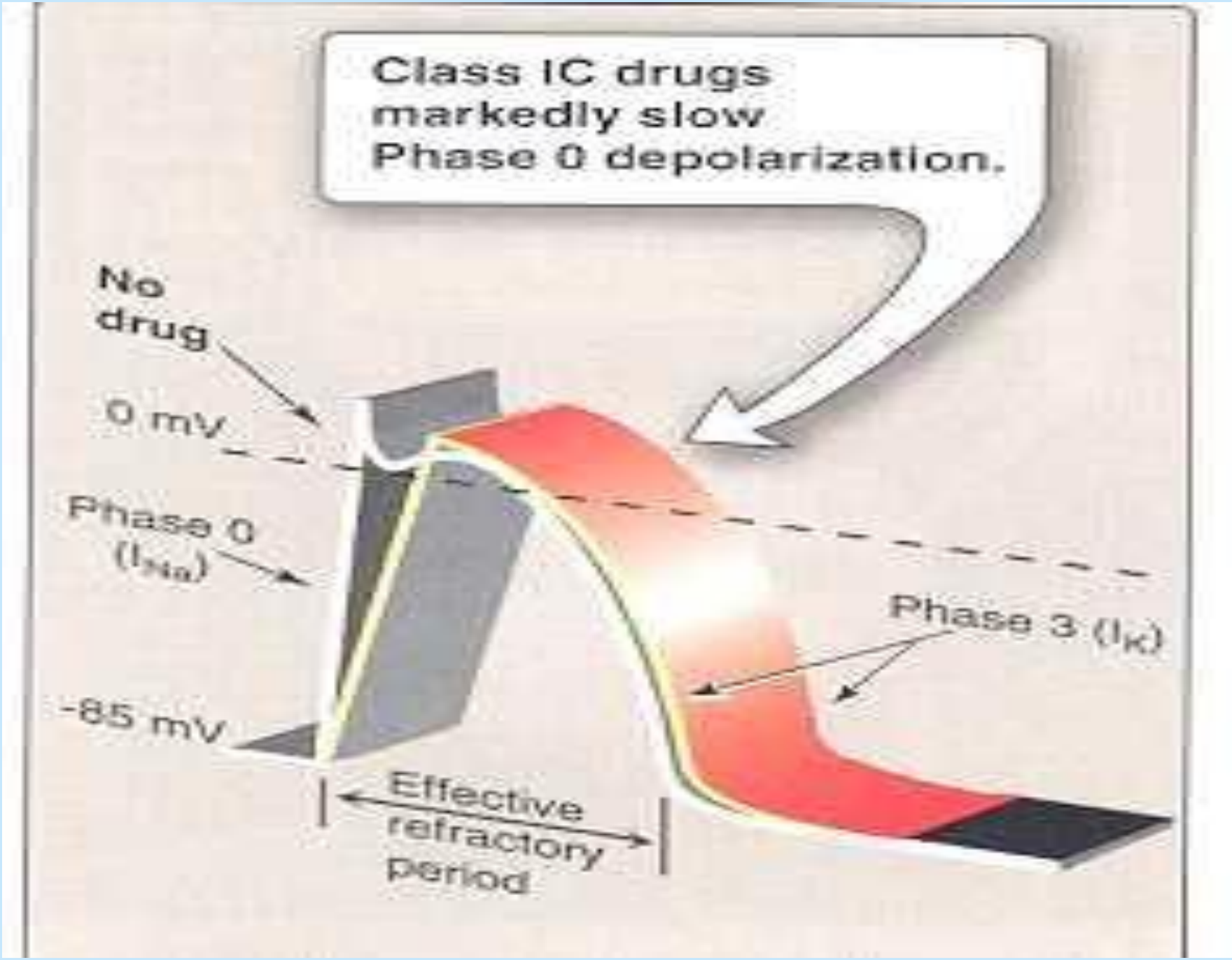
**3- arrhythmias & hypotension**

# 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**

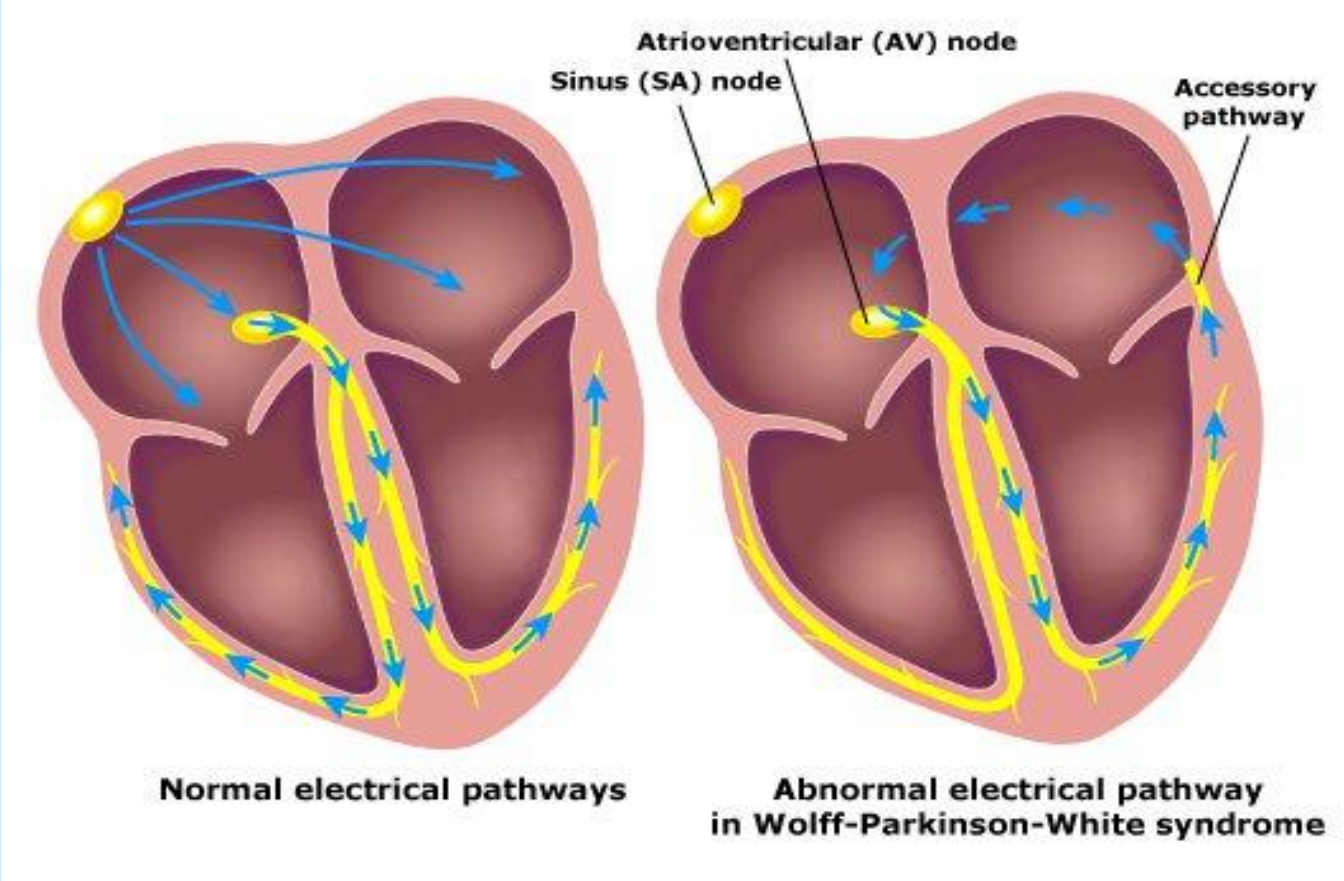
- **Wolff-Parkinson-White syndrome**

- **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 $\beta_1$- receptors in the heart**

↓

**reduce the sympathetic effect on the heart**

↓

**1 - decrease automaticity of S.A. node and ectopic pacemakers**

**2 - prolong refractory period ( 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 :

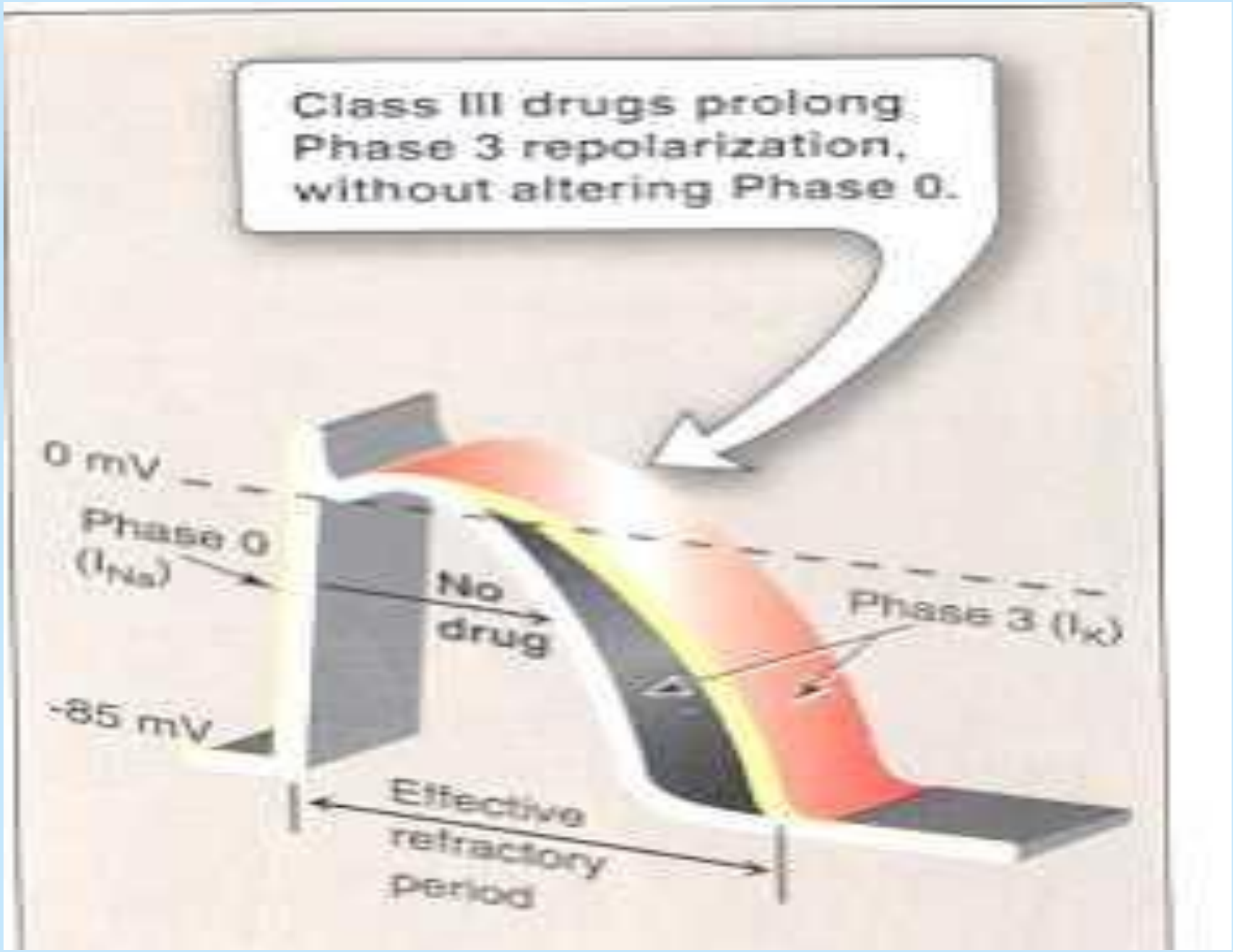
- very short acting ( half-life = 9 min. )
- given I.V. for rapid control of ventricular rate in patients with atrial flutter or fibrillation

### 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 and refractory period**
- **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 and therefore prolongs refractory period ( Main effect )
- additional class Ia, II & IV effects
- vasodilating effects

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

# CLASS III DRUGS

## AMIODARONE

### Therapeutic uses :

**1- main use : serious resistant ventricular arrhythmias**

**2- maintenance of sinus rhythm after D.C. cardio version**

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

# CLASS III DRUGS

## AMIODARONE

## Adverse effects:

- bradycardia & heart block, heart failure
- pulmonary fibrosis
- hyper- or hypothyroidism
- photodermatitis & skin deposits

( patients should avoid exposure to the sun)

- may cause bluish discoloration of the skin

# CLASS III DRUGS

## AMIODARONE

**Adverse effects:**

- **CNS: tremor, headache, ataxia, paresthesia**
- **constipation**
- **corneal micro deposits**
- **hepatocellular necrosis**
- **peripheral neuropathy**

# CLASS III DRUGS

## AMIODARONE

**Pharmacokinetics:**

- extremely long $t_{1/2}$ = 13 - 103 DAYS
- metabolized to its major active metabolite N-desethylamiodarone by cytochrome P450 3A4 and CYP2C8
- eliminated primarily by hepatic metabolism
- cross placenta and appear in breast milk

# CLASS III DRUGS

## AMIODARONE

### Drug Interactions:

1 - As amiodarone is metabolized by CYP3A4 & CYP2C8, drugs (or substances) that inhibit these enzymes

↓

increase serum concentration of amiodarone

e.g. : Loratadine

Ritonavir

Trazodone

Cimetidine

Grapefruit juice

# CLASS III DRUGS

## AMIODARONE

**Drug Interactions:**

**2 - drugs that are inducers of these enzymes**

**↓**

**decrease serum concentration of amiodarone**

**e.g. : Rifampin**

**3 - Reduces clearance of several drugs e.g.**

**quinidine, warfarin, procaiamide, flecainide**

# 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 effective refractory period**

# Class 1V
# calcium channel blockers

## Therapeutic uses :

**1- atrial arrhythmias**

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

**3- NOT effective in ventricular arrhythmias**

# CLASS V
# MISCELLENIOUS ANTIARRHYTHMIC DRUGS

- **ADENOSINE**
- **DIGITALIS**

# ADENOSINE

- endogenous nucleoside

## Mechanism of action :

- inhibits cAMP by binding to adenosine A1 receptors causing the following actions:

1 - Opening of potassium channels (hyperpolarization)

# ADENOSINE

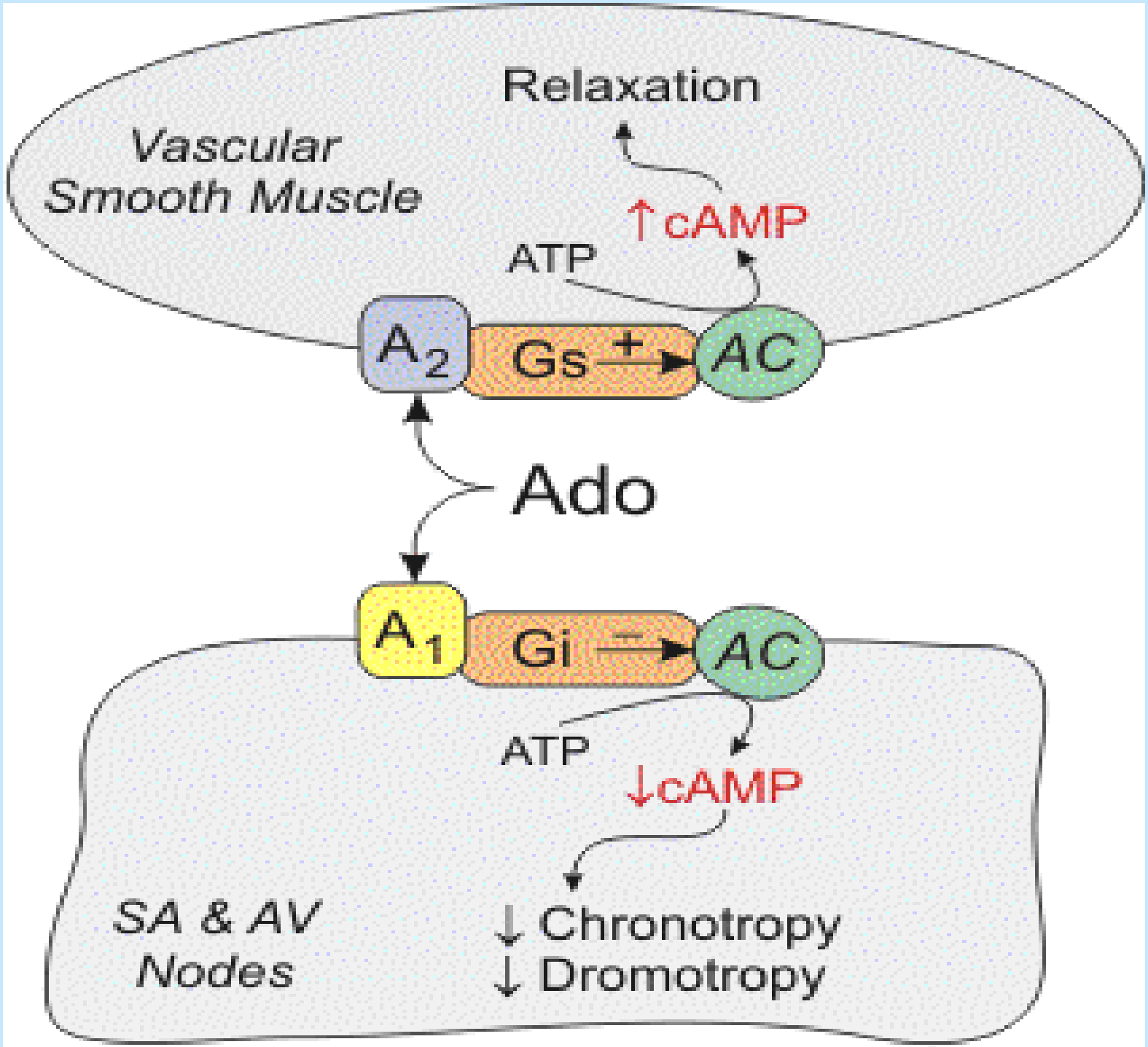
**Mechanism of action :**

**2 - decreasing conduction velocity mainly at AVN**

**( negative dromotropic effect )**

**3- inhibiting phase 4 pacemaker action potential ( SAN )**

**( 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 :

- **half-life = less than 10 sec.**

- **drug of choice for acute management of paroxysmal supraventricular tachycardia**

- **preferred over verapamil – safer and does not depress contractility**

# ADENOSINE

## Adverse effects:

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

# BRADYARRHYTHMIAS

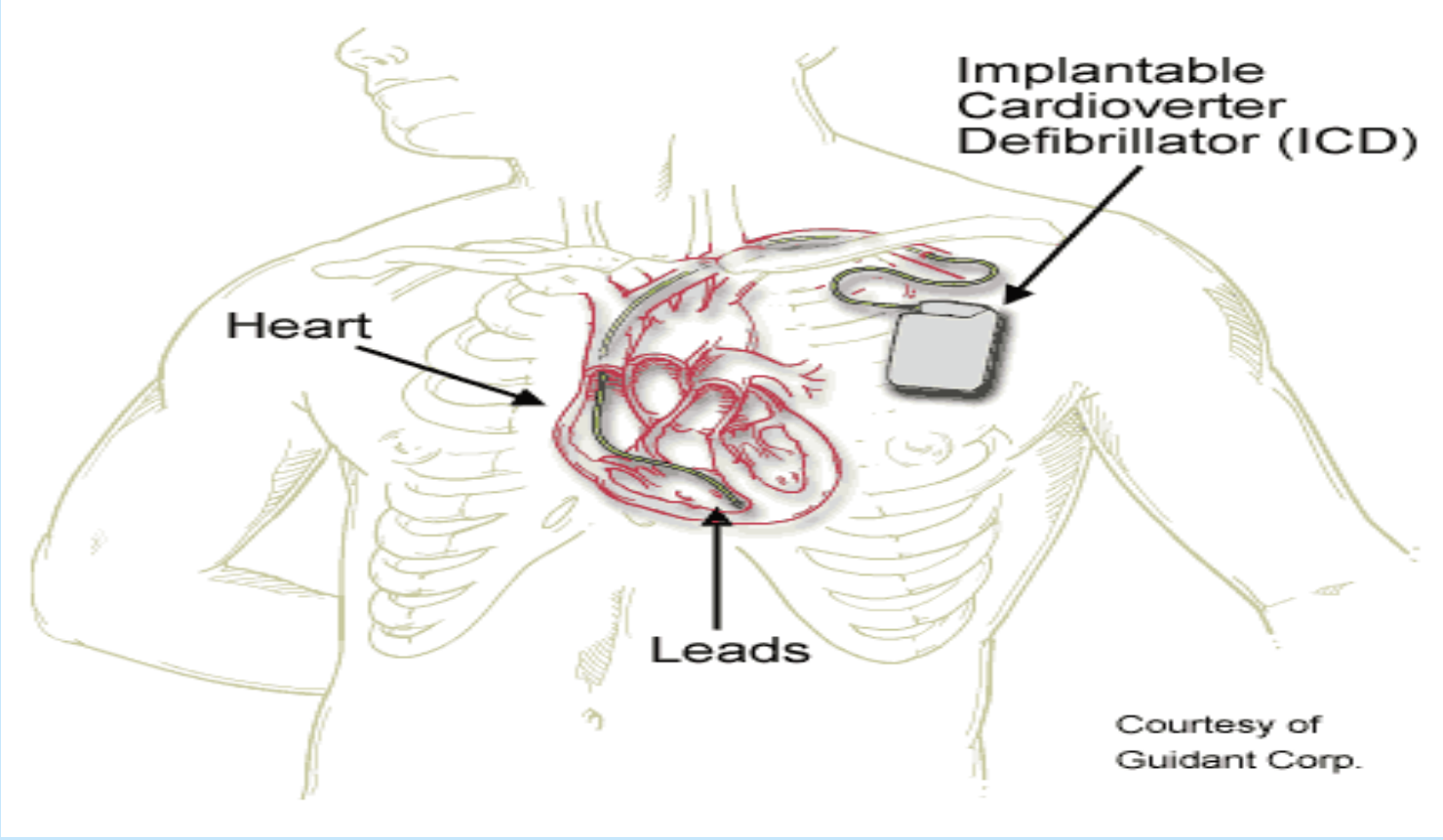
## ATROPINE

- used in sinus bradycardia after myocardial infarction and 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 and treat fatal arrhythmias such as ventricular fibrillation




Thank you