Antiarrhythmic Drugs

Assistant Prof. Dr. Najlaa Saadi
PhD Pharmacology
Faculty of Pharmacy
University of Philadelphia

- Cardiac arrhythmias occurring in
  25% of patients treated with digitalis
  50% of anesthetized patients
  80% of patients with acute myocardial infarction.
- Arrhythmias may require treatment because rhythms that are too rapid, too slow, or asynchronous can reduce cardiac output.
- Some arrhythmias can precipitate more serious or even lethal rhythm disturbances

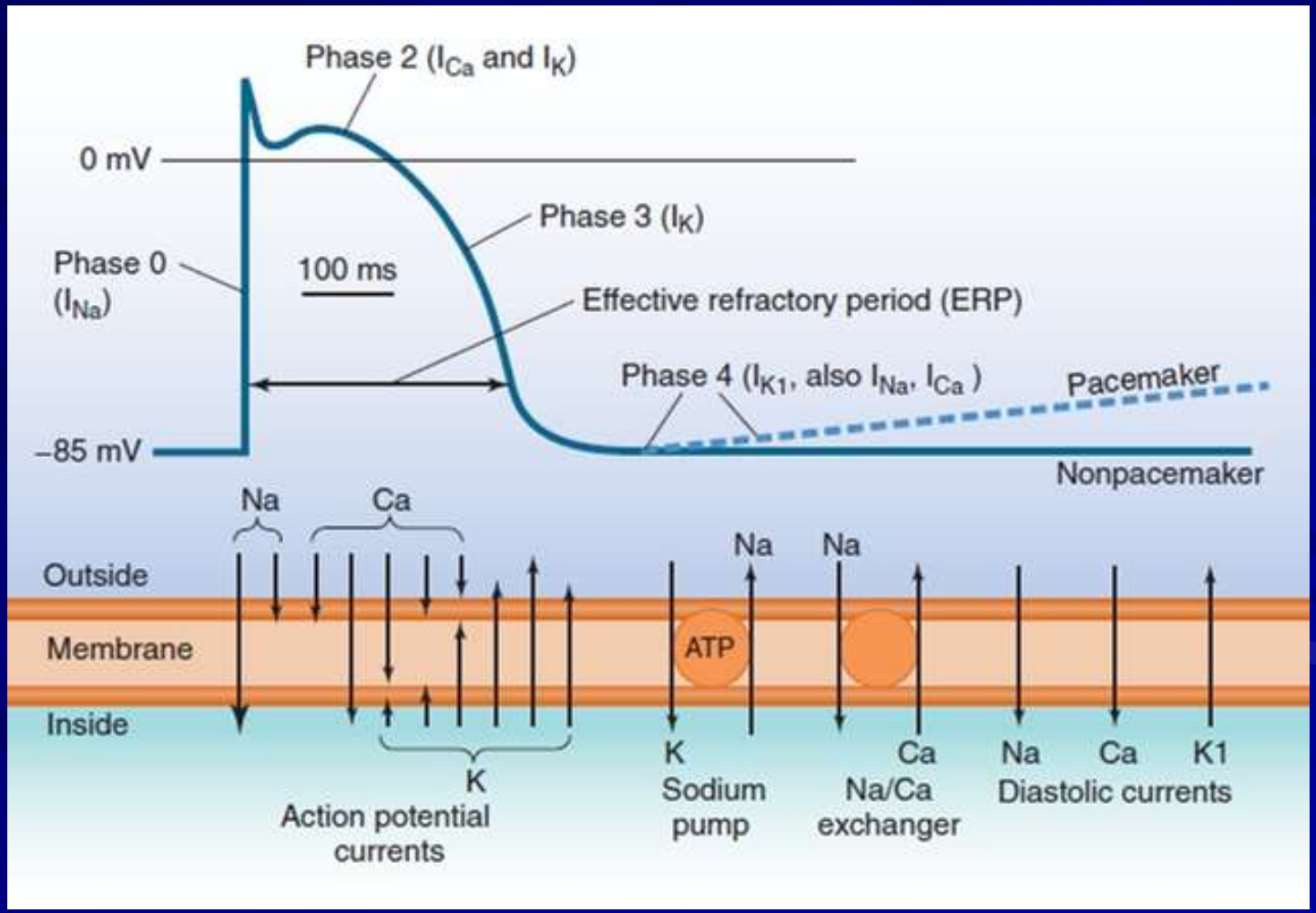
Normal Electrical Cardiac Function (Normal Sinus Rhythm)

- Is depended on generation of an impulse in the normal sinoatrial (SA) node pacemaker and its conduction through the atrial muscle, through the AV node, through the purkinje conduction system, to the ventricular muscle.
- Normal pacemaking and conduction require normal action potentials (depended on sodium, calcium and potassium channel activity) under appropriate autonomic control

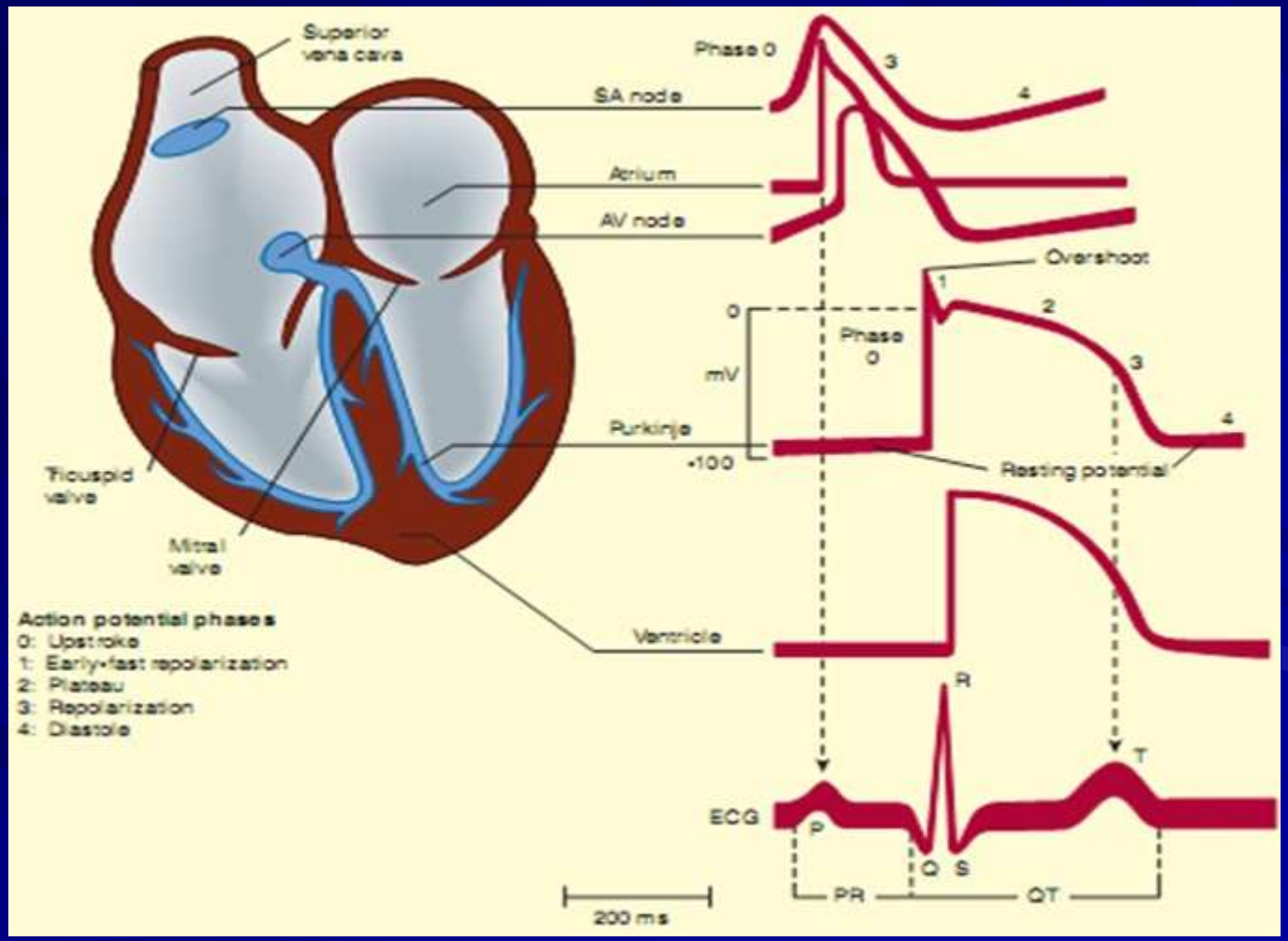
- Phases 0-3, are generated by several ionic currents.
- The actions of the sodium pump and sodium-calcium exchanger are mainly involved in maintaining ionic steady state during repetitive activity
- In most parts of the heart, sodium channel (I_{Na}) dominates phase 0 of the action potential (AP) and is the most important determinant of its conduction velocity.
- After a very brief activation, the sodium current enters a more prolonged period of inactivation.
- In the calcium-dependent AV node, calcium current (I_{Ca}) dominates the upstroke and the AP conduction velocity.

- The plateau of the AP (phase 2) is dominated by calcium current (I_{Ca}) and one or more potassium I_K - repolarizing currents .
- At the end of the plateau, I_K causes rapid repolarization (phase 3).
- Significant currents occur during diastole (phase 4) in addition to the pump and exchanger activity.
  - In non-pacemaker cells, the outward potassium current during phase 4 is sufficient to maintain a stable negative resting potential
  - In pacemaker cells, however, the potassium current is smaller and the depolarizing currents (sodium, calcium, or both) during phase 4 are large enough to gradually depolarize the cell during diastole

Components of the membrane action potential (AP) in a typical Purkinje or ventricular cardiac cell.



Schematic representation of the heart and normal cardiac electrical activity (intra cellular recording from areas indicated and ECG)

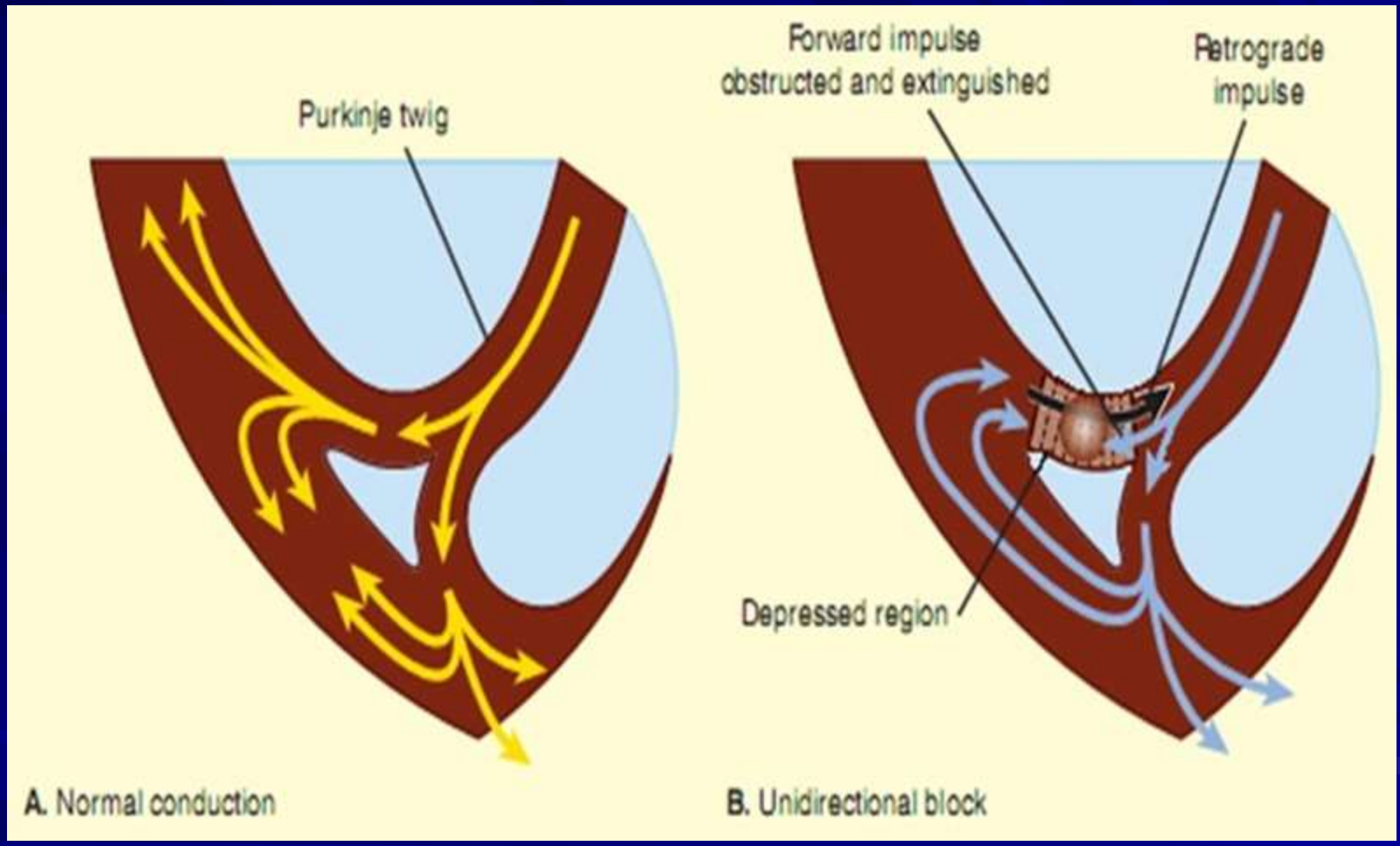


Many Factors Can Precipitate Arrhythmias:

- Ischemia
- Hypoxia
- Acidosis or alkalosis
- Anesthesia
- Electrolyte abnormalities
- Excessive catecholamine exposure
- Autonomic influences
- Drug toxicity (digitalis or antiarrhythmic drugs)

Mechanisms of Arrhythmias:

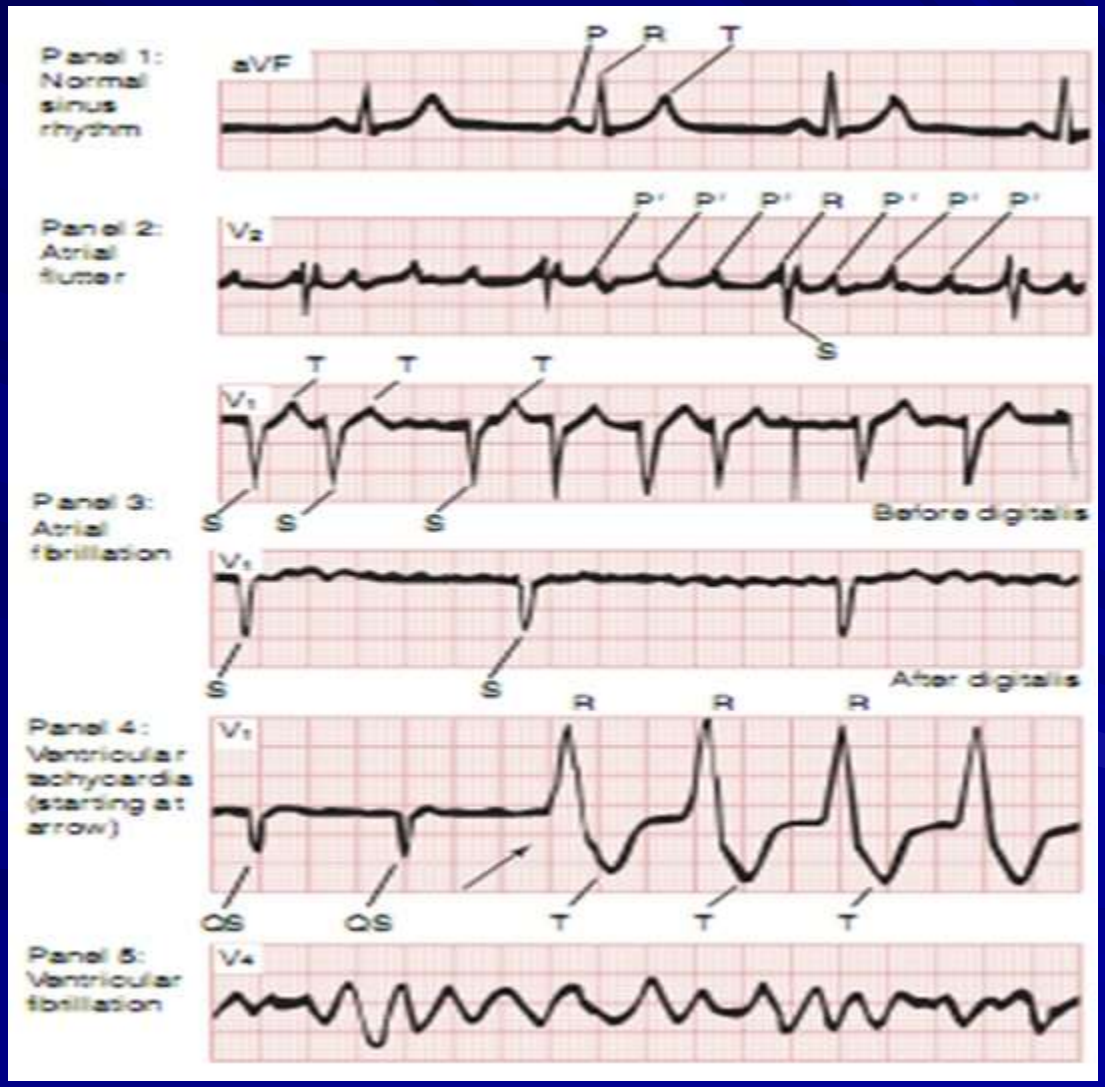
- Abnormal automaticity (pacemaker activity that originates anywhere other than in the sinoatial node)
- Abnormal conduction (conduction of an impulse that dose not follow the normal path or reenters tissue previously excited


Purkinje twig
A. Normal conduction
Forward impulse
obstructed and extinguished
Retrograde
impulse
Depressed region
B. Unidirectional block

Clinically Important Types of Arrhythmias are:

- Atrial flutter
- Atrial fibrillation
- Atrioventricular nodal reentry (a common type of supraventricular tachycardia SVT)
- Premature ventricular beats
- Ventricular tachycardia
- Ventricular fibrillations
- Torsades de pointes

Typical ECGs of normal sinus rhythm and some common arrhythmias



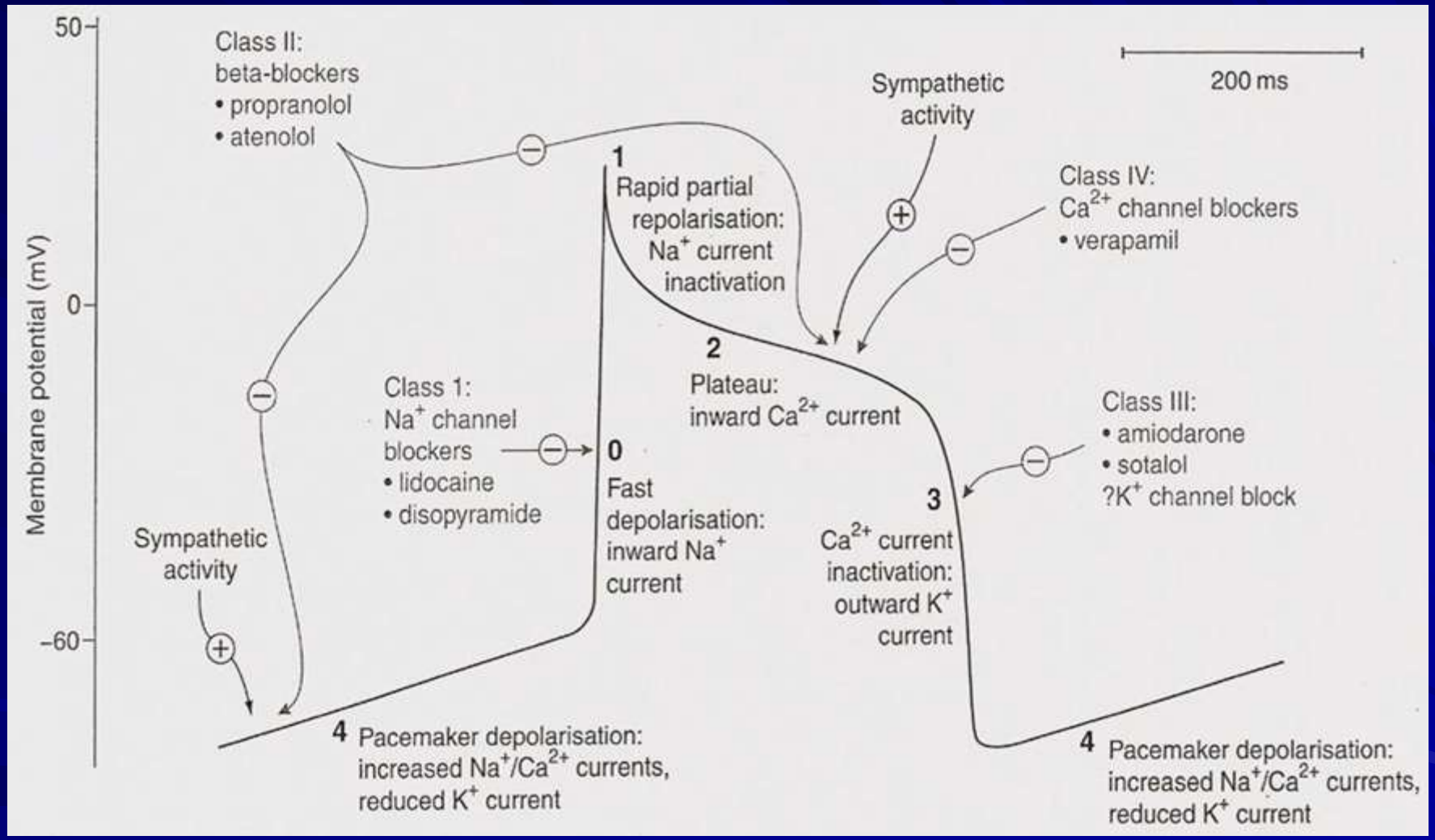
Torsades de Pointes:

- Is ventricular arrhythmia, it is induced by anti arrhythmic and other drugs that change the shape of the action potential and prolong the QT interval
- It has the ECG morphology of a polymorphic ventricular tachycardia
- A heritable abnormal prolongation of QT interval caused by mutations in the I_k or I_{Na} channel proteins

Classes of Antiarrhythmic Drugs:

- Class I: Sodium channel blocking agents
  Quinidine, procainamide, disopyramide,
  Lidocaine, tocainide and mexiletine
- Class II: Beta - adrenoceptor blocking drugs
- Class III: Drugs that prolong effective refractory period by prolonging action potential
  Bretylium, sotalol and amiodarone
- Class IV: Calcium channel blocking drugs

Other Antiarrhythmic Drugs: Cardiac glycosides, Adenosine


50
0
−60
Membrane potential (mV)
200 ms
Class II:
beta-blockers
• propranolol
• atenolol
Sympathetic activity
1
Rapid partial repolarisation: Na+ current inactivation
Class IV:
Ca2+ channel blockers
• verapamil
2
Plateau: inward Ca2+ current
Class 1:
Na+ channel blockers
• lidocaine
• disopyramide
0
Fast depolarisation: inward Na+ current
Class III:
• amiodarone
• sotalol
?K+ channel block
3
Ca2+ current inactivation: outward K+ current
Sympathetic activity
4 Pacemaker depolarisation: increased Na+/Ca2+ currents, reduced K+ current
4 Pacemaker depolarisation: increased Na+/Ca2+ currents, reduced K+ current

Class I (Sodium channel blockade):
Drugs with local anesthetic action block sodium channels and reduce the sodium current

- These drugs restrict the rapid inflow of Na during phase 0
- Slow the maximum rate of depolarization (membrane stabilizing activity)

Class I

The Drugs May be Subclassified as:

- Class IA: Drugs that lengthen action potential duration
  Quinidine, Disopyramide and Procainamide
- Class IB: Drugs that shorten action potential duration
  Lignocaine, Mexiletine, Tocaininde and Phenytoin
- Class IC: Drugs that have negligible effect on action potential duration
  Flecaininde and Propafenone.

Class IA

Procainamide

Mechanism of Action of Procainamide

- I_{Na} blockade (primary)
- I_K blockade (secondary)
- Slows conduction velocity and pacemaker rate
- Prolongs action potential duration
- Dissociates from I_{Na} channel with intermediate kinetics
- Direct depressant effects on sinoatrial (SA) and atrioventricular (AV) node

Class IA

Clinical Applications of Procainamide

- Most atrial and ventricular arrhythmias
- Sustained ventricular arrhythmias associated with acute myocardial infarction

Class IA

Pharmacokinetics of Procainamide

- Oral, IV, IM
- Eliminated by hepatic metabolism to N-acetylprocainamide (NAPA) and renal elimination

Class IA
Side Effects of Procainamide

- Cardiotoxic effects :excessive action potential prolongation, QT-interval prolongation and induction of torsades de pointes arrhythmia, syncope. Hypotension is usually associated with excessively rapid procainamide infusion.
- Syndrome resembling lupus erythematosus arthritis. pleuritis, pericarditis, or parenchymal pulmonary disease
- Serologic abnormalities (increased antinuclear antibody titer)
- Nausea and diarrhea, rash, fever and hepatitis

Class IA
Quinidine
Mechanism of Action of Quinidine

- Has actions similar to those of procainamide, it slows the upstroke of the action potential, slows conduction, prolongation of the QRS duration of the ECG

Class IA

Quinidine

Pharmacokinetics:

- It is readily absorbed from the GI tract and eliminated by hepatic metabolism.

Therapeutic Use:

- It is rarely used because of cardiac and extracardiac adverse effects and the availability of better-tolerated antiarrhythmic drugs.

Class IA

Side Effects of Quinidine

- Diarrhea, nausea and vomiting
- Syndrome of Headache, Dizziness Tinnitus (Cinchonism)
- Hypersensitivity, fever, rash and angioedema.
- Thrombocytopenia.
- Prolongs the action potential duration by blockade of several potassium channels. Its toxic cardiac effects include excessive QT-interval prolongation and induction of torsades de pointes arrhythmia

Class IA

Disopyramide

- Similar to procainamide but significant antimuscarinic effects
- may precipitate heart failure; not commonly used

Class IB

Lidocaine

Mechanism of Action of Lidocaine

- Sodium channel (I_{Na}) blockade
- Blocks activated and inactivated channels with fast kinetics
- Does not prolong and may shorten action potential

Class IB

Lidocaine

- It is used in ventricular tachycardias
- Prevent ventricular fibrillation after cardioversin

Class IB

Lidocaine

- IV
- First-pass hepatic metabolism
- Reduce dose in patients with heart failure or liver disease

Side Effects of Lidocaine:

- Neurologic symptoms
- Hypotension

Class IB

Mexiletine:

Orally active congener of lidocaine; used in ventricular arrhythmias

Class IC
Flecainide

- Sodium channel (I_{Na}) blockade
- Dissociates from channel with slow kinetics
- No change in action potential duration

Class IC
Flecainide

- It is used in Supraventricular arrhythmias in patients with normal heart
- Do not use in ischemic conditions (post-myocardial infarction)

Class IC

Flecainide

- Oral
- Hepatic and kidney eliminatioin
- Half life ~ 20 h

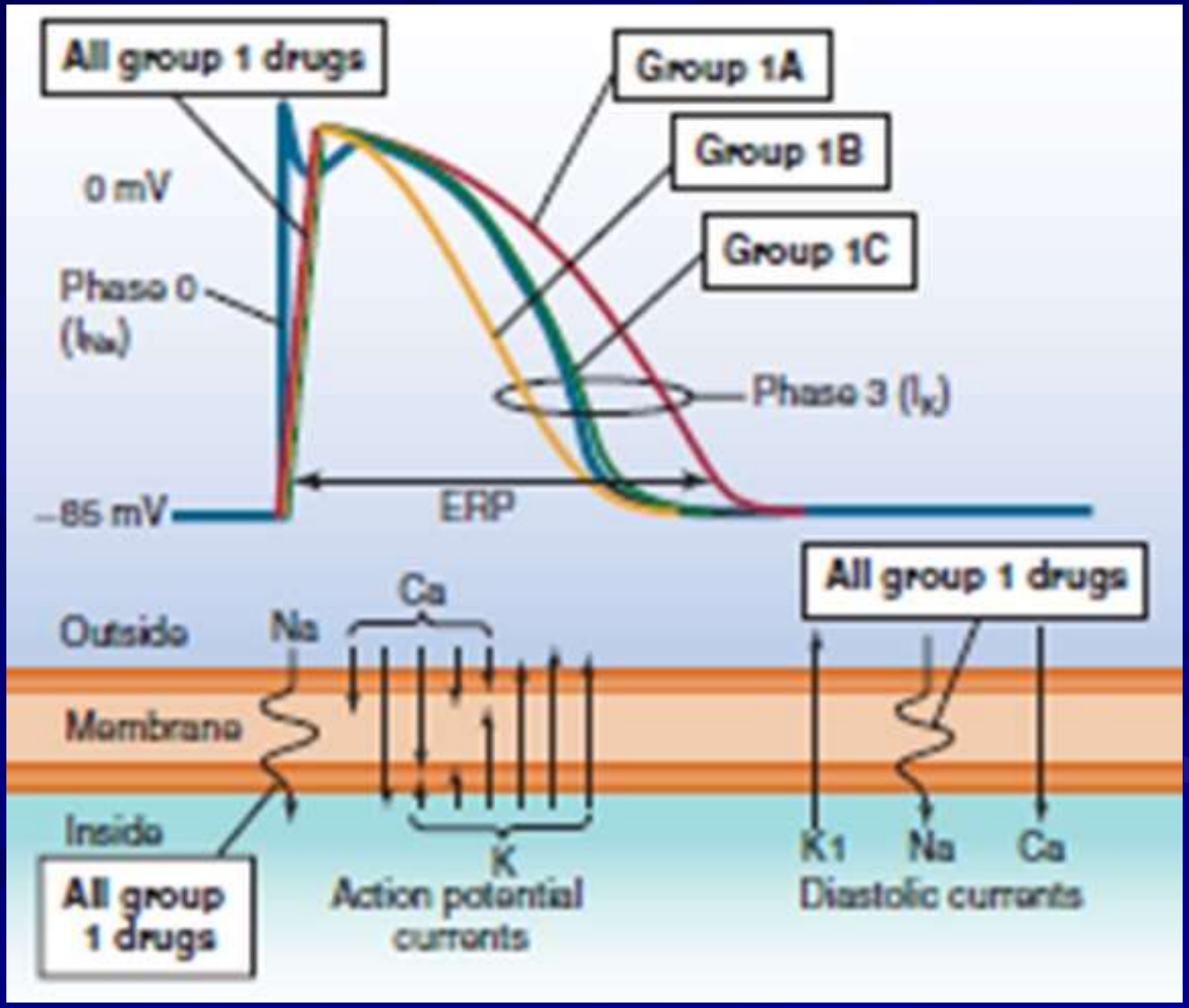
Side Effects of Flecainide

- Cardiac failure
- Ventricular arrhythmias
- Blurred vision
- Paraesthesia
- Metalic taste

The Effects of Class I Agents.

- All group 1 drugs reduce both phase 0 and phase 4 sodium currents in susceptible cells.
- Group 1A drugs also reduce phase 3 potassium current (I_K) and prolong the action potential (AP) duration. This results in significant prolongation of the effective refractory period (ERP).
- Group 1B and group 1C drugs have different (or no) effects on potassium current and thus shorten or have no effect on the AP duration.
- All group 1 drugs prolong the ERP by slowing recovery of sodium channels from inactivation.

The Effects of Class I Agents



Class II
β-Adrenoceptor Blockade

- Propranolol and similar drugs have antiarrhythmic properties by their β-receptor-blocking action and direct membrane effects.
- Their efficacy for suppression of ventricular ectopic depolarizations is lower than that of sodium channel blockers.
- These agents can prevent recurrent infarction and sudden death in patients recovering from acute myocardial infarction

Class II

Propranolol

- β-Adrenoceptor Blockade
- Direct membrane effects (sodium channel block)
- Prolongation of action potential duration
- Slows SA node automaticity and AV nodal conduction velocity

Class II

Propranolol

- Oral, parenteral
- Duration 4-6 h

Side Effects :

Asthma, AV blockade, acute heart failure

Interactions:

With other cardiac depressants and hypotensive drugs

Esmolol

- IV only
- Short-acting β blocker used primarily as an antiarrhythmic
- Drug for intraoperative and other acute arrhythmias.

Class III

Amiodarone

- Blocks I_K, I_{Na}, I_{Ca} -L channels, β adrenoceptors
- Prolongs action potential duration and QT interval, slows heart rate and AV node conduction, low incidence of torsades de pointes

Class III

Amiodarone

- Its clinical applications in Serious ventricular arrhythmias and supraventricular arrhythmias

Class III

Amiodarone

- Oral, IV, large V_d
- Hepatic metabolism, elimination complex and slow

Side Effects:

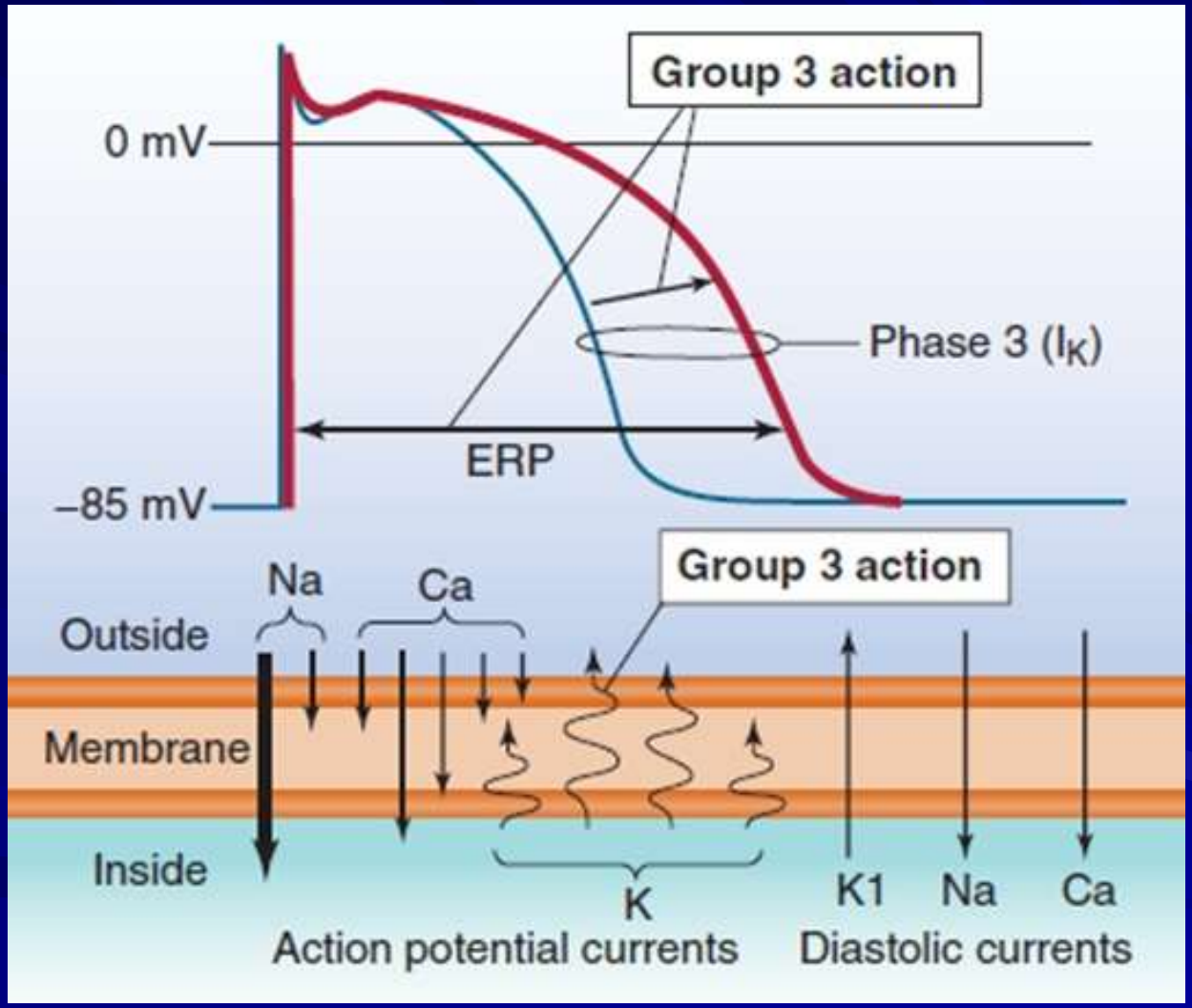
- Bradycardia and heart block
- Photosensitive rashes
- Gery/blue discoloration of skin
- Pulmonary fibrosis
- Hyper- or hypothyroidism
- CNS and GIT side effect

Interactions: Many, based on CYP metabolism

The Effects of Class III Agents

- All class3 drugs prolong the AP duration in susceptible cardiac cells by reducing the outward (repolarizing) phase 3 potassium current (I_K).
- The main effect is to prolong the effective refractory period (ERP).
- The phase 4 diastolic potassium current (I_{K1}) is not affected by these drugs.

The Effects of Class III Agents

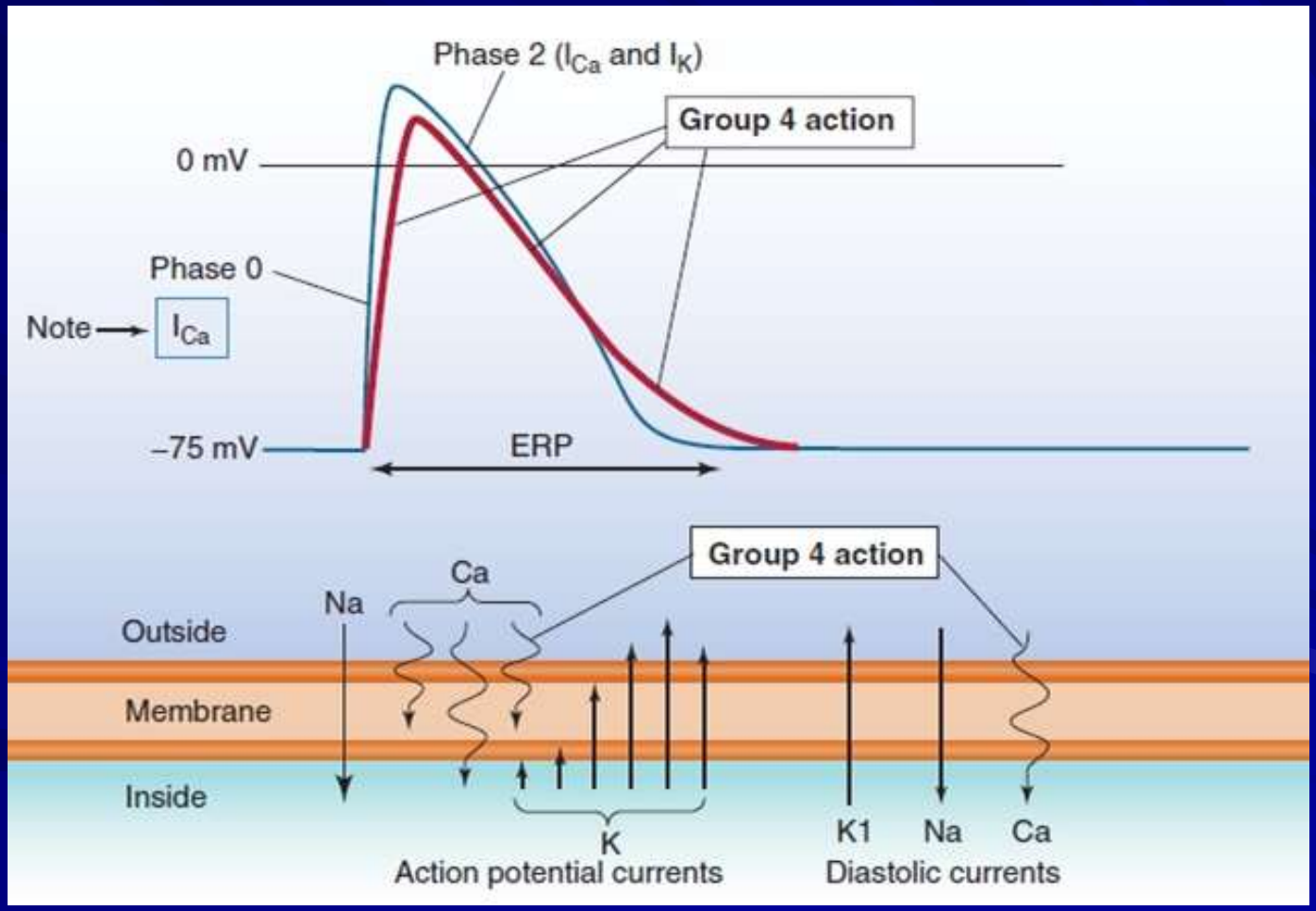


Class IV Drugs
(Ca+2 Channel Blockers)

- Verapamil and diltiazem also have antiarrhythmic effects.
- The dihydropyridines (eg, nifedipine) do not share antiarrhythmic efficacy and may precipitate arrhythmias.

- Class IV drugs reduce inward calcium current during the AP and during phase 4 conduction velocity is slowed in the AV node and refractoriness is prolonged.
- Pacemaker depolarization during phase 4 is slowed as well it caused by excessive calcium current

Schematic diagram of the effects of group **IV** drugs in a calcium-dependent cardiac cell in the AV node (note that the AP upstroke in this figure is due mainly to calcium current)



Class IV Drugs
(Ca+2 Channel Blockers)

- Verapamil blocks L-type calcium channels.
- AV nodal conduction time and effective refractory period are consistently prolonged by therapeutic concentrations.
- Verapamil usually slows the SA node by its direct action, but its hypotensive action may occasionally result in a small reflex increase of SA rate.
- Verapamil can induce AV block when used in large doses or in patients with AV nodal disease.

Diltiazem

- It appears to be similar in efficacy to verapamil in the management of supraventricular arrhythmias, including rate control in atrial fibrillation.

Miscellaneous Drugs

Digoxin

- Shortens the refractory period in atrial and ventricular myocardial cells
- Prolonging the refractory period and diminishing conduction velocity in the AV node.
- Digoxin is used to control the ventricular response rate in atrial fibrillation and flutter.
- At toxic concentrations, digoxin causes ectopic ventricular beats that may result in ventricular tachycardia and fibrillation.

Note: This arrhythmia is usually treated with lidocaine or phenytoin.

Adenosine

- Is a nucleoside that occurs naturally throughout the body.
- Its half-life in the blood is less than 10 seconds.
- Its mechanism of action involves activation of an inward K + current and inhibition of calcium current. The results of these actions are marked hyperpolarization and suppression of calcium-dependent action potentials.

- It is usually given in a bolus dose of 6 mg followed, if necessary, by a dose of 12 mg.
- The drug is less effective in the presence of adenosine receptor blockers such as theophylline or caffeine,

- When given as a bolus dose, adenosine directly inhibits AV nodal conduction and increases the AV nodal refractory period but has lesser effects on the SA node.

Magnesium

- Magnesium therapy appears to be indicated in patients with digitalis-induced arrhythmias with hypomagnesemia and also indicated in some patients with torsades de pointes even if serum magnesium is normal.
- Magnesium infusion has been found to have antiarrhythmic effects in some patients with normal serum magnesium levels.
- Magnesium is influence Na+/K+ -ATPase, sodium channels, certain potassium channels and calcium channels

Potassium

- Potassium therapy appears to be indicated in patients with digitalis-induced arrhythmias with hypokalemia
- Potassium depresses ectopic pacemakers and slows conduction.

Properties of the prototype antiarrhythmic drugs.

Drug	Group	PR Interval	QRS Duration	QT Interval
Procainamide, disopyramide, quinidine	1A	↑ or ↓[a]	↑↑	↑↑
Lidocaine, mexiletine	1B	—	—[b]	—, ↓[c]
Flecainide	1C	↑ (slight)	↑↑	—
Propranolol, esmolol	2	↑↑	—	—
Amiodarone	3, 1A, 2, 4	↑	↑↑	↑↑↑↑
Ibutilide, dofetilide	3	—	—	↑↑↑
Sotalol	3, 2	↑↑	—	↑↑↑
Verapamil	4	↑↑	—	—
Adenosine	Misc	↑↑↑	—	—