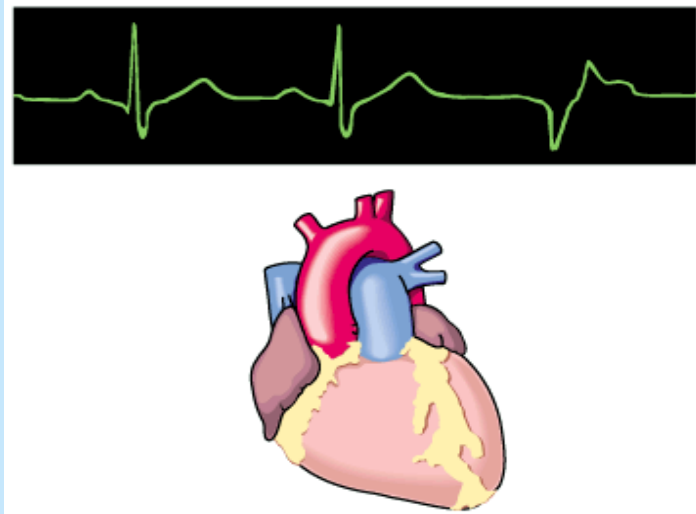


Antiarrhythmic Drugs

Prof. Abdulrahman Almotrefi



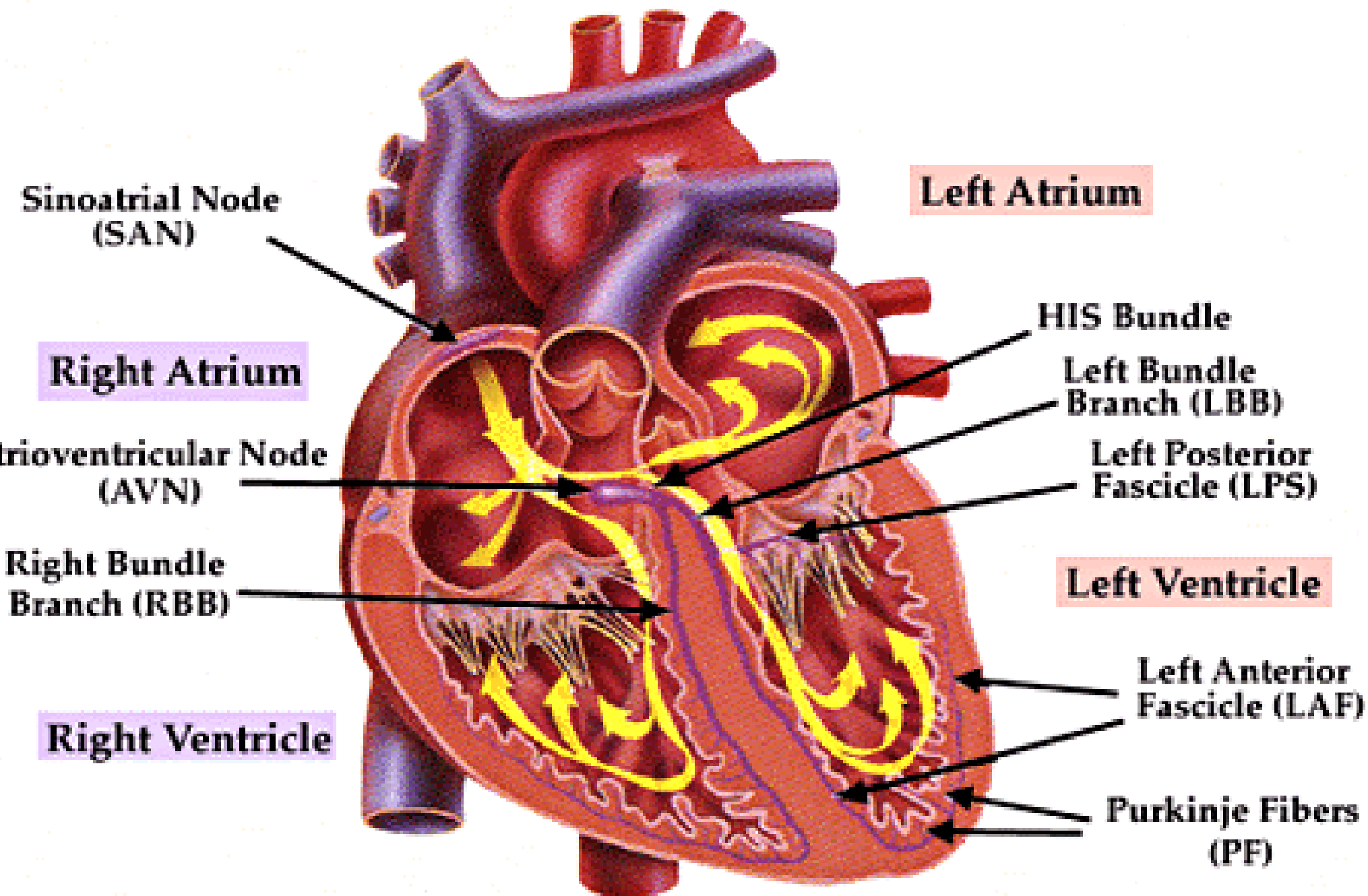
Cardiovascular Pharmacology

- **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.

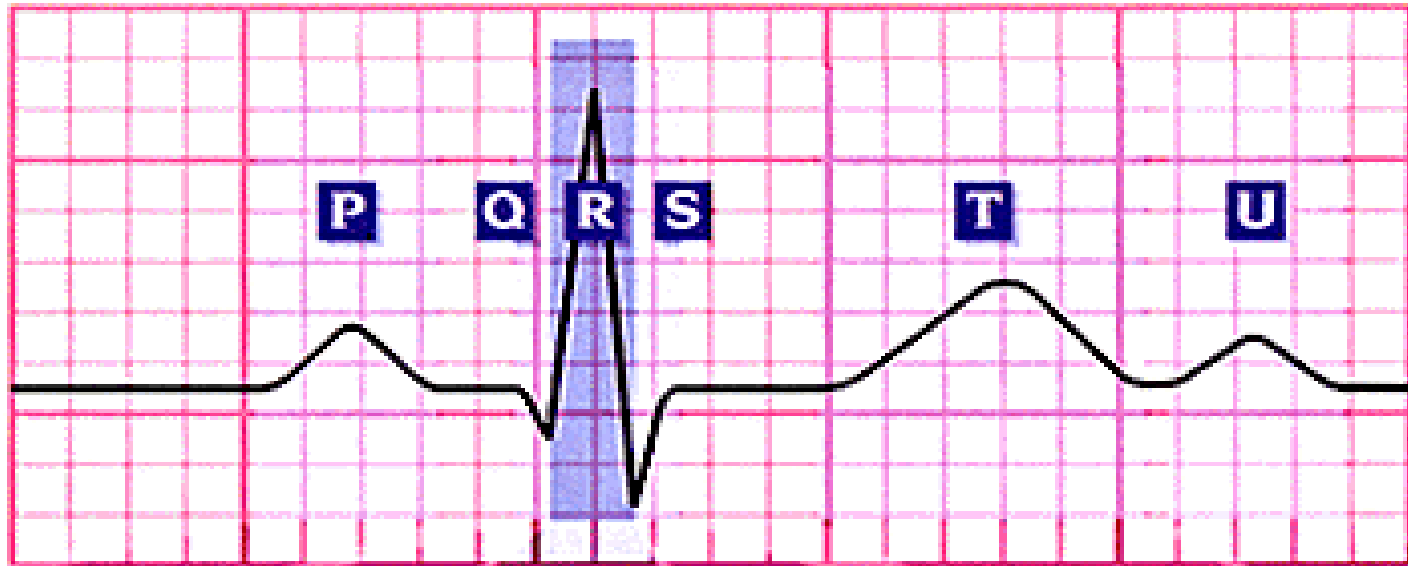


Cardiac Conduction System

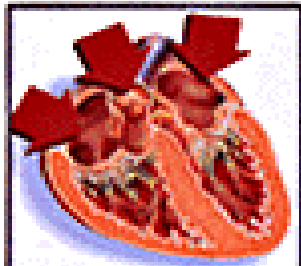
CARDIAC CONDUCTION SYSTEM

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

Electrocardiogram (ECG)



**Atrial
Excitation**



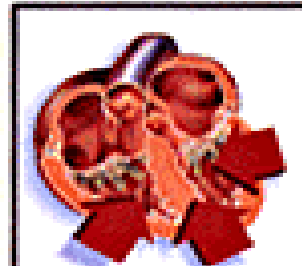
**Atrial
Systole**



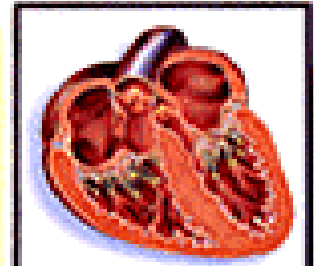
**Atrial
Diasystole**



**Ventricular
Excitation**



**Ventricular
Systole**

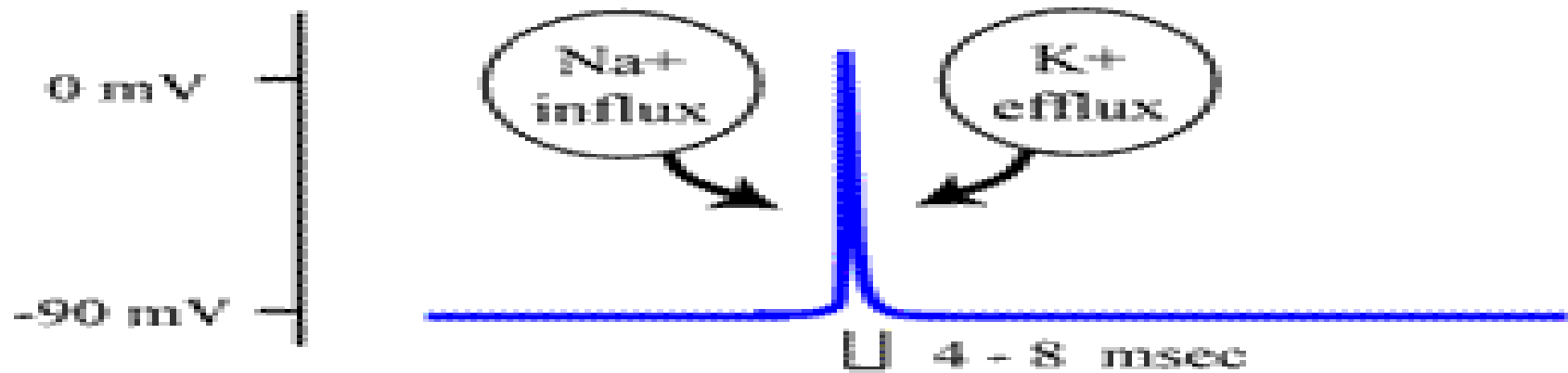


**Ventricular
Diasystole**

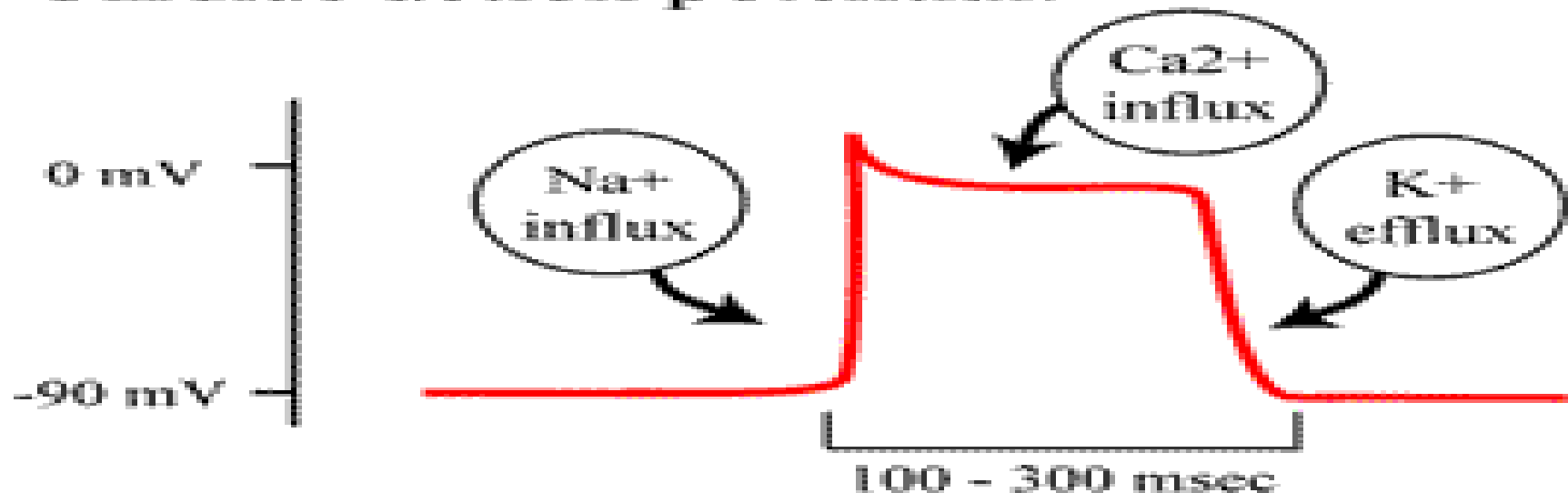
Electrical and Mechanical Events

CARDIAC ACTION POTENTIAL

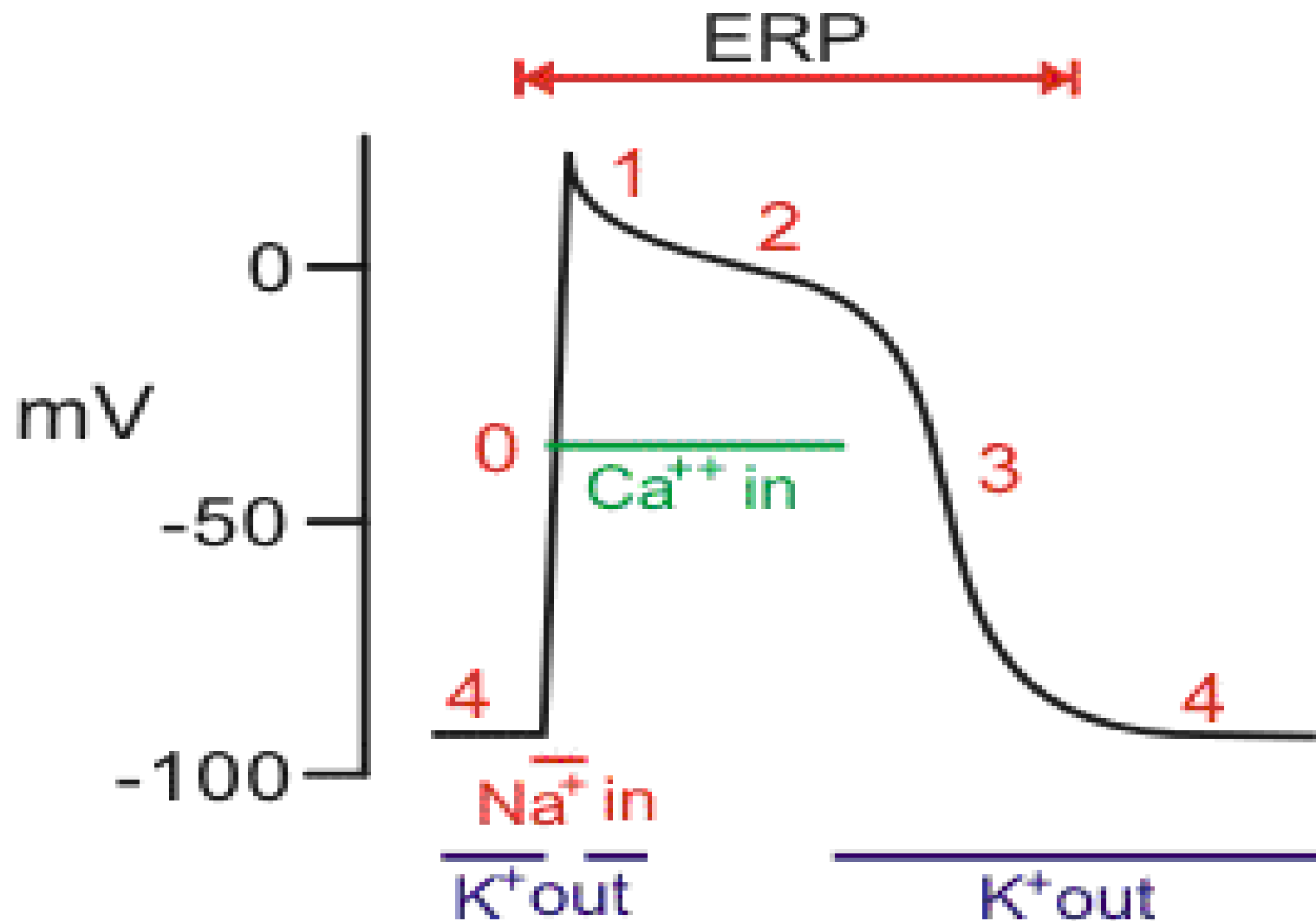
Skeletal action potential:



Cardiac action potential:

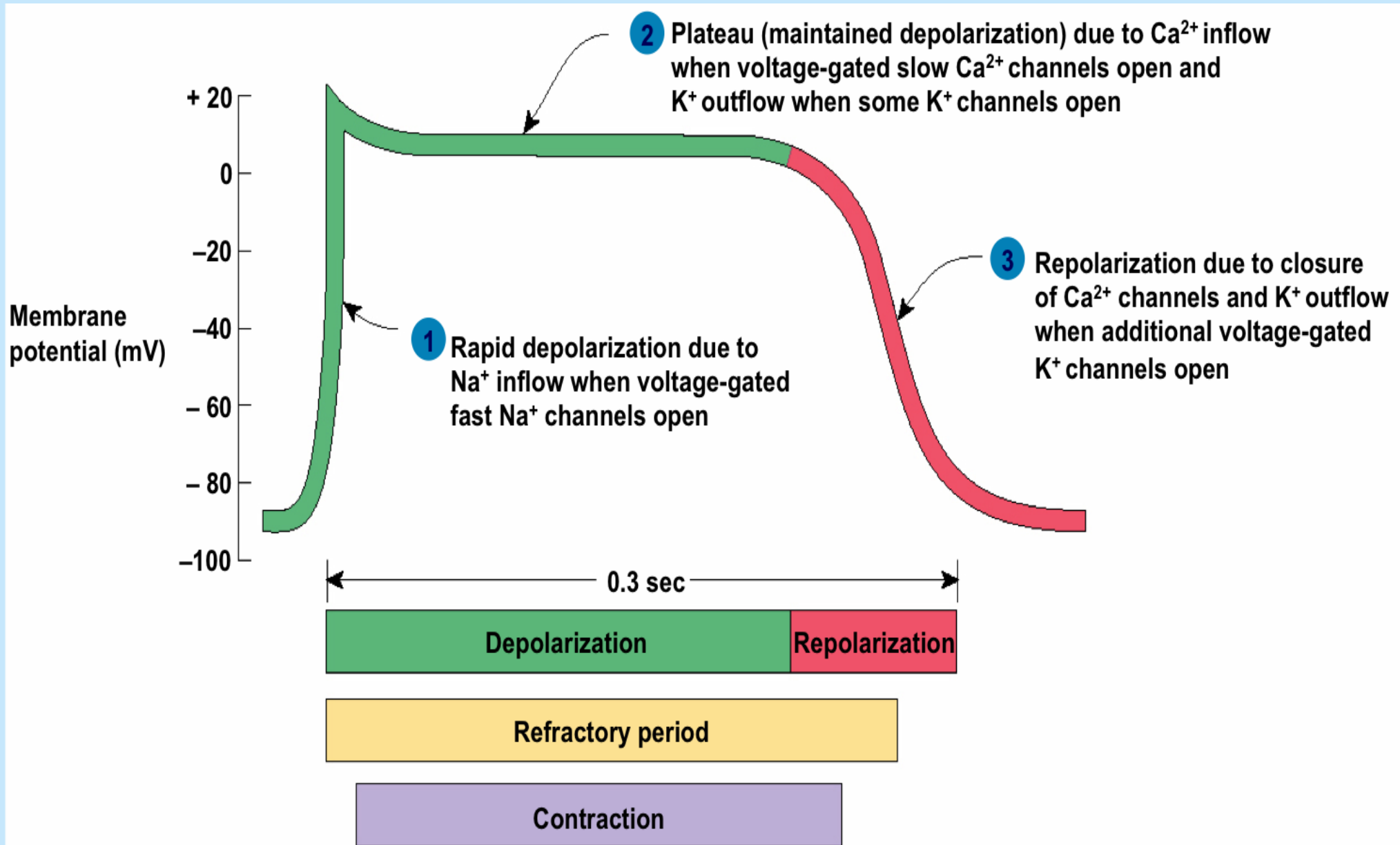


Fast-Response Action Potential (e.g., ventricular myocyte)



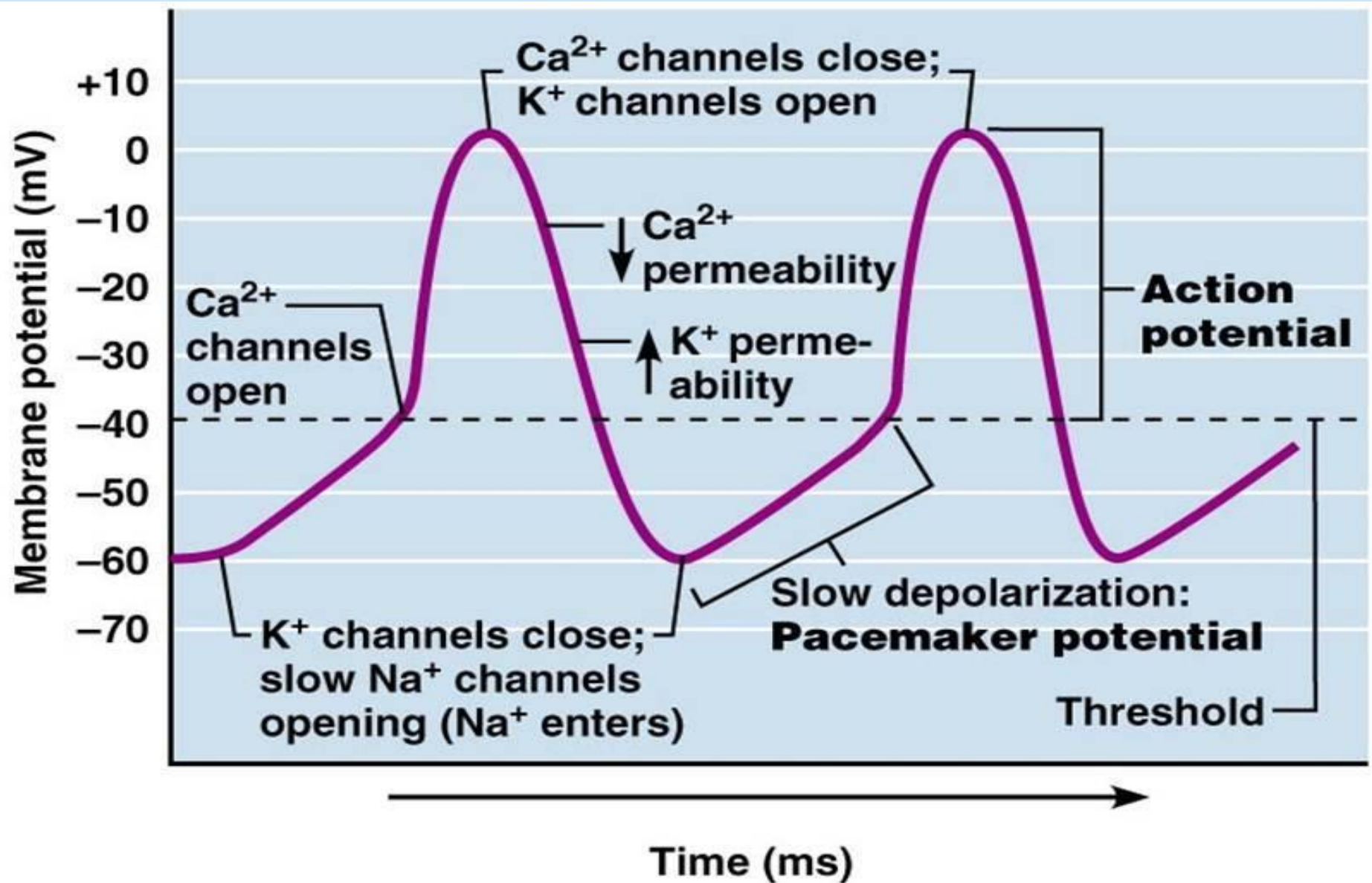
CARDIAC ACTION POTENTIAL

Non-pacemaker (ventricular muscle)



CARDIAC ACTION POTENTIAL

Pacemaker (SA node)



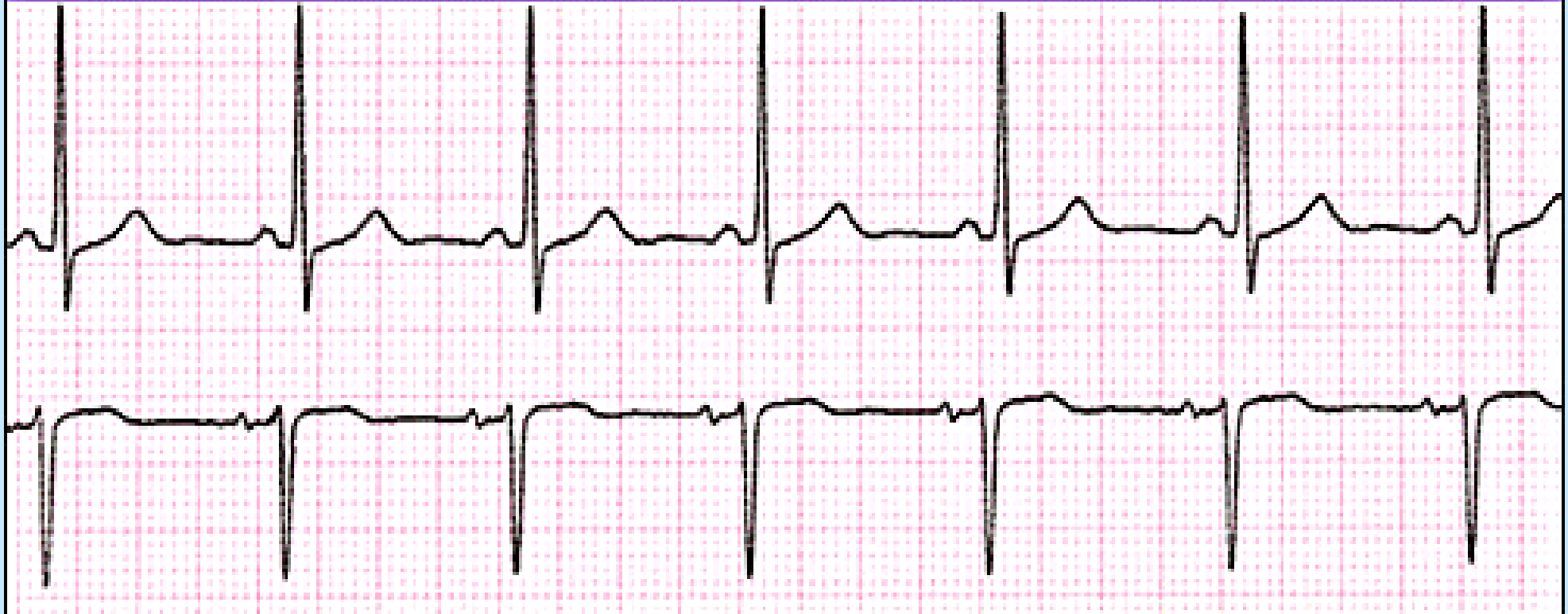
WHAT IS ARRHYTHMIA?

An **abnormality** in the :

■ rate high= tachycardia

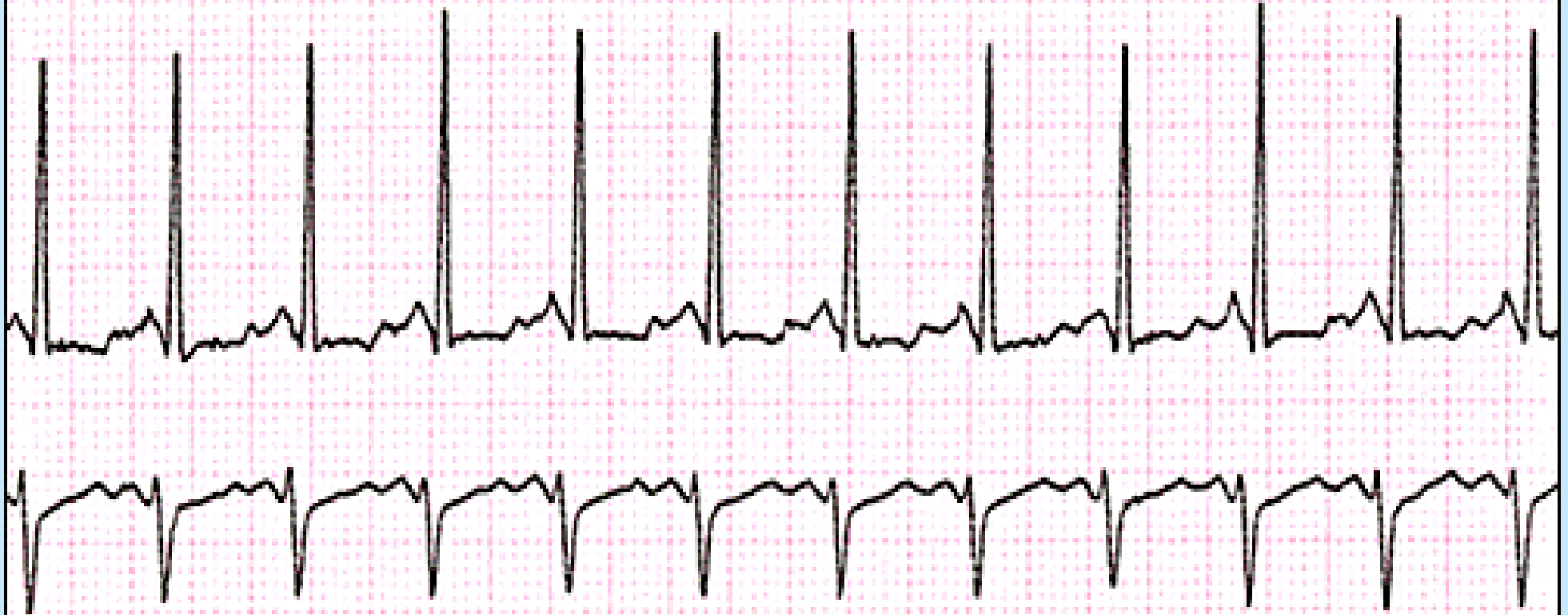
low = bradycardia

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

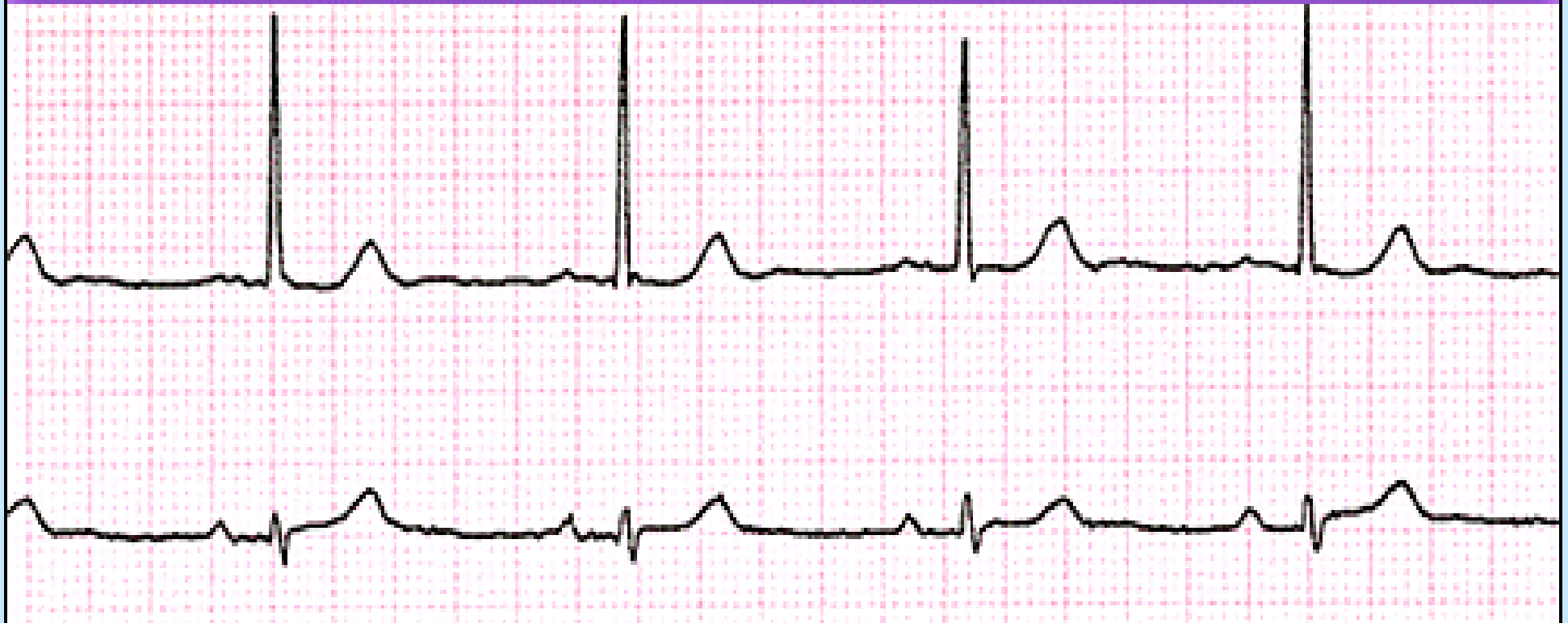
Regular

**Before each
QRS, identical**

.12 to .20

<.12

Sinus Bradycardia



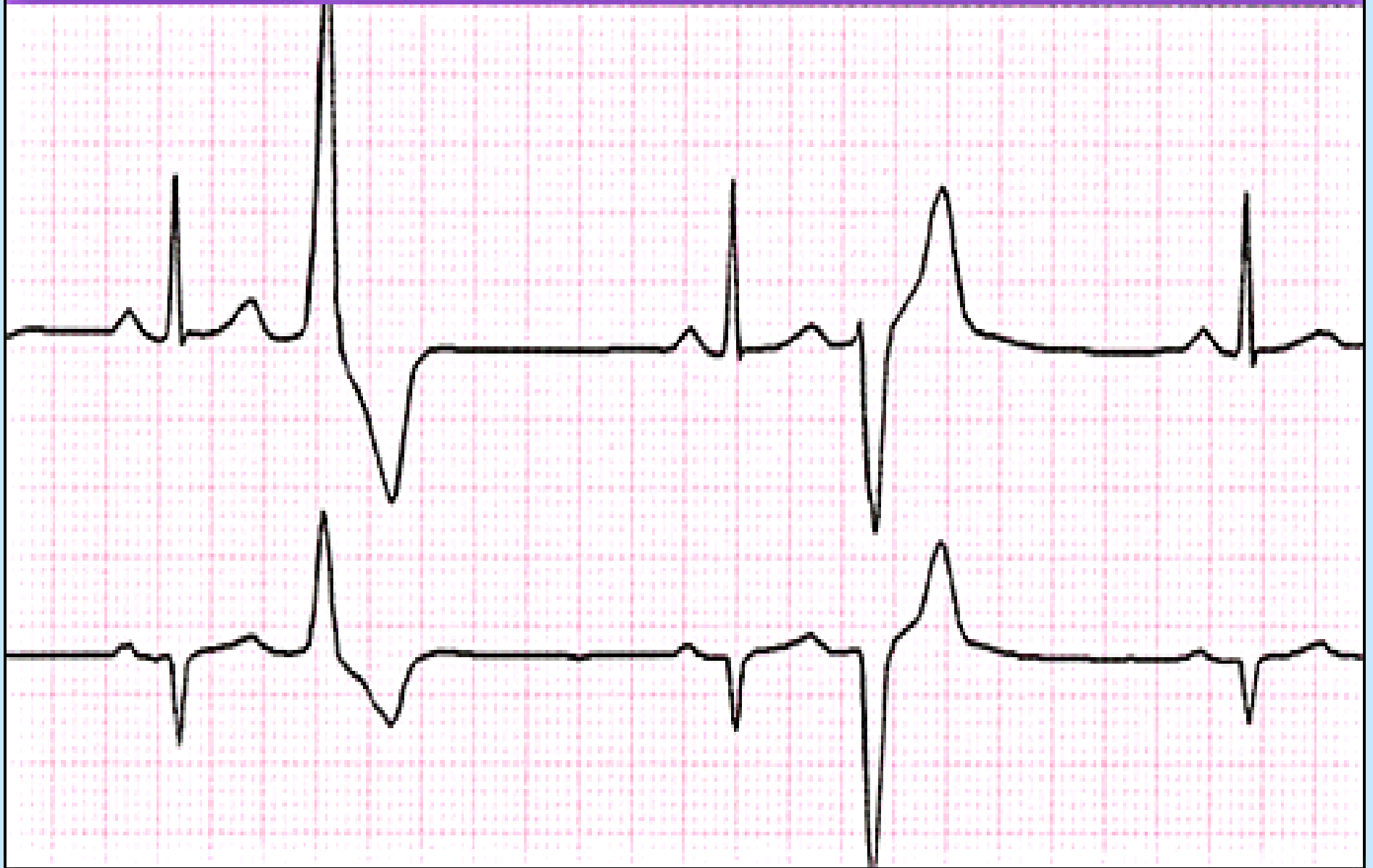
Heart Rate	Rhythm	P Wave	PR interval (in seconds)	QRS (in seconds)
< 60 bpm	Regular	Before each QRS, identical	.12 to .20	<.12

WHAT IS ARRHYTHMIA?

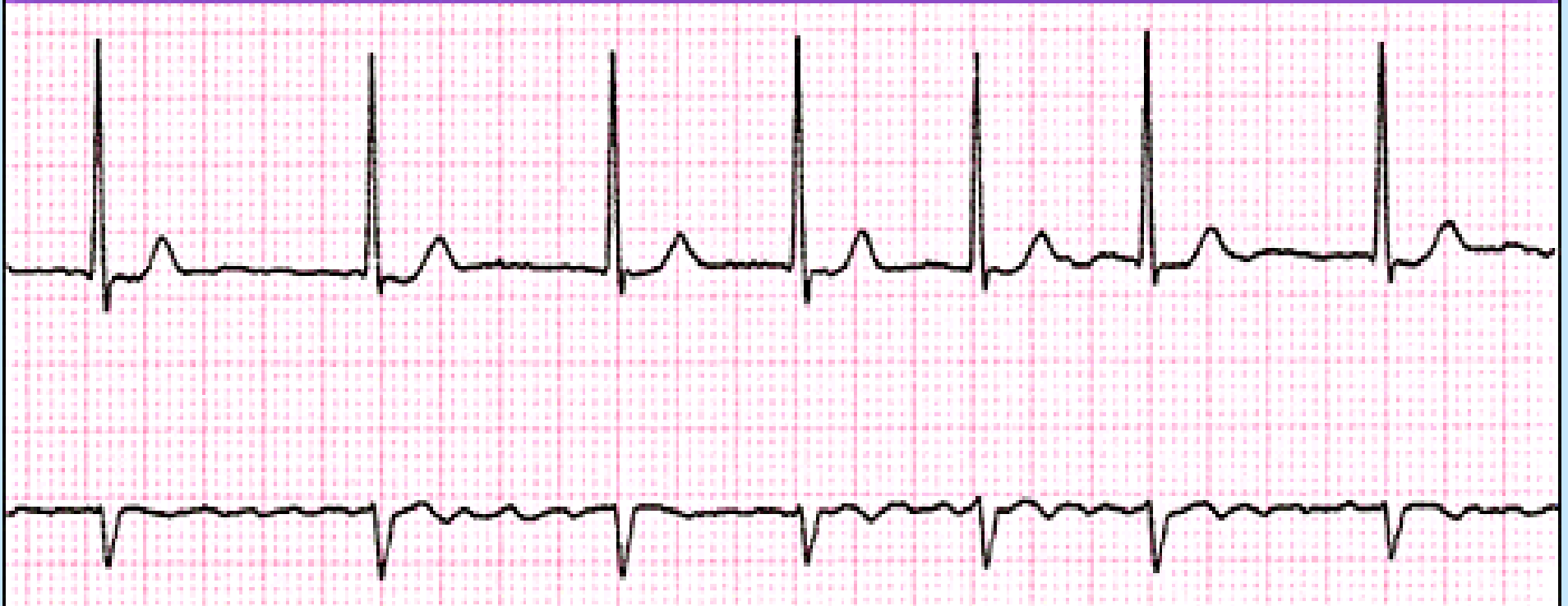
An **abnormality** in the :

- 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 V: Slow to rapid	Irregular	Fibrillatory (fine to coarse)	N/A	<.12

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

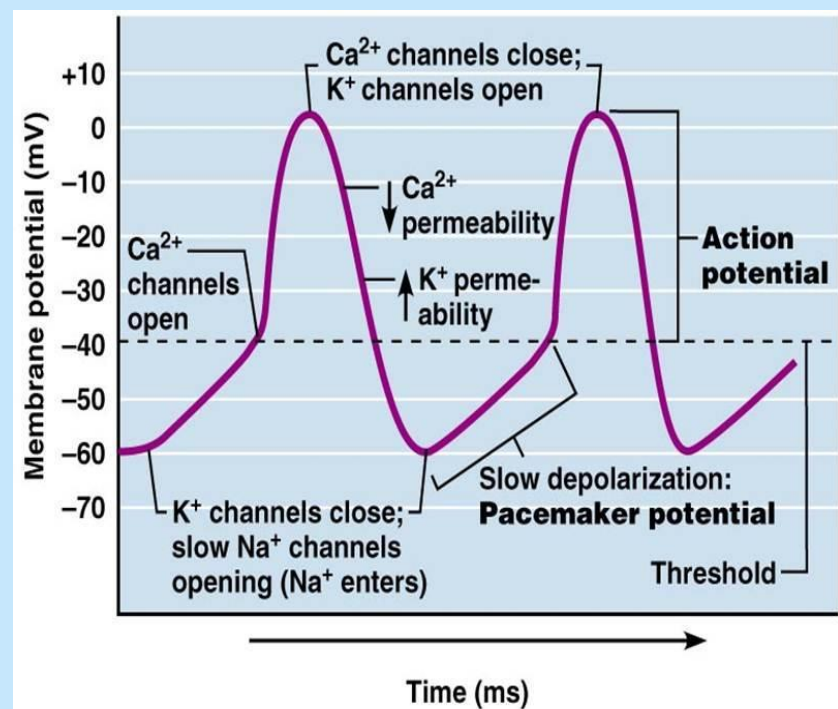
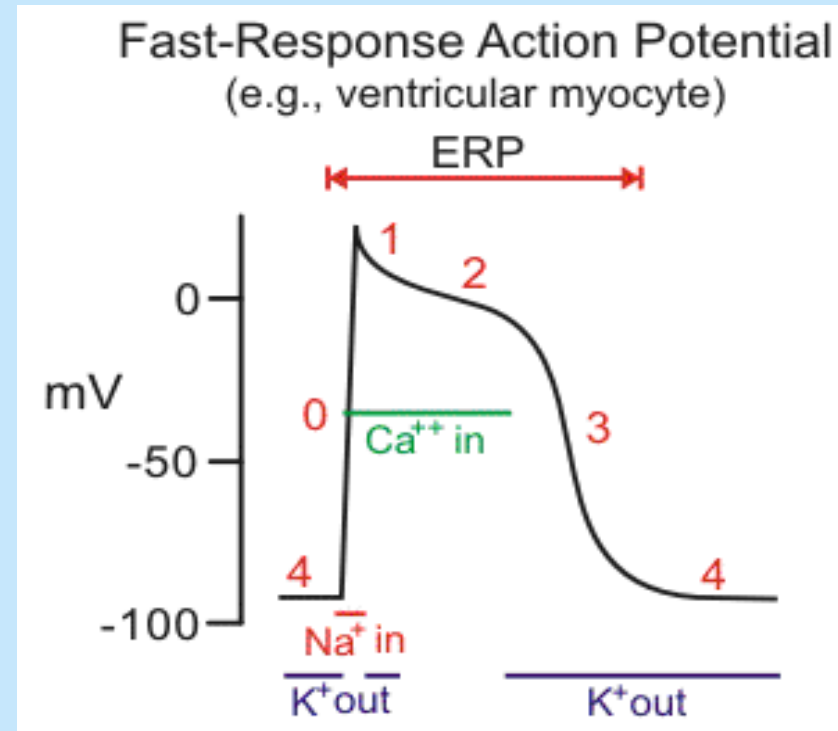
Drugs that block the influx of **Na ions** through **Na channels**



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

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 :**
 - **la** : prolong action potential duration
 - **lb** : shorten action potential duration
 - **lc** : no effect on action potential duration

CLASS I a

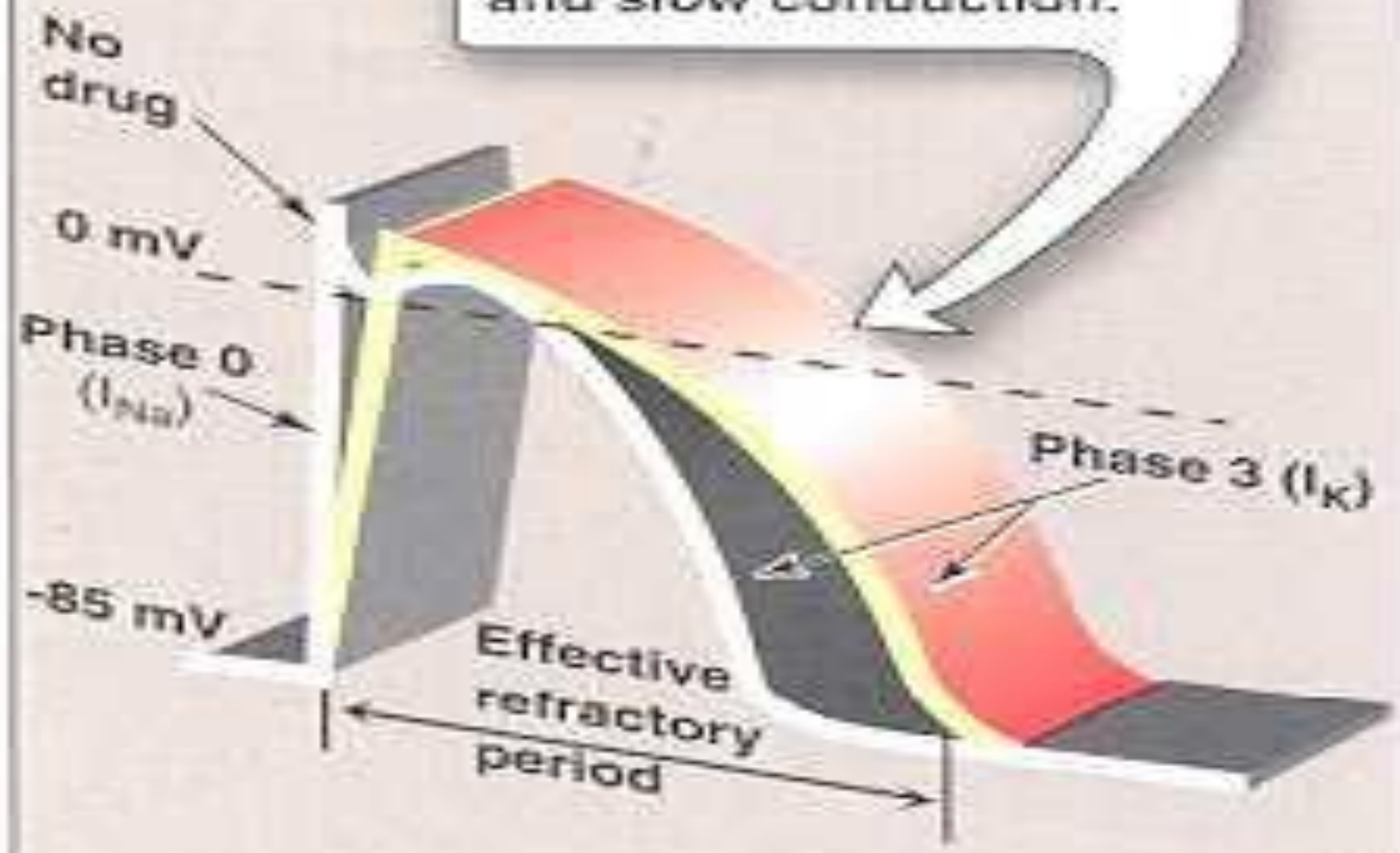
Ia : prolong action potential duration

e.g.

Quinidine

Procainamide

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



CLASS I a QUINIDINE

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

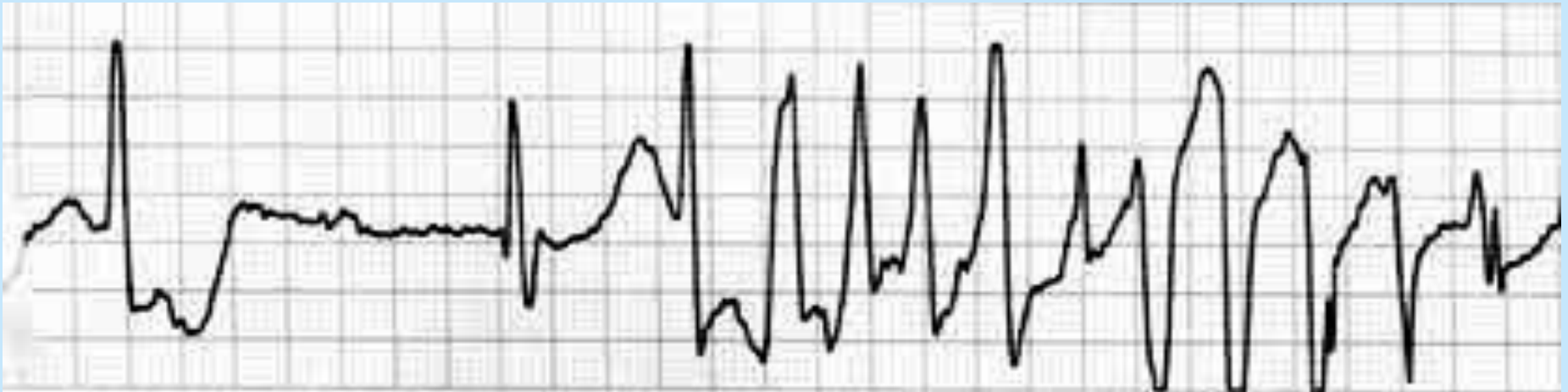
Therapeutic uses:

- **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



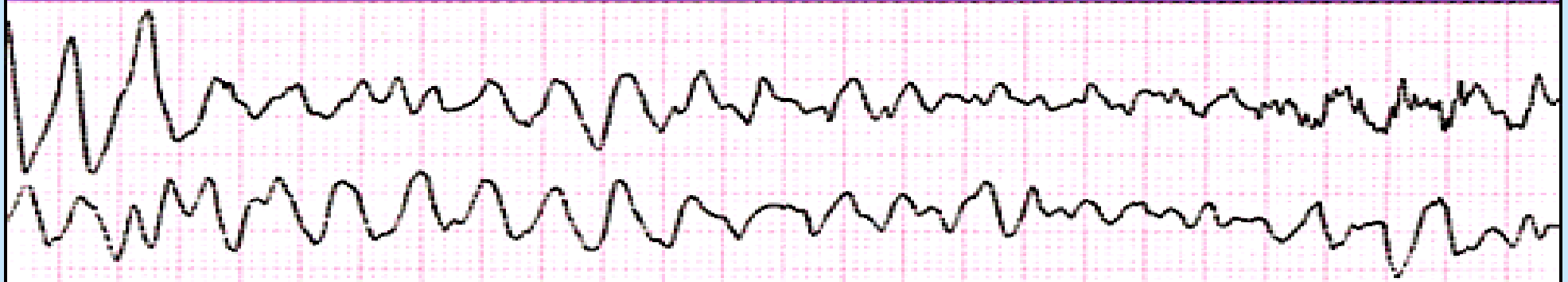
Torsades de pointes

- may terminate spontaneously or lead to



fatal ventricular fibrillation

Ventricular Fibrillation



Heart Rate	Rhythm	P Wave	PR interval (in seconds)	QRS (in seconds)
300-600	Extremely irregular	Absent	N/A	Fibrillatory baseline

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

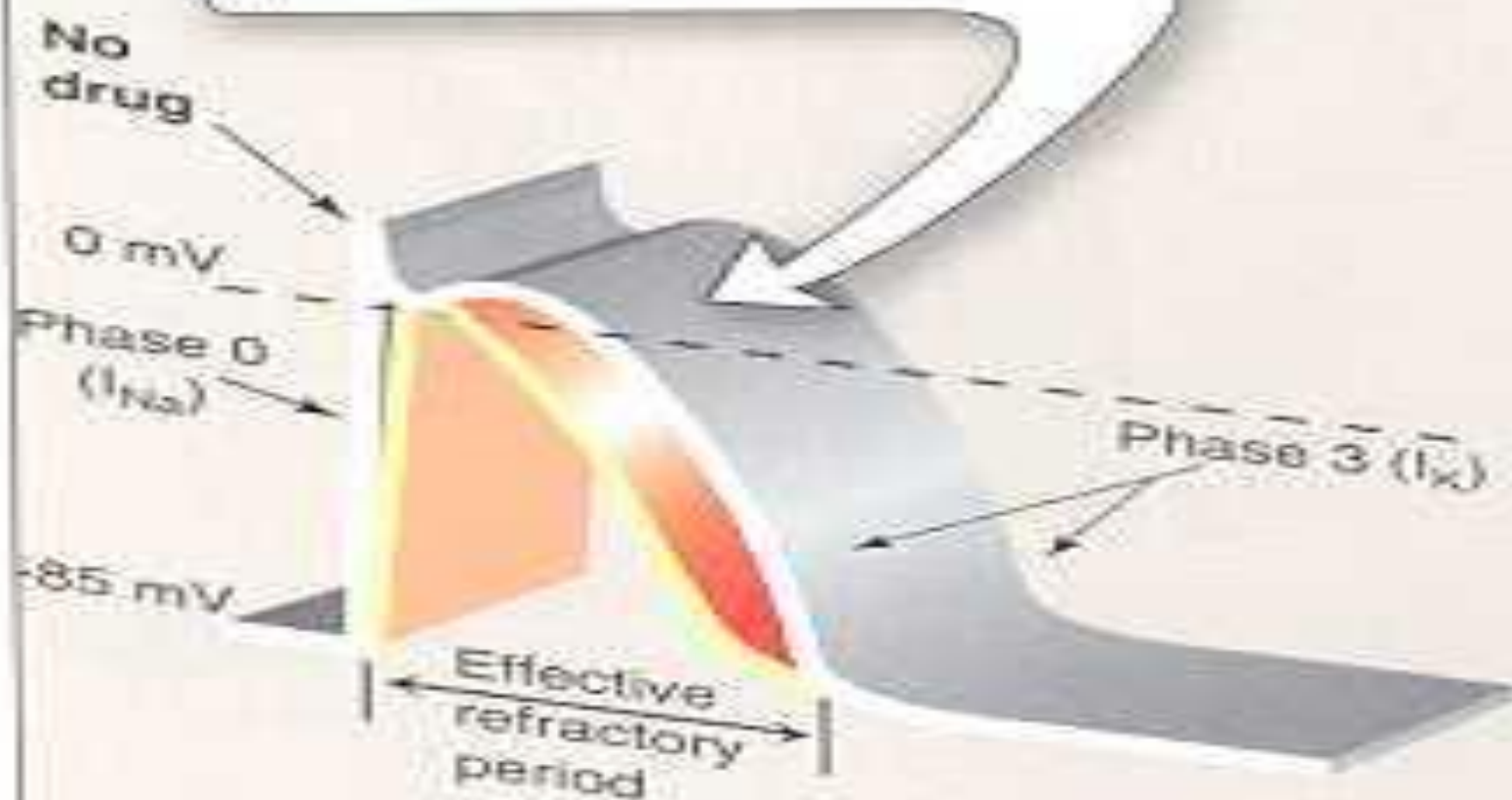
- **Shorten action potential duration**

e.g.

Lidocaine

Mexiletine

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



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

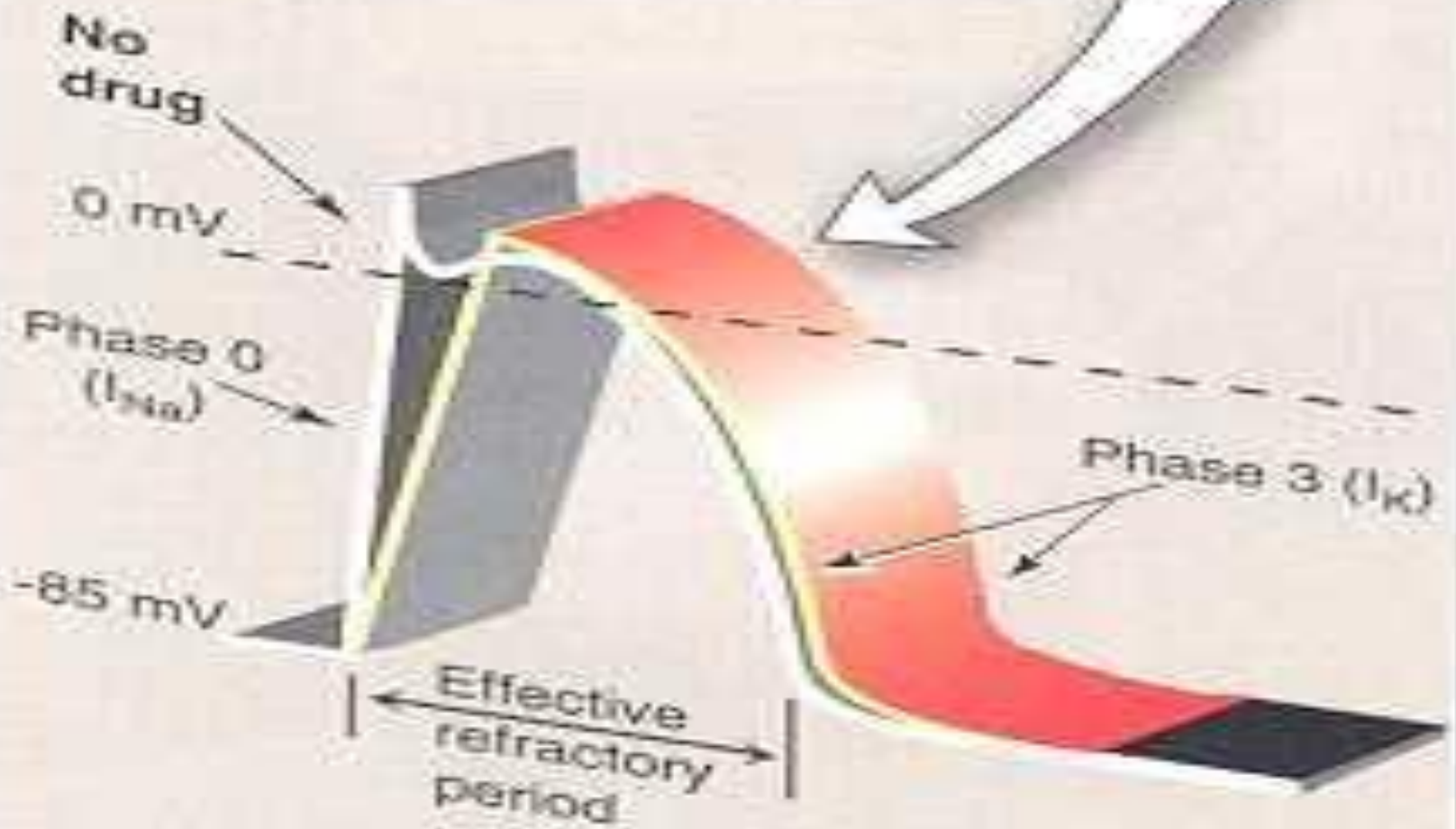
CLASS Ic

- have no effect on action potential duration

e.g.

Flecainide

Class IC drugs markedly slow Phase 0 depolarization.



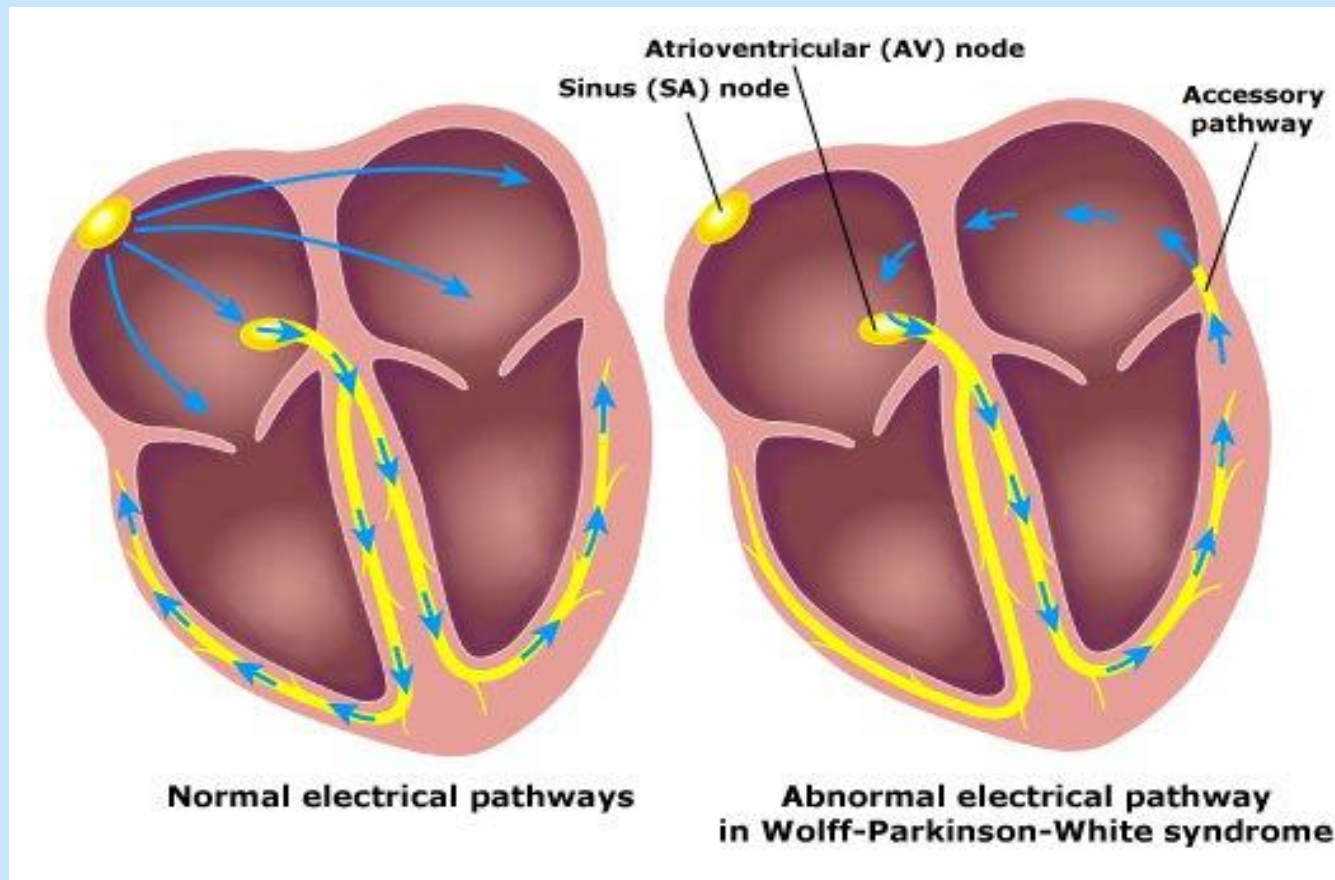
CLASS Ic
FLECAINIDE

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 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.



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

MISCELLANEOUS 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

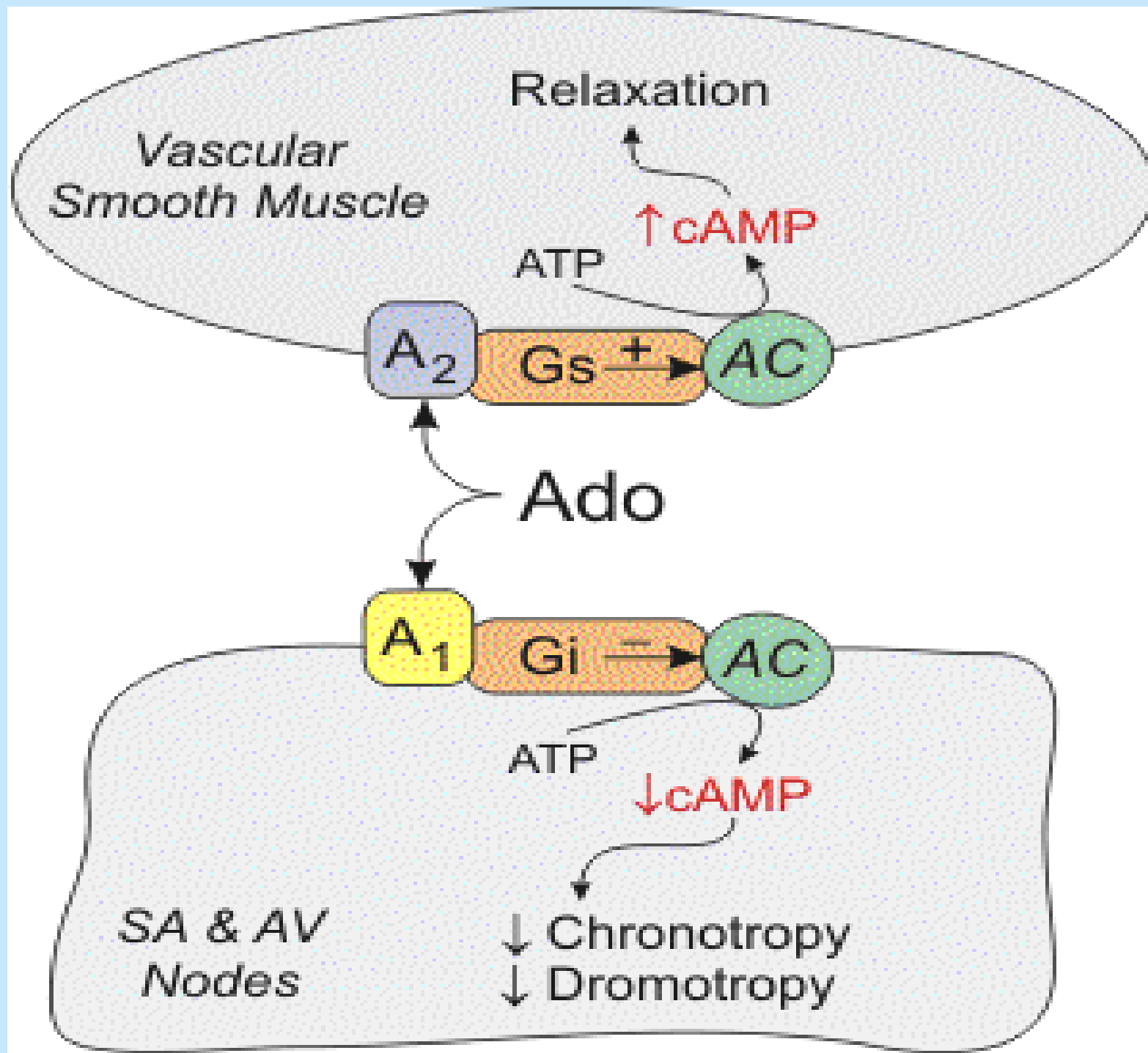
Mechanism of action :

2 - decreasing conduction velocity mainly at AVN

(negative dromotropic effect)

3- inhibiting phase 4 pacemaker action potential (SAN)

(negative chronotropic effect)



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

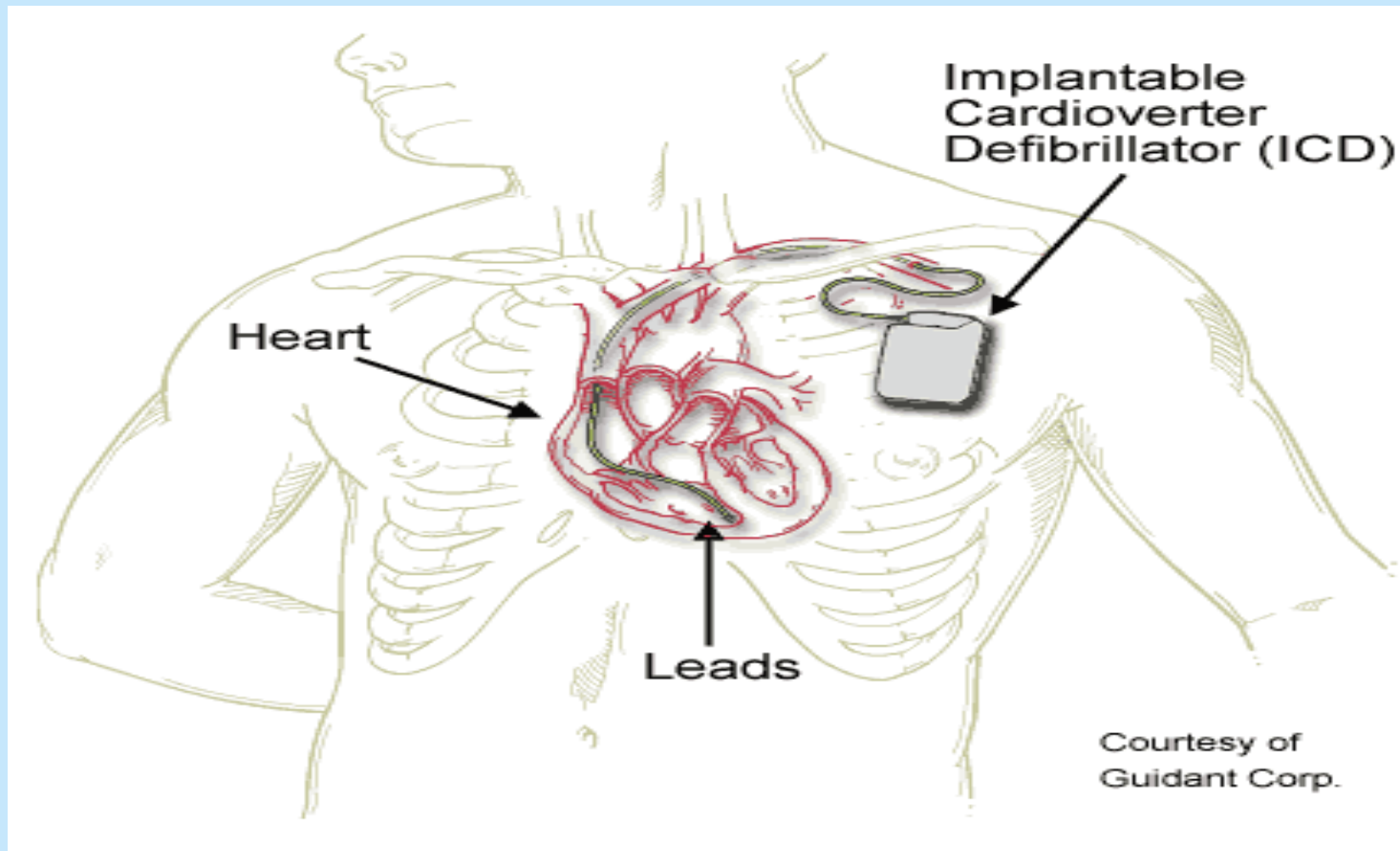
ATROPINE

- 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

