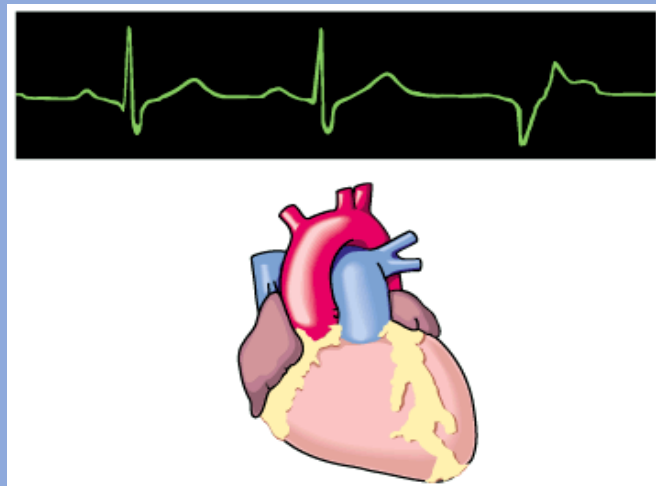


# Cardiovascular Pharmacology

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

# Antiarrhythmic Drugs

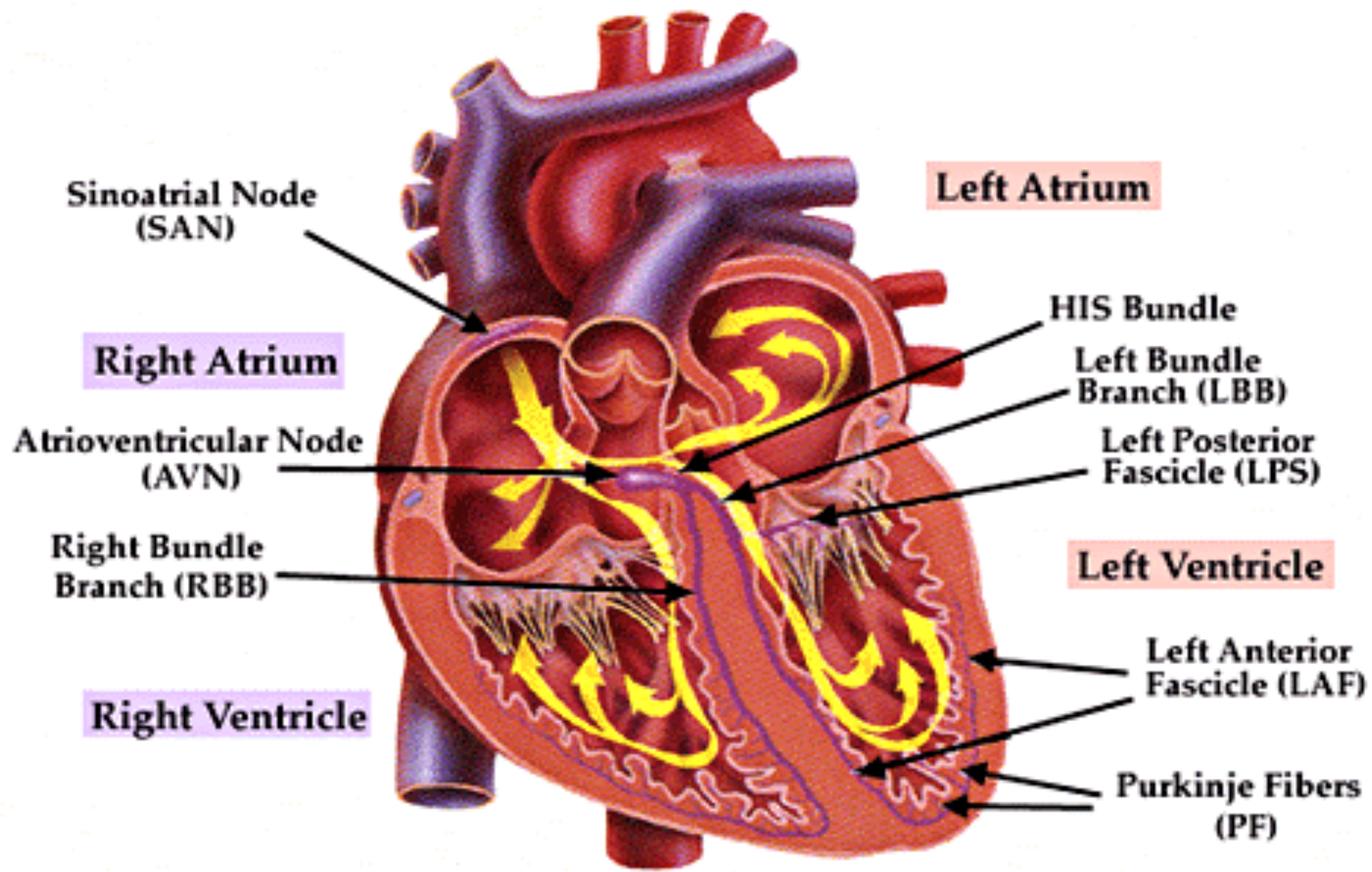
Dr. Aliah Alshanwani



# 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.

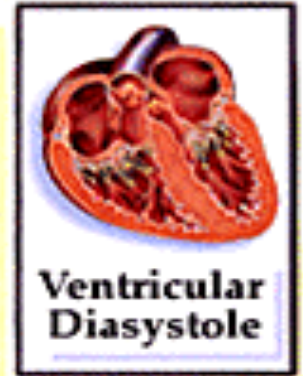
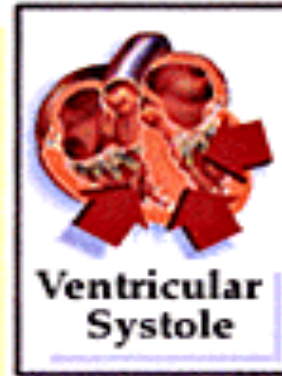
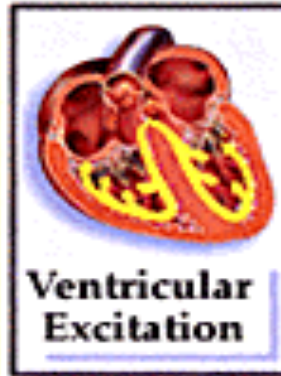
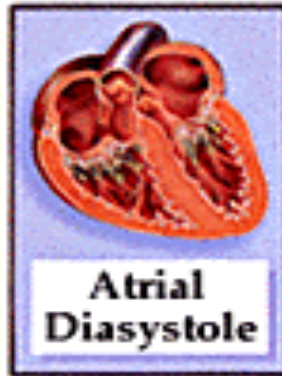
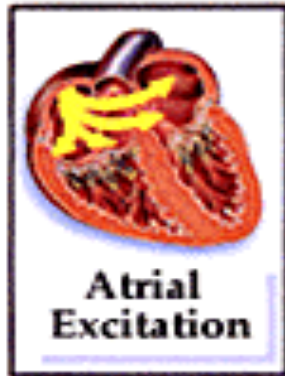
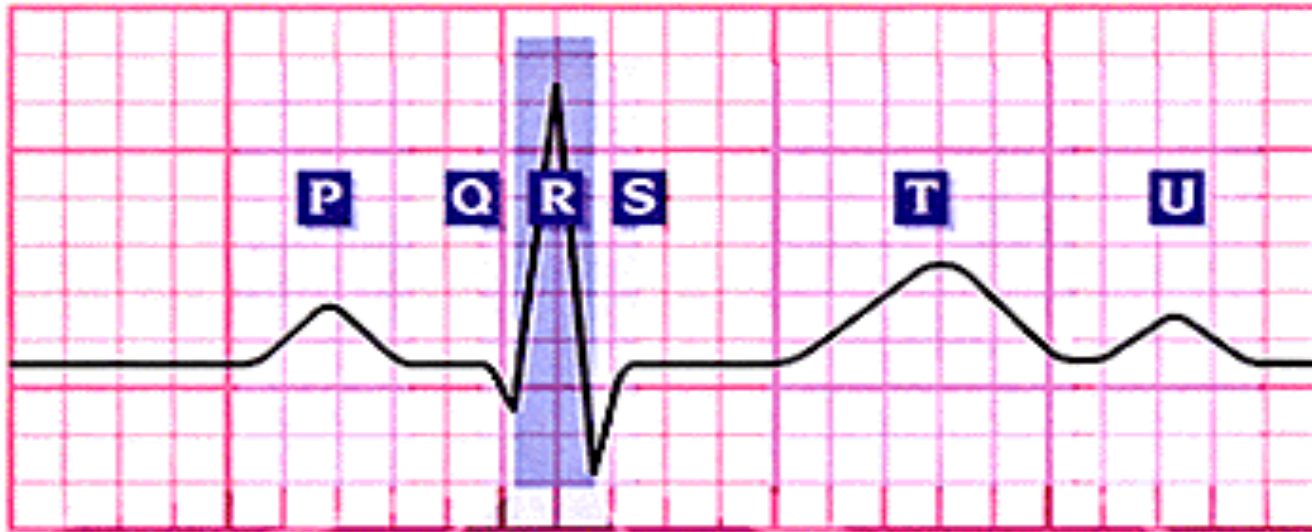


## Cardiac Conduction System

# CARDIAC CONDUCTION SYSTEM

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

# Electrocardiogram (ECG)

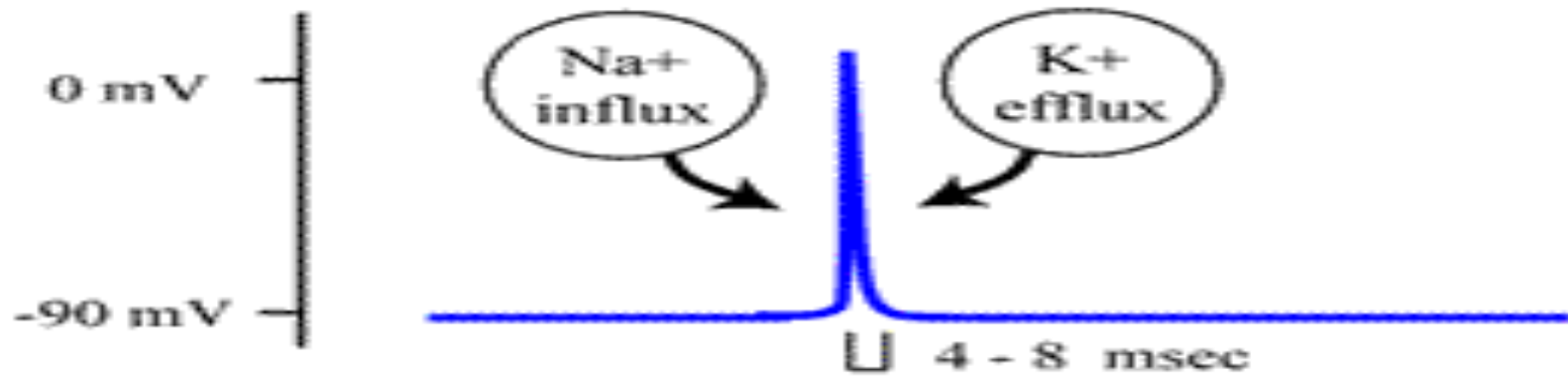


**Electrical and Mechanical Events**

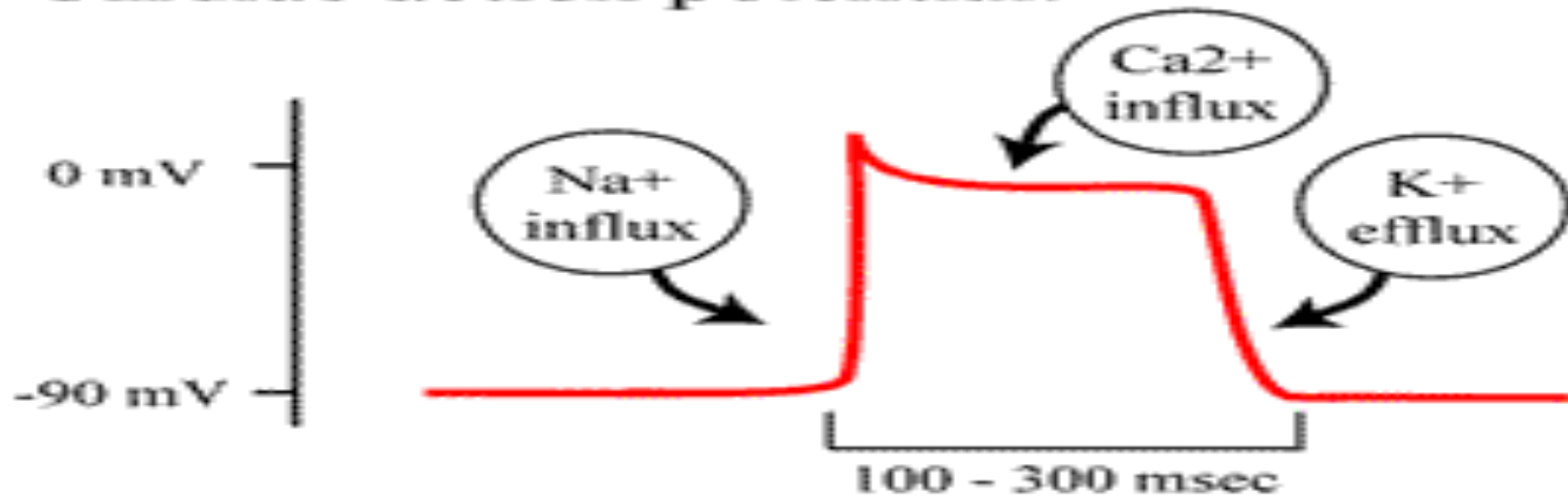


# CARDIAC ACTION POTENTIAL

## Skeletal action potential:

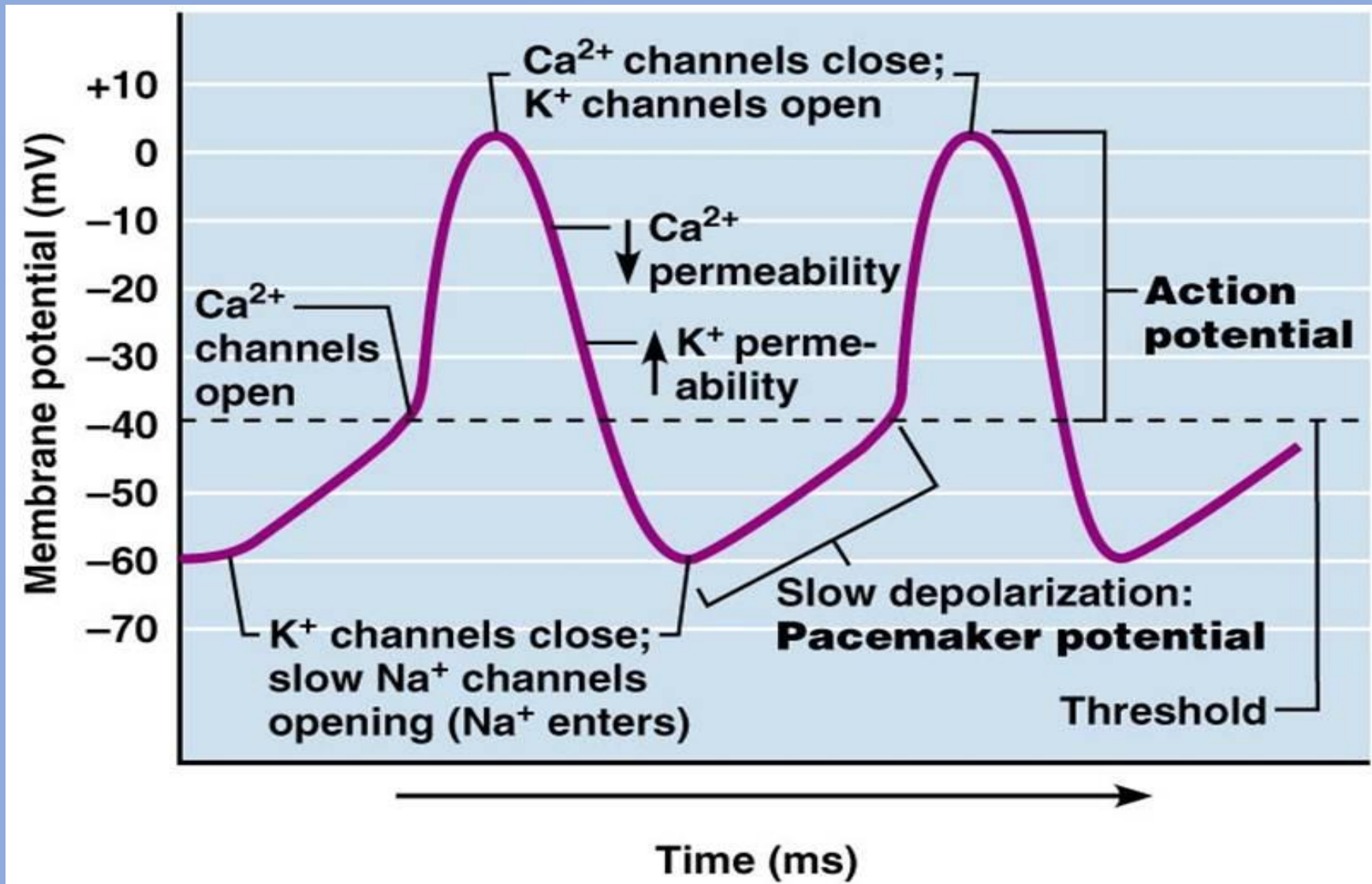


## Cardiac action potential:



# CARDIAC ACTION POTENTIAL

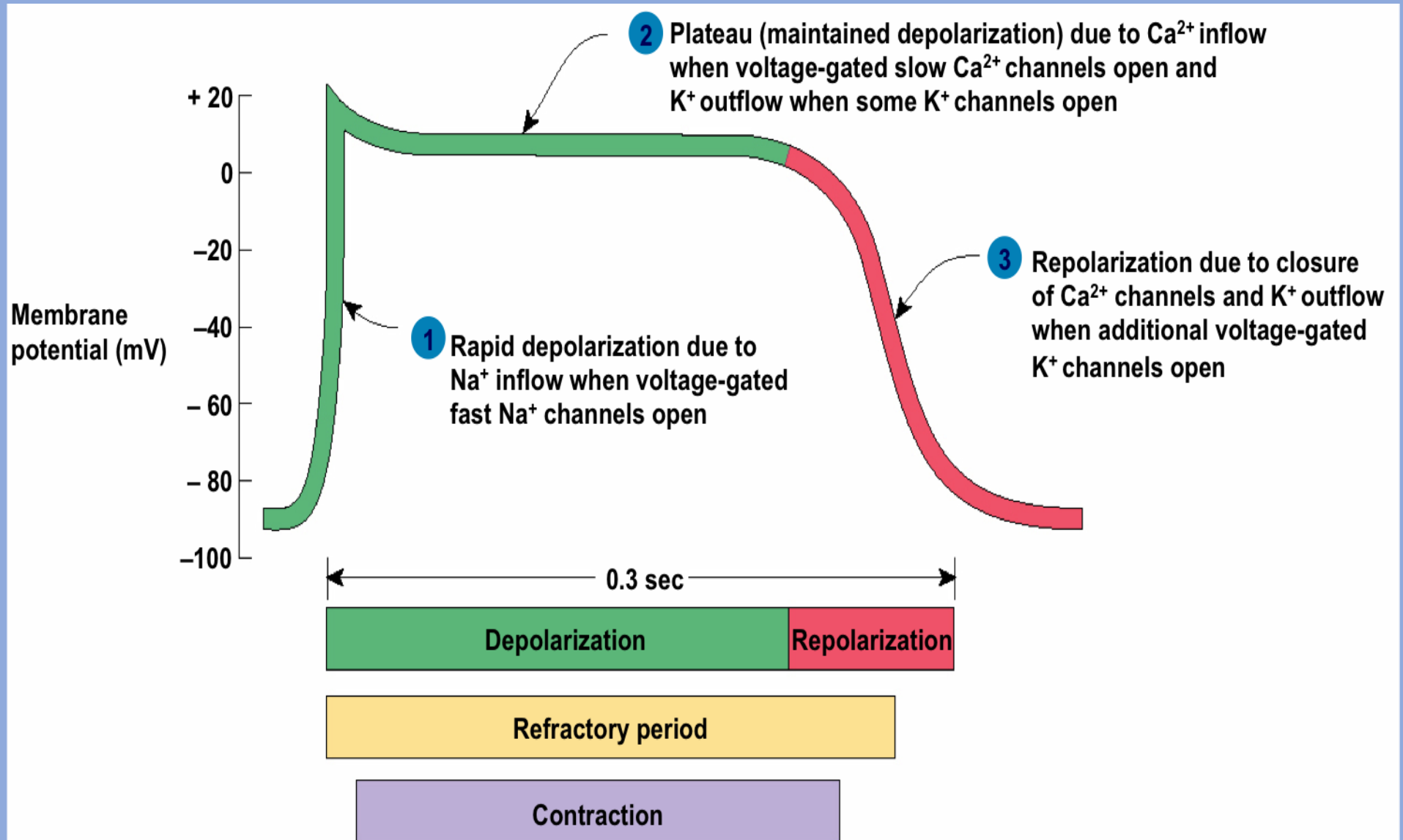
## Pacemaker (SA node)



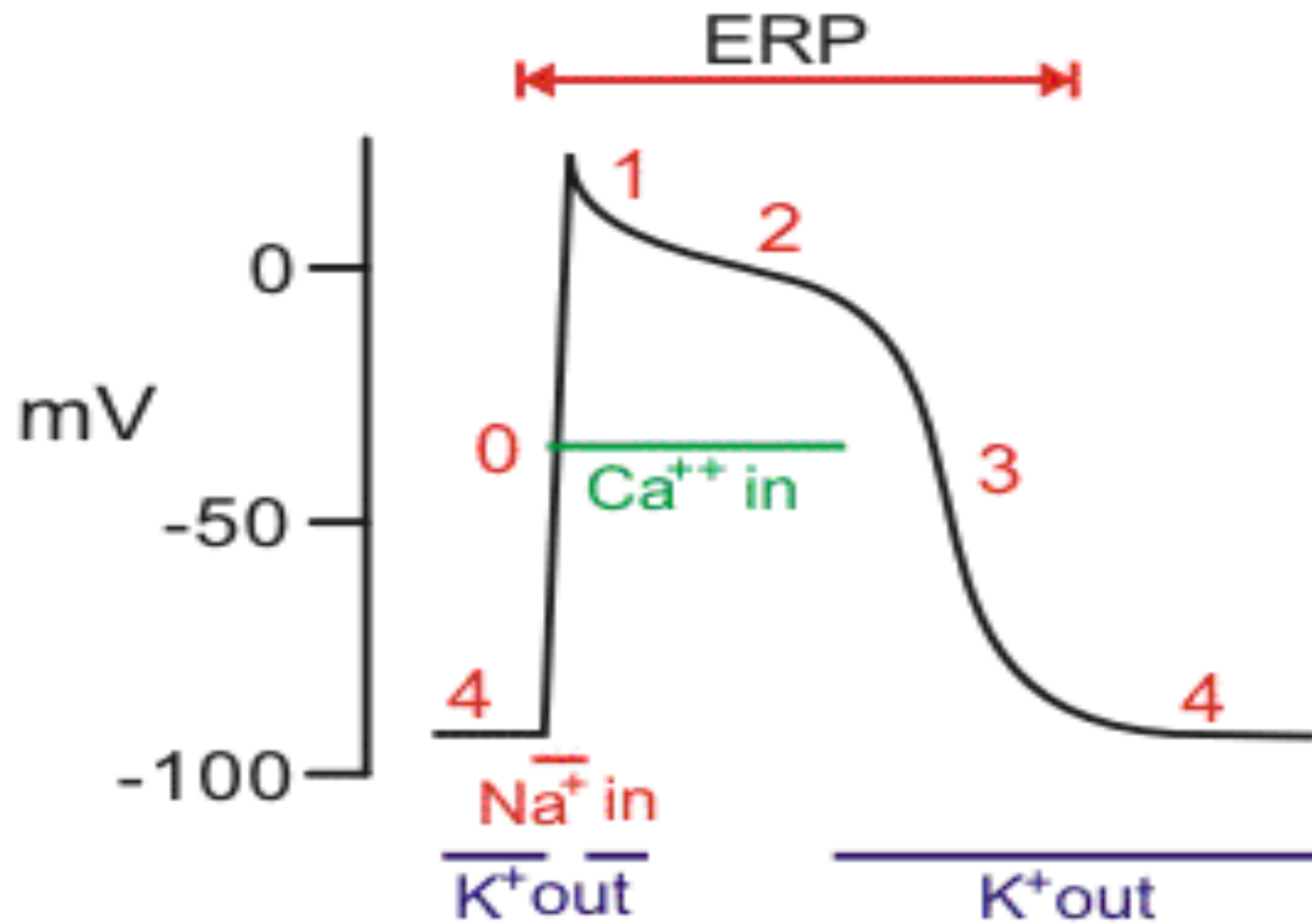


# CARDIAC ACTION POTENTIAL

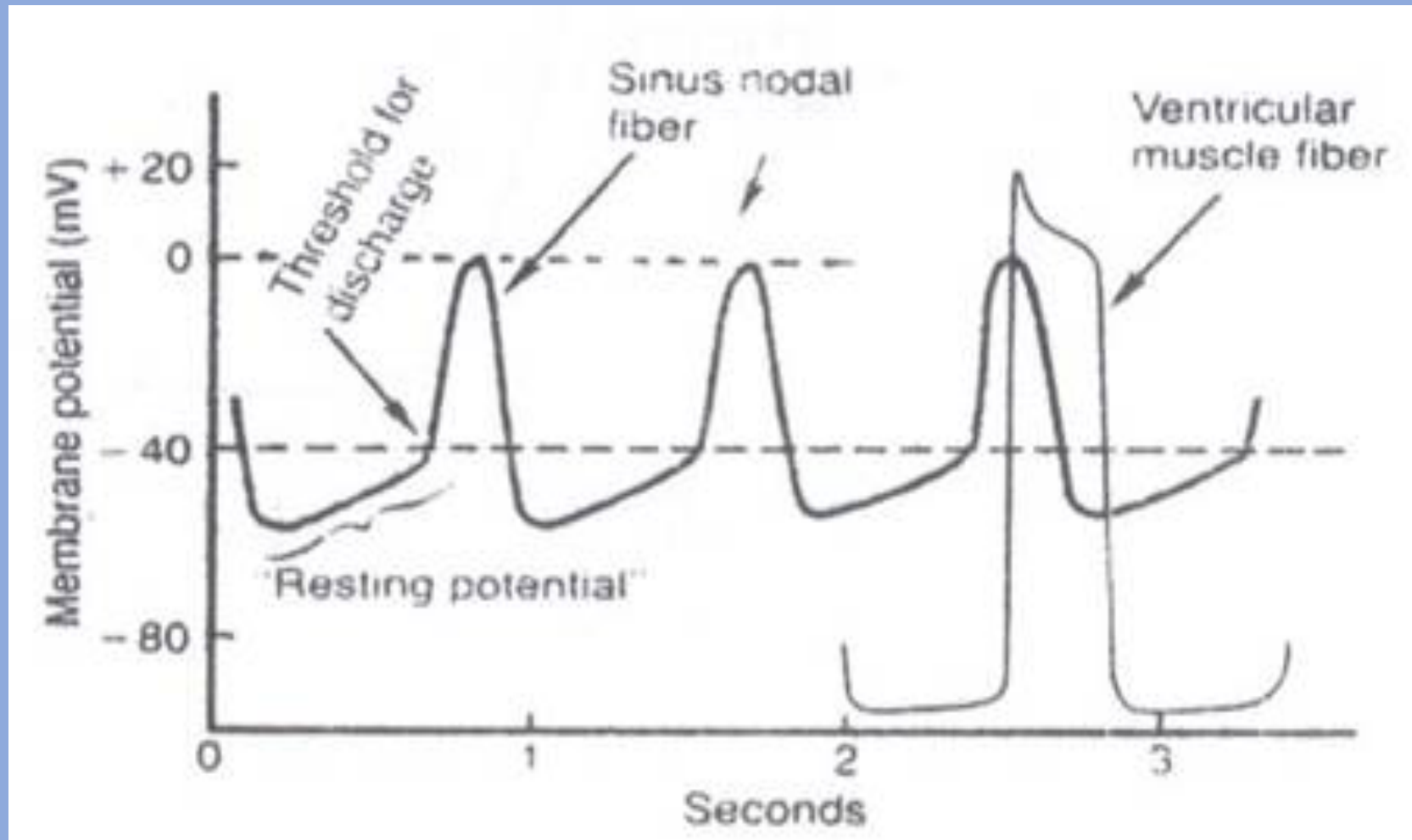
## Non-pacemaker (ventricular muscle)



# Fast-Response Action Potential (e.g., ventricular myocyte)



## Difference between pacemaker and non-pacemaker action potential

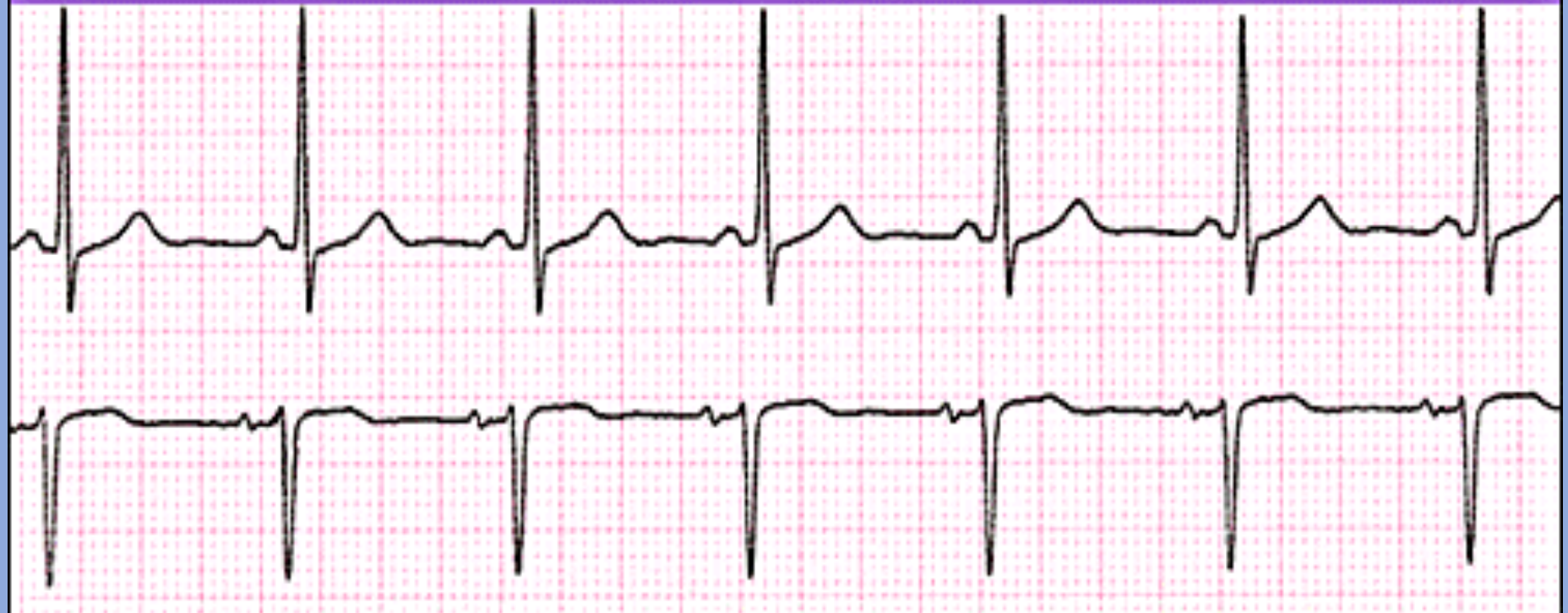


## WHAT IS ARRHYTHMIA?

An **abnormality** in the :

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

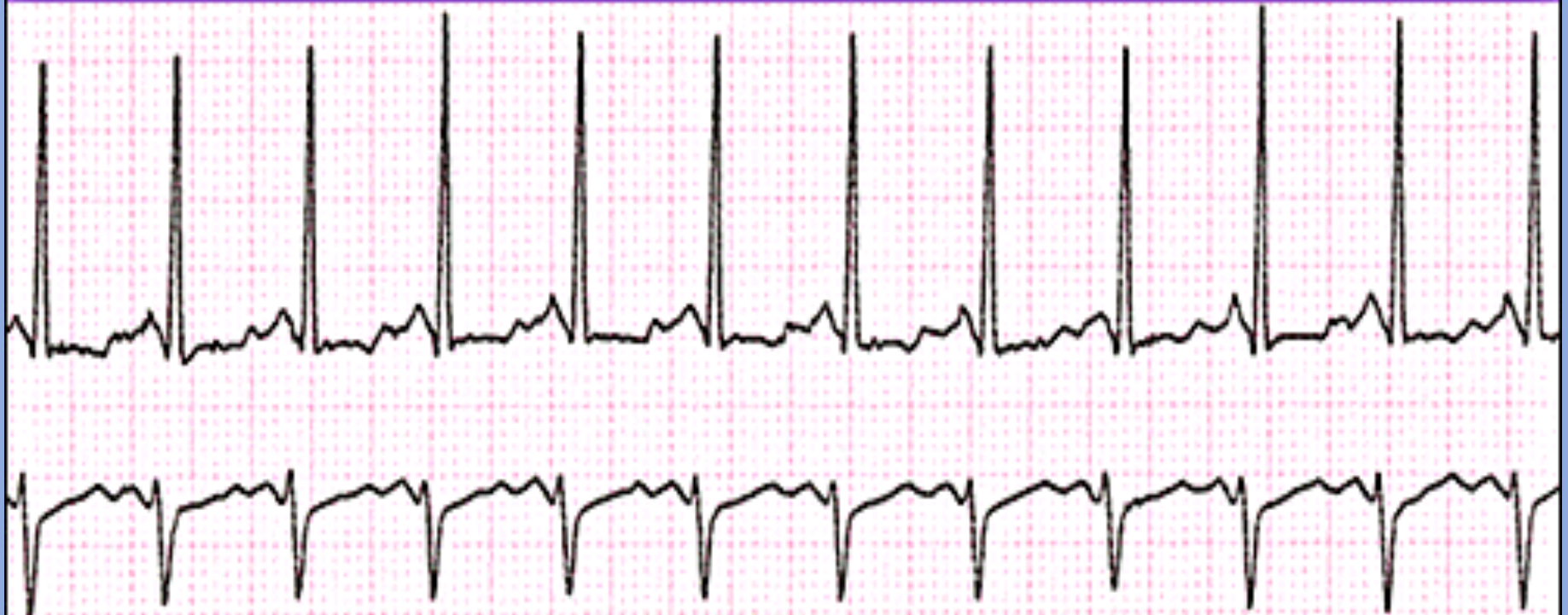
## Normal Sinus Rhythm



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



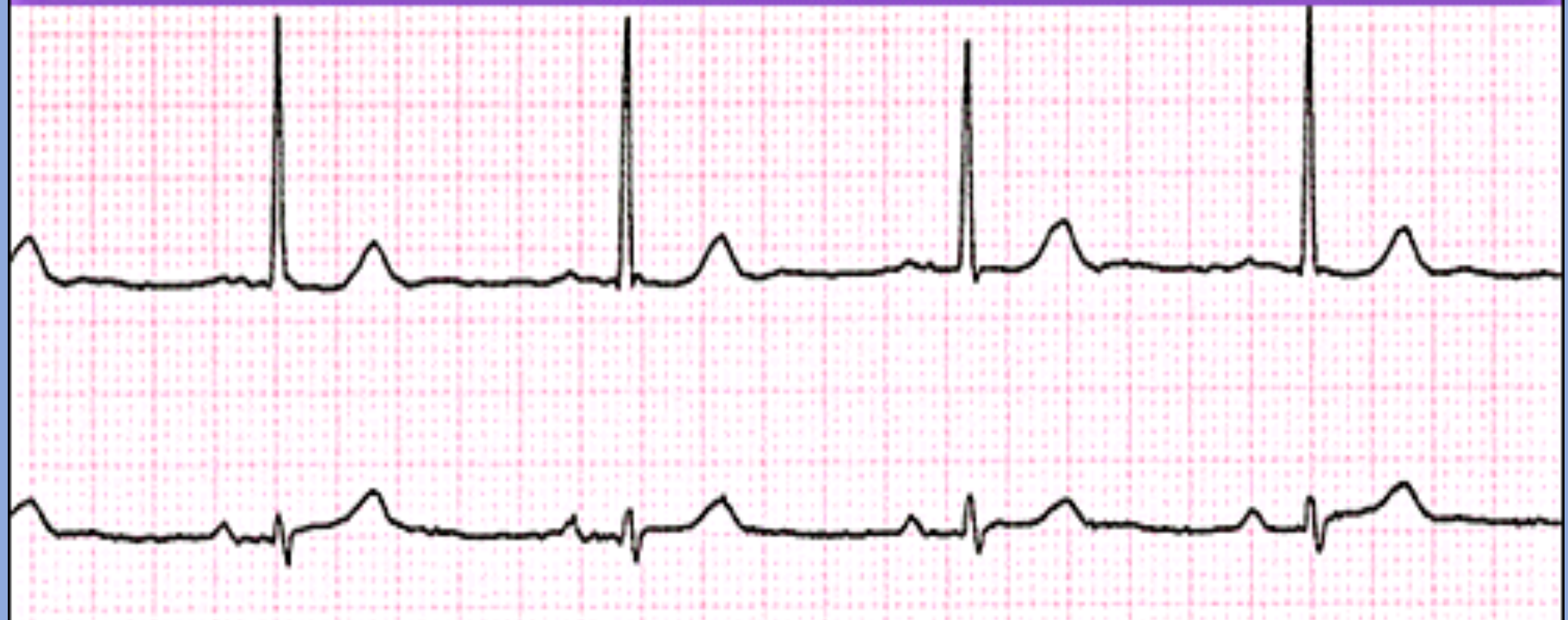
## Sinus Tachycardia



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



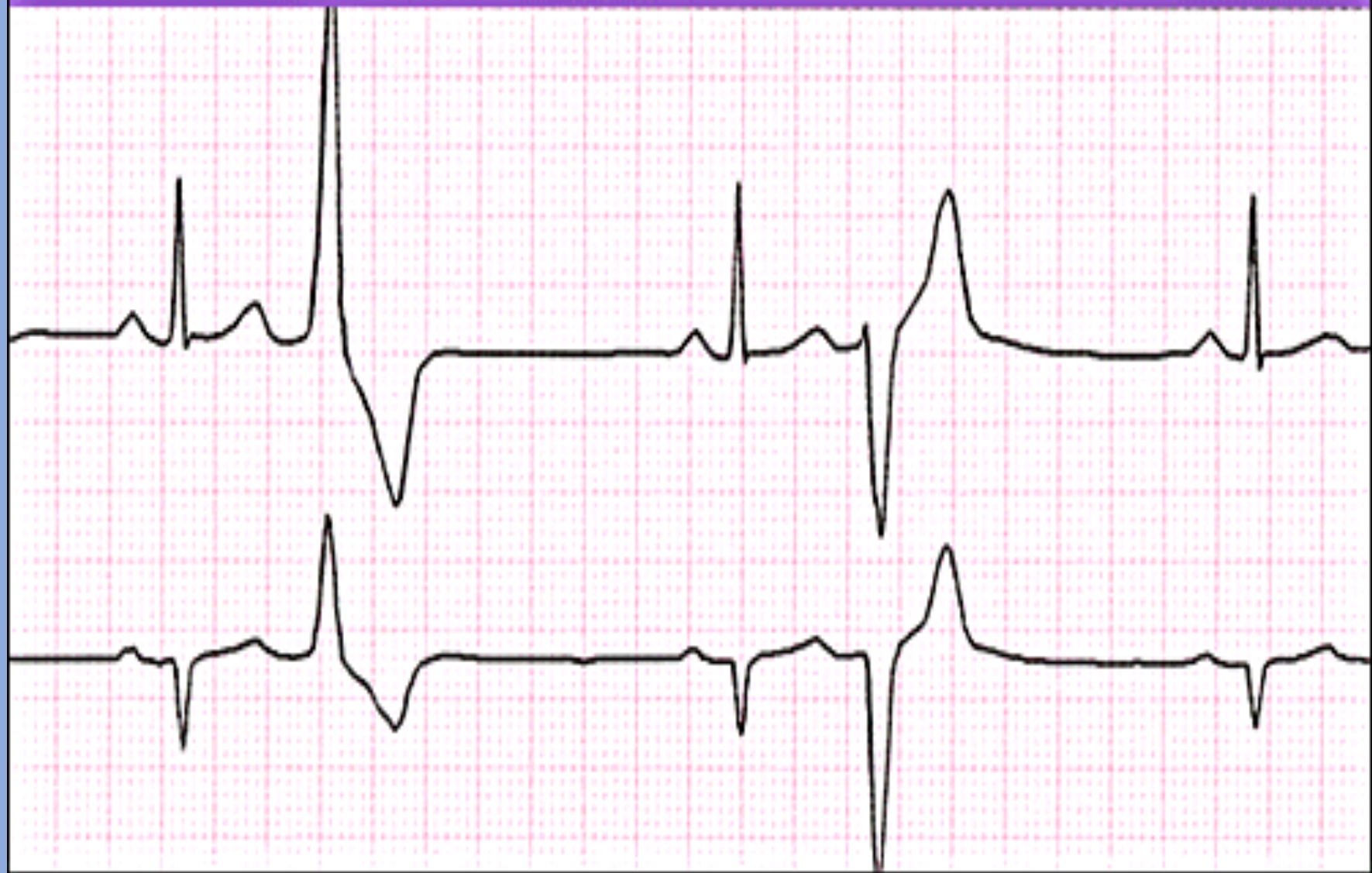
Heart Rate	Rhythm	P Wave	PR interval (in seconds)	QRS (in seconds)
< 60 bpm	Regular	Before each QRS, identical	.12 to .20	<.12

# WHAT IS ARRHYTHMIA?

An **abnormality** in the :

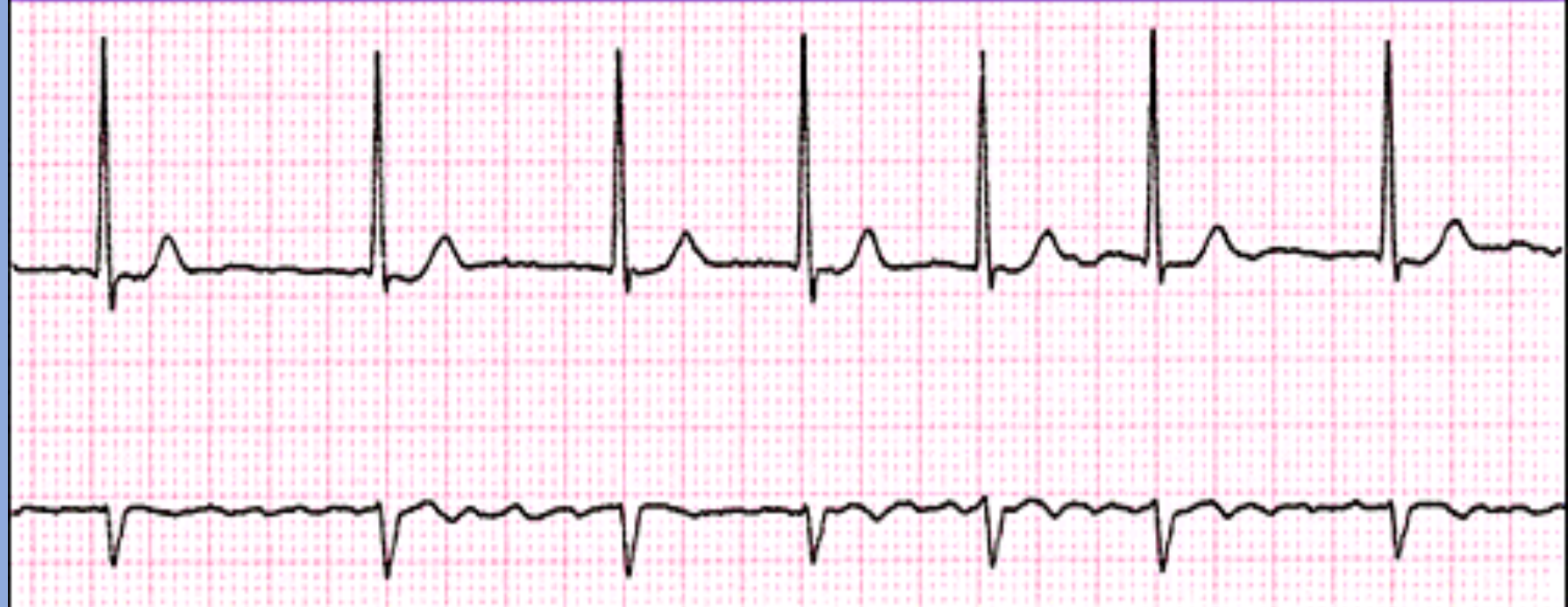
- rate ..... high= tachycardia  
low = bradycardia
- regularity ..... Extrasystoles  
(PAC, PVC)

## 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

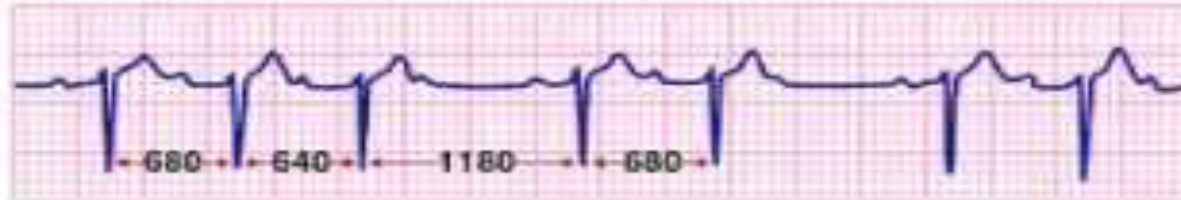


# Disturbances in conduction

1st degree AV Block



2nd degree AV Block  
Wenkebach/Mobitz I



2nd degree AV Block  
Mobitz II



3rd degree AV Block

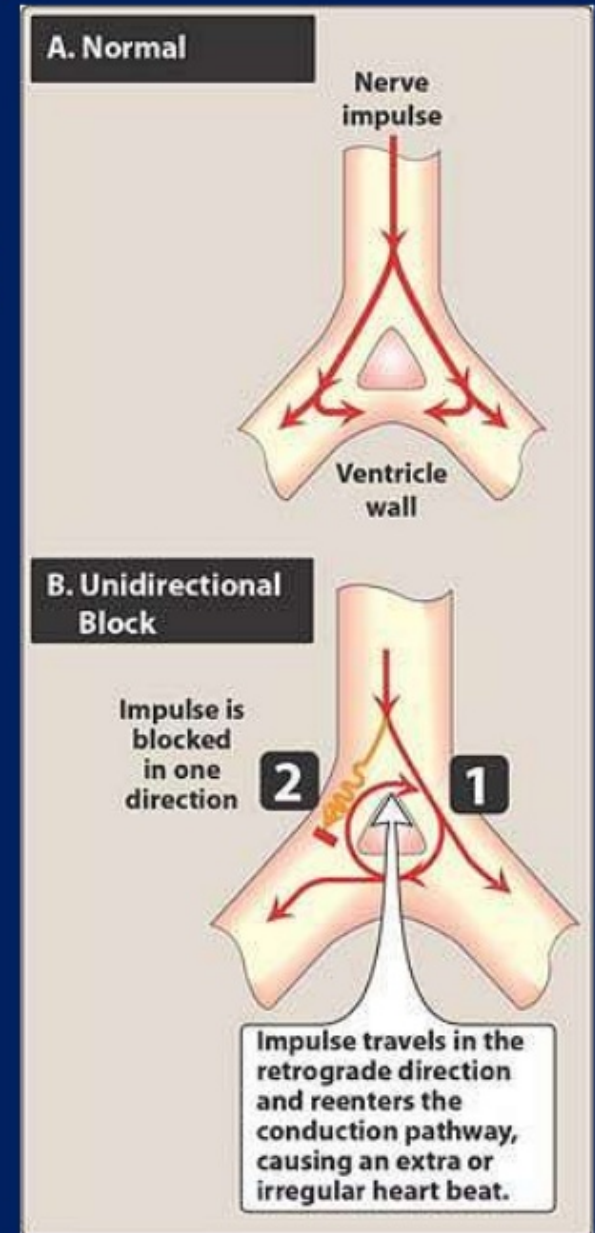
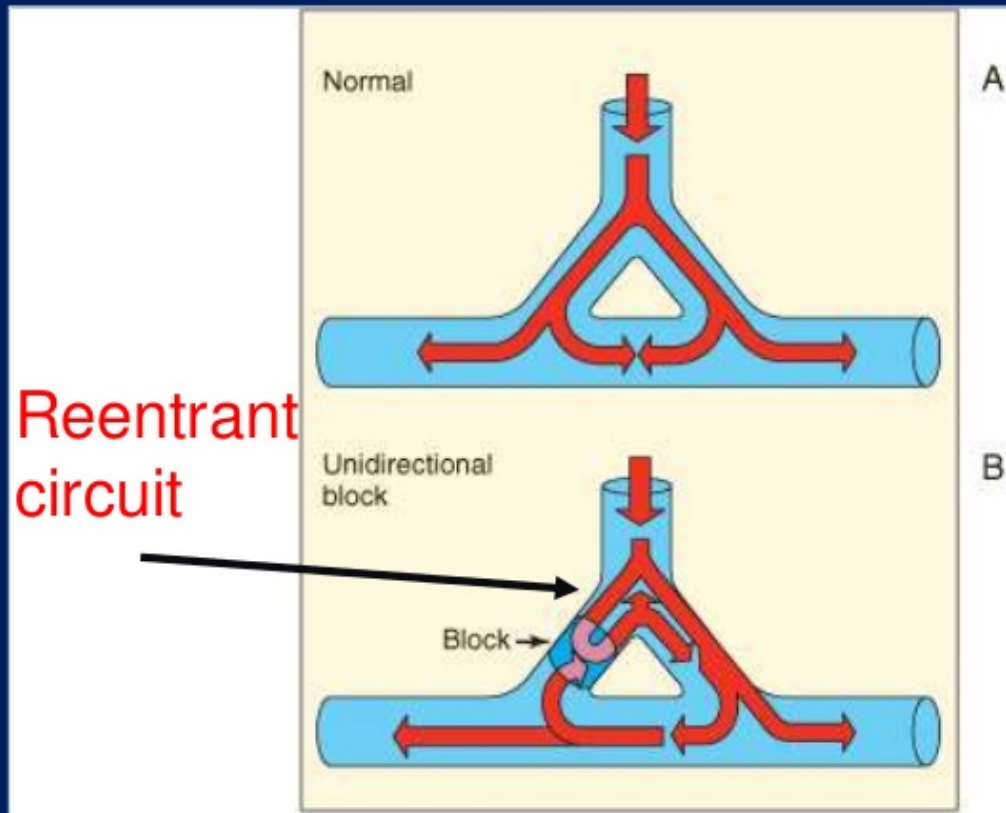




## 2. Disorders of impulse conduction

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<sup>+</sup> 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

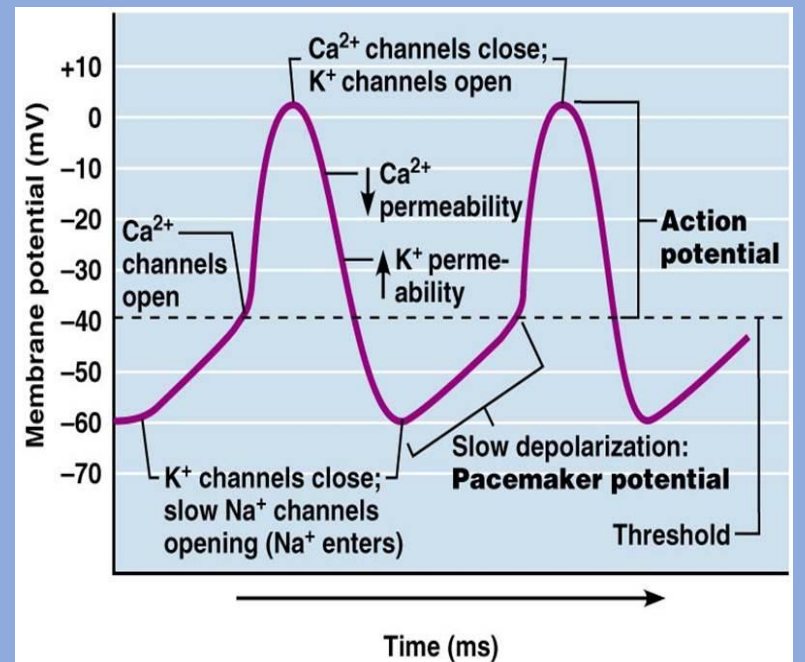
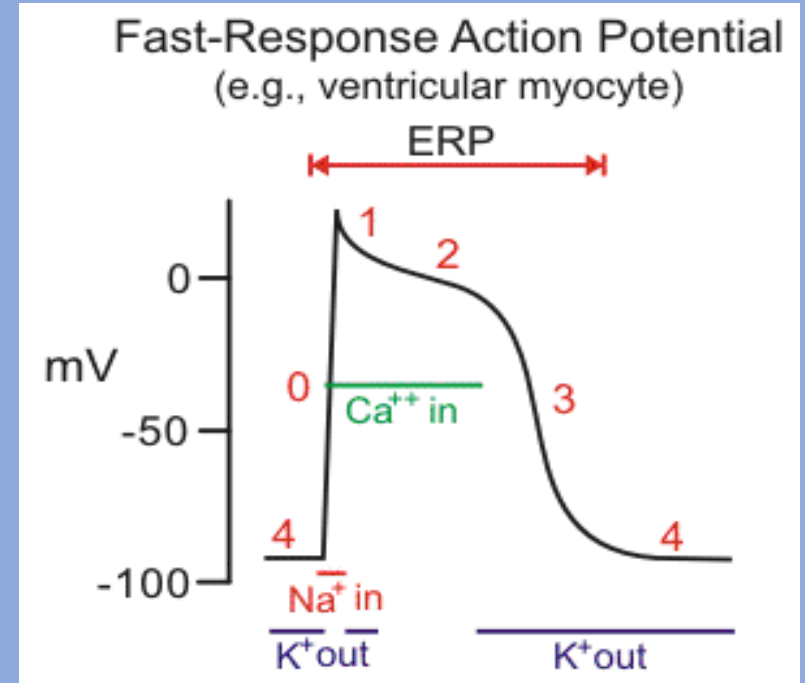
Drugs that block the influx of **Na ions** through **Na channels**



1- decrease the rate of rise of rapid depolarization (Phase 0)

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

(membrane stabilizing effect)





# CLASS I

- **Sub classified according to their effect on action potential duration :**
  - **la** : prolong action potential duration
  - **lb** : shorten action potential duration
  - **lc** : no effect on action potential duration

# CLASS I a

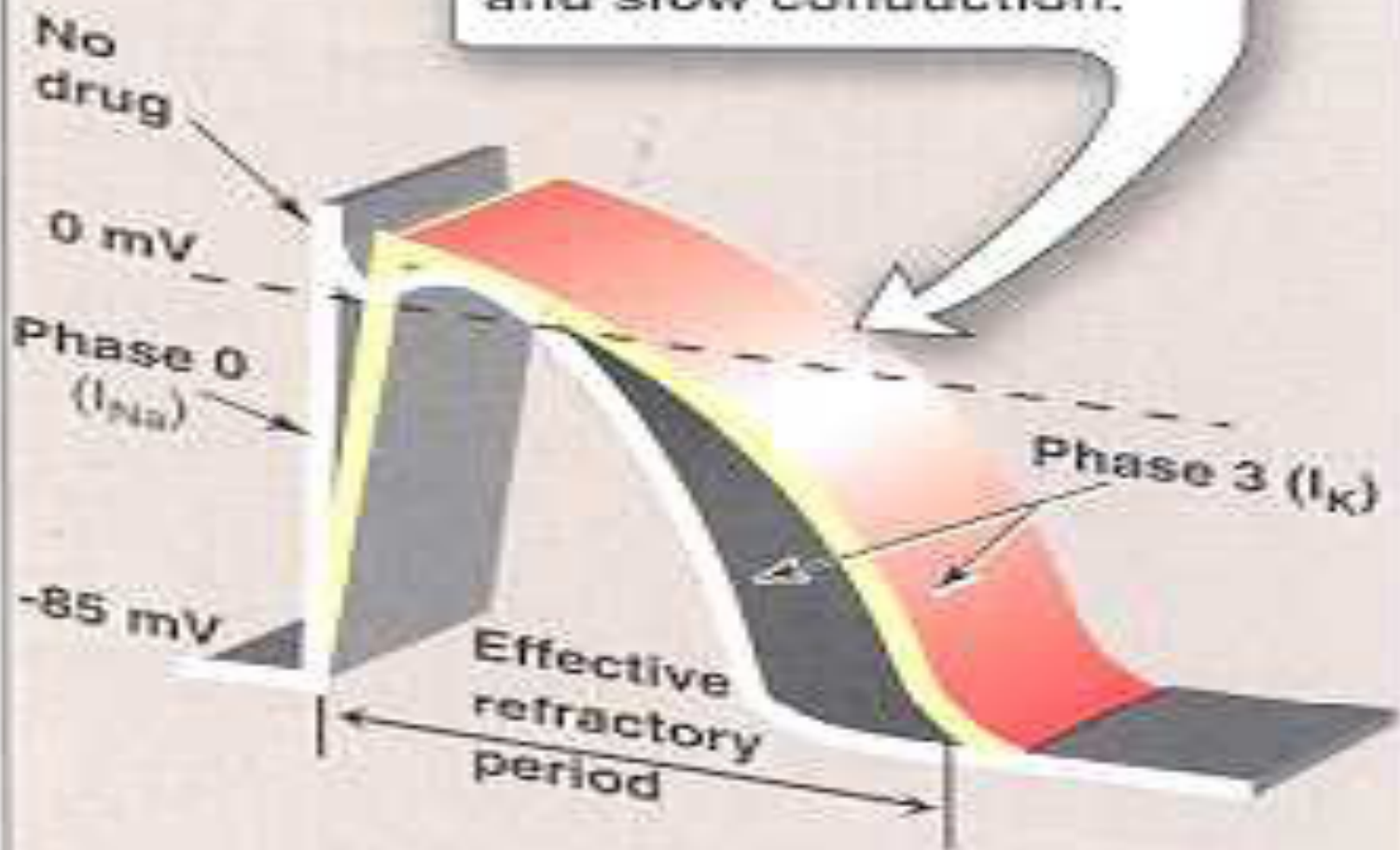
**Ia** : prolong action potential duration

e.g.

**Quinidine**

**Procainamide**

Class IA drugs slow Phase 0 depolarization, prolong action potential, and slow conduction.



# CLASS I a

## QUINIDINE

### Other pharmacological actions :

1- Anticholinergic effect:



Increase conduction through the A.V. node

(risk of ventricular tachycardia)

2-  $\alpha$ -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**

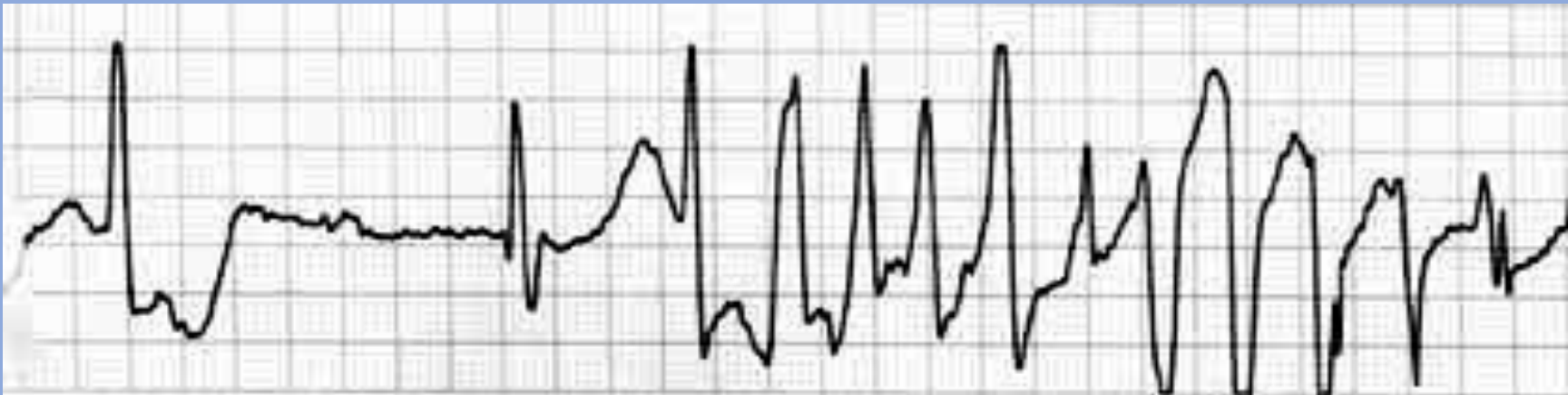
**Therapeutic uses:**

- **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



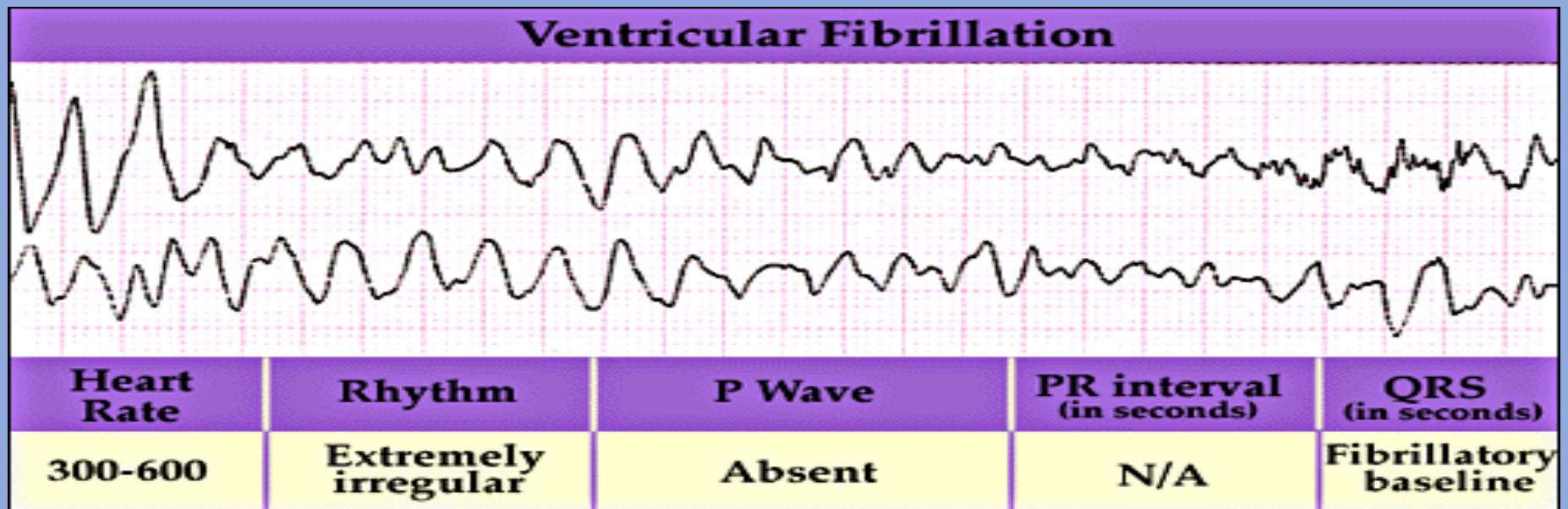


# Torsades de pointes

- 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  $\alpha$ -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**

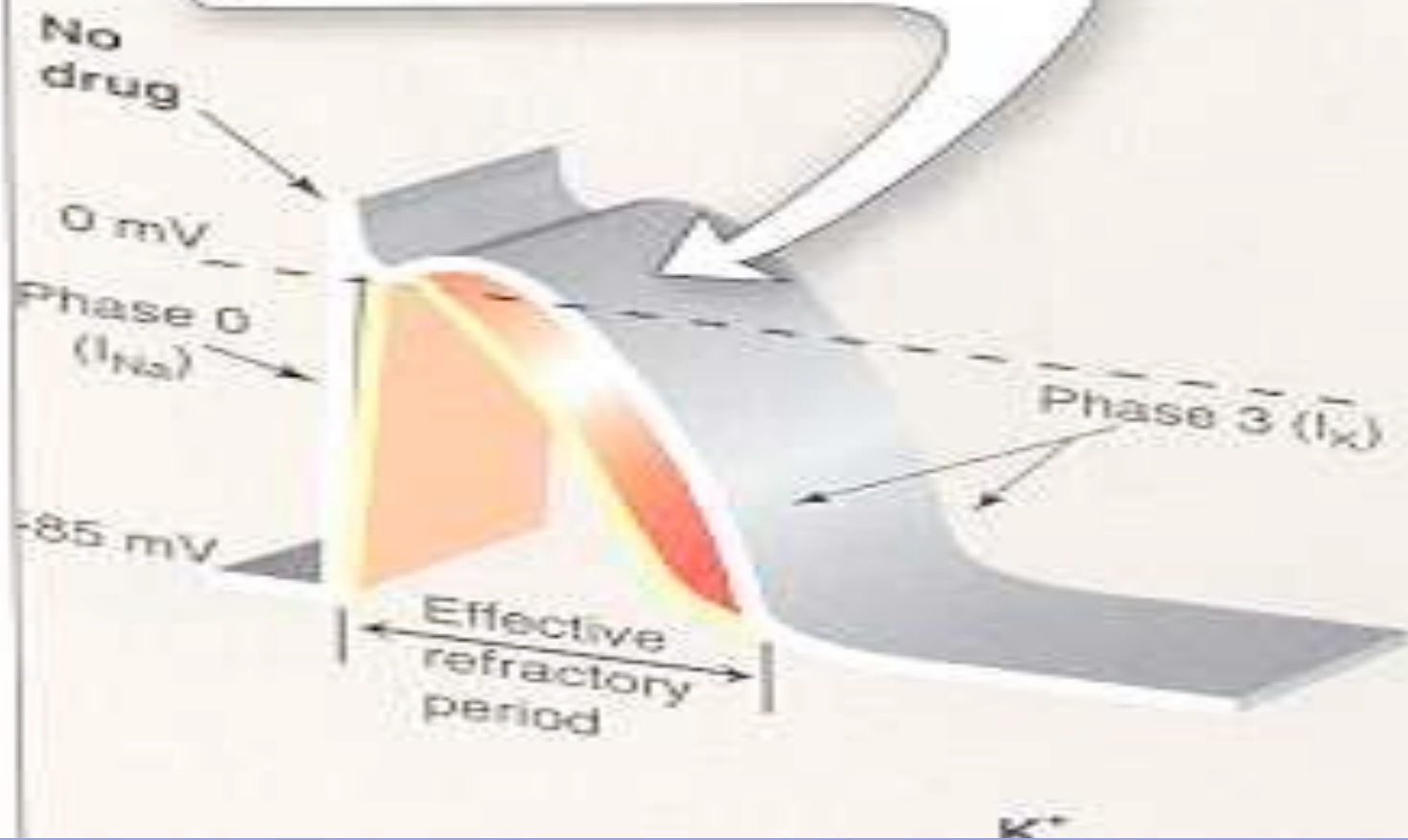
**e.g.**

**Lidocaine**

**Mexiletine**



Class IB drugs shorten Phase 3 repolarization and decrease the duration of the action potential.



**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

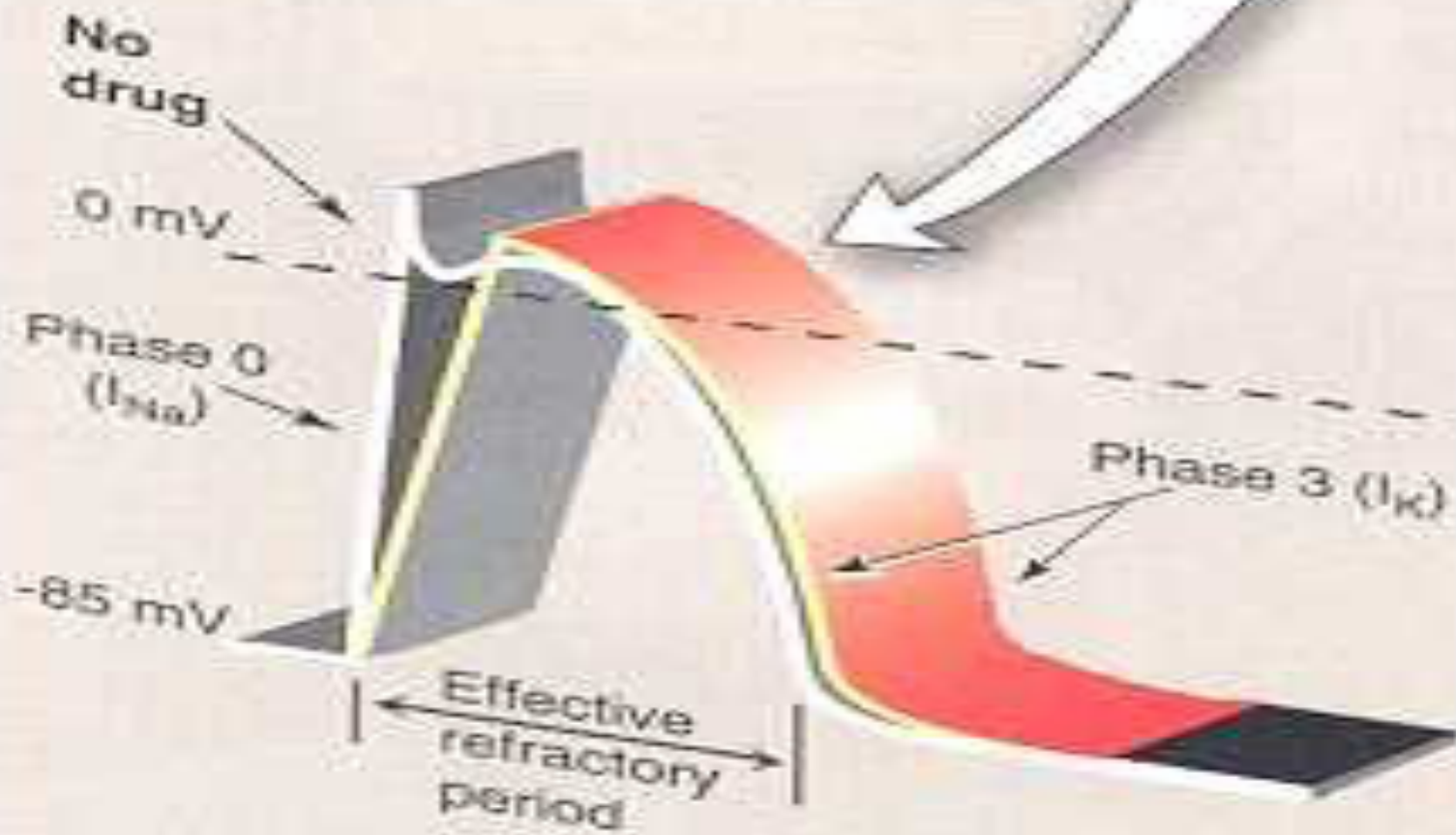
## CLASS Ic

- have no effect on action potential duration

e.g.

**Flecainide**

Class IC drugs  
markedly slow  
Phase 0 depolarization.





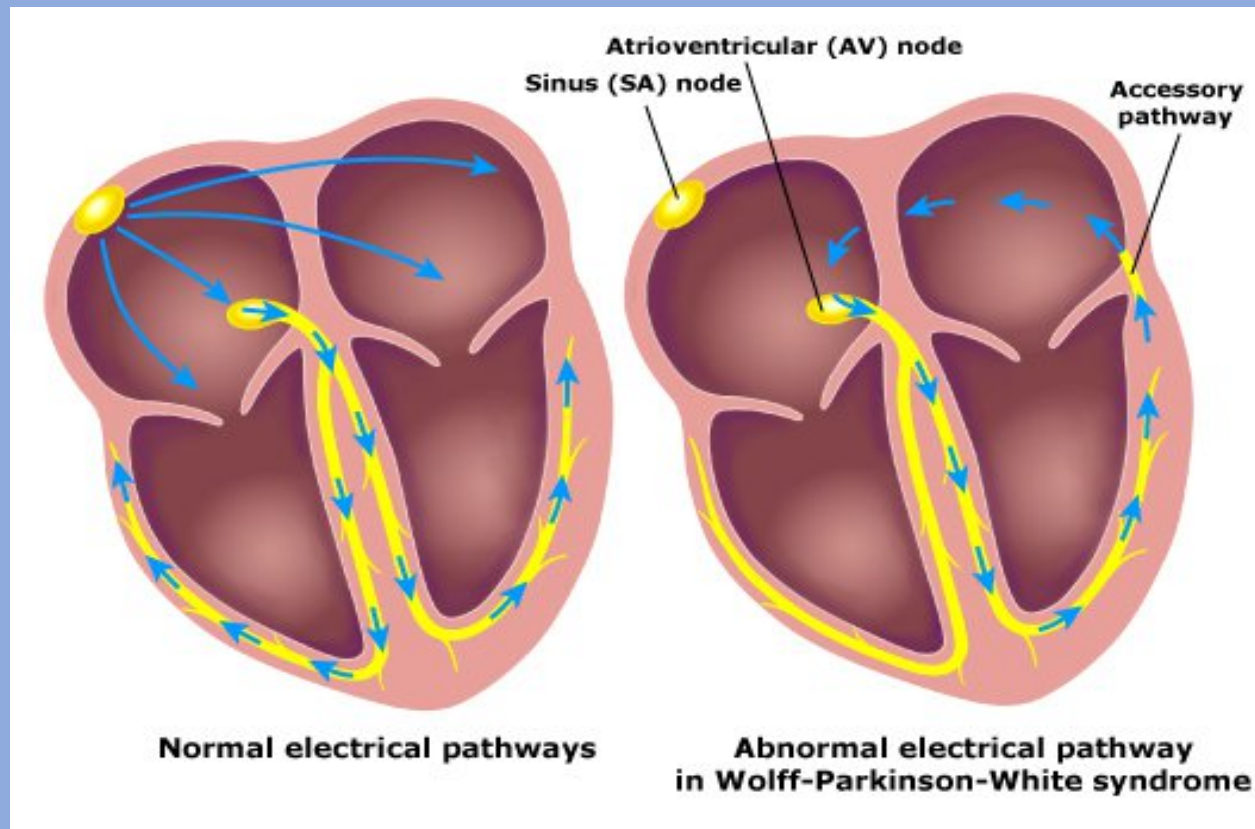
**CLASS Ic**  
**FLECAINIDE**

**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

## $\beta$ - 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 &  
ectopic pacemakers

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

# CLASS II DRUGS

## $\beta$ -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.



# 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  $\alpha$ - &  $\beta$ -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  $t_{1/2} = 13 - 103 \text{ DAYS}$
- 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

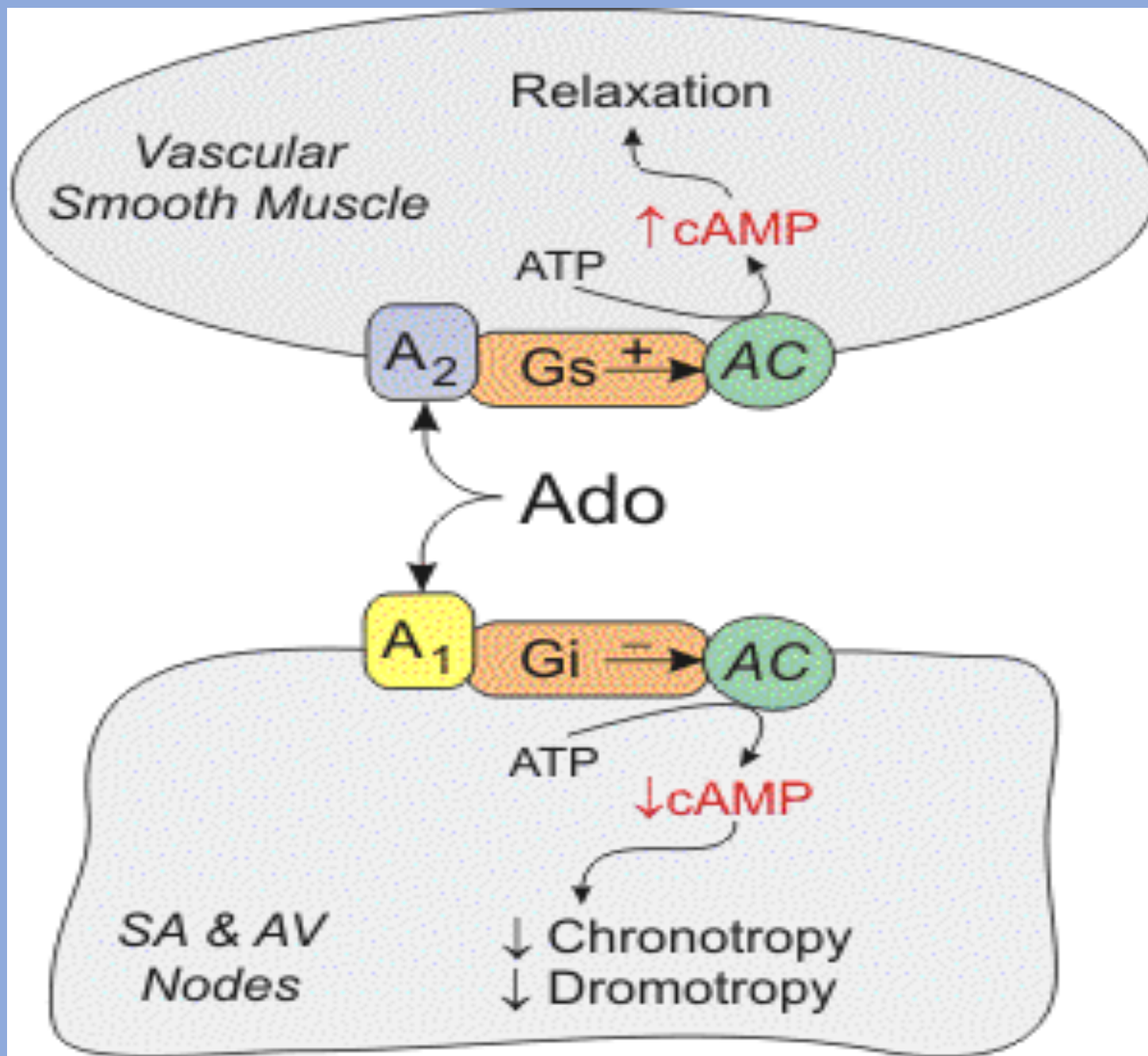
(hyperpolarization)

2 - decreasing conduction velocity mainly at AV node

(negative dromotropic effect)

3- inhibiting phase 4 pacemaker action potential at SA node

(negative chronotropic effect)



# 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

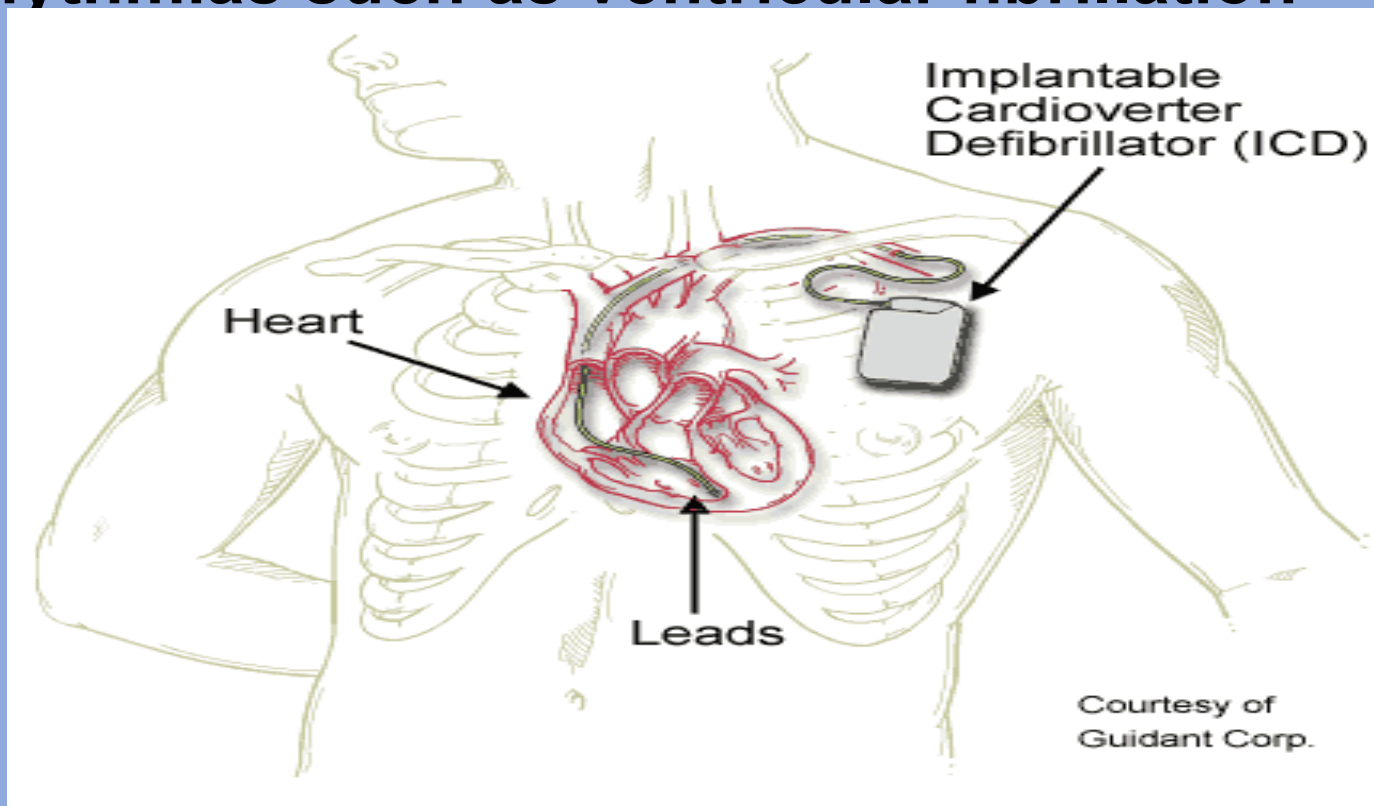
## ATROPINE

- 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

