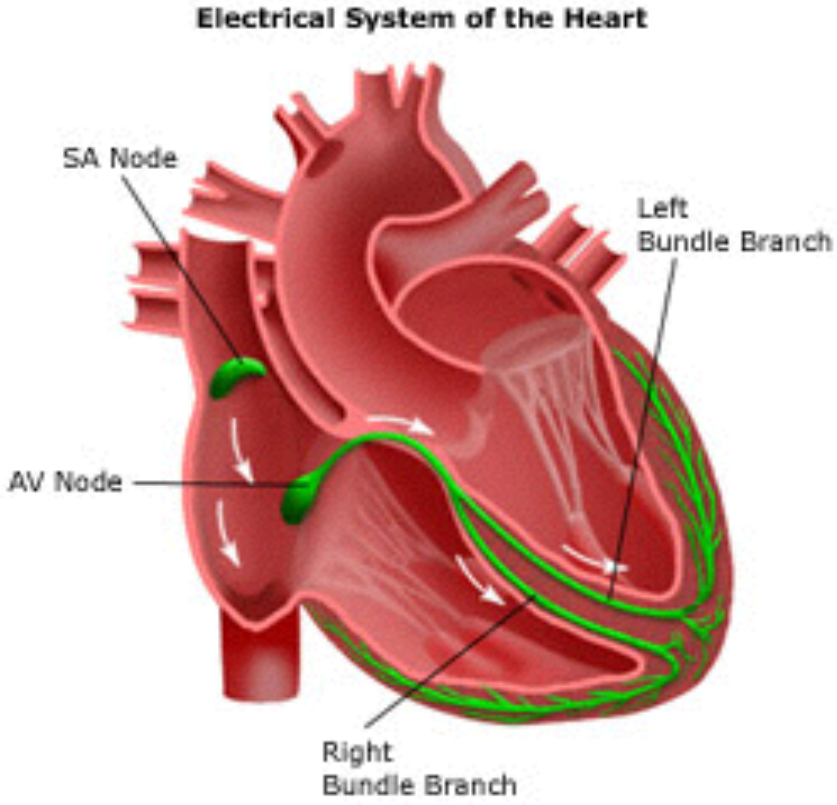
Anti-arrhythmic Drugs

Dr. Alia Shatanawi



Cardiac Arrhythmias

- Definition.
- Etiology:
- Hereditary
- Acquired
- Types:
- Abnormalities of Impulse Formation:
- Rate disturbances.
- Triggered automaticity.
- Abnormalities of Impulse Conduction:
- Blocks.
- Reentry.

Cardiac Arrhythmias

1. Disorders of rate, rhythm, electrical impulse generation or conduction in the heart.
2. Disorders can range from benign to life threatening.
3. Anti-arrhythmic drugs alter movement of ions in cardiac cells.
4. All these drugs can aggravate or generate arrhythmias.

Cardiac Causes of Arrhythmias

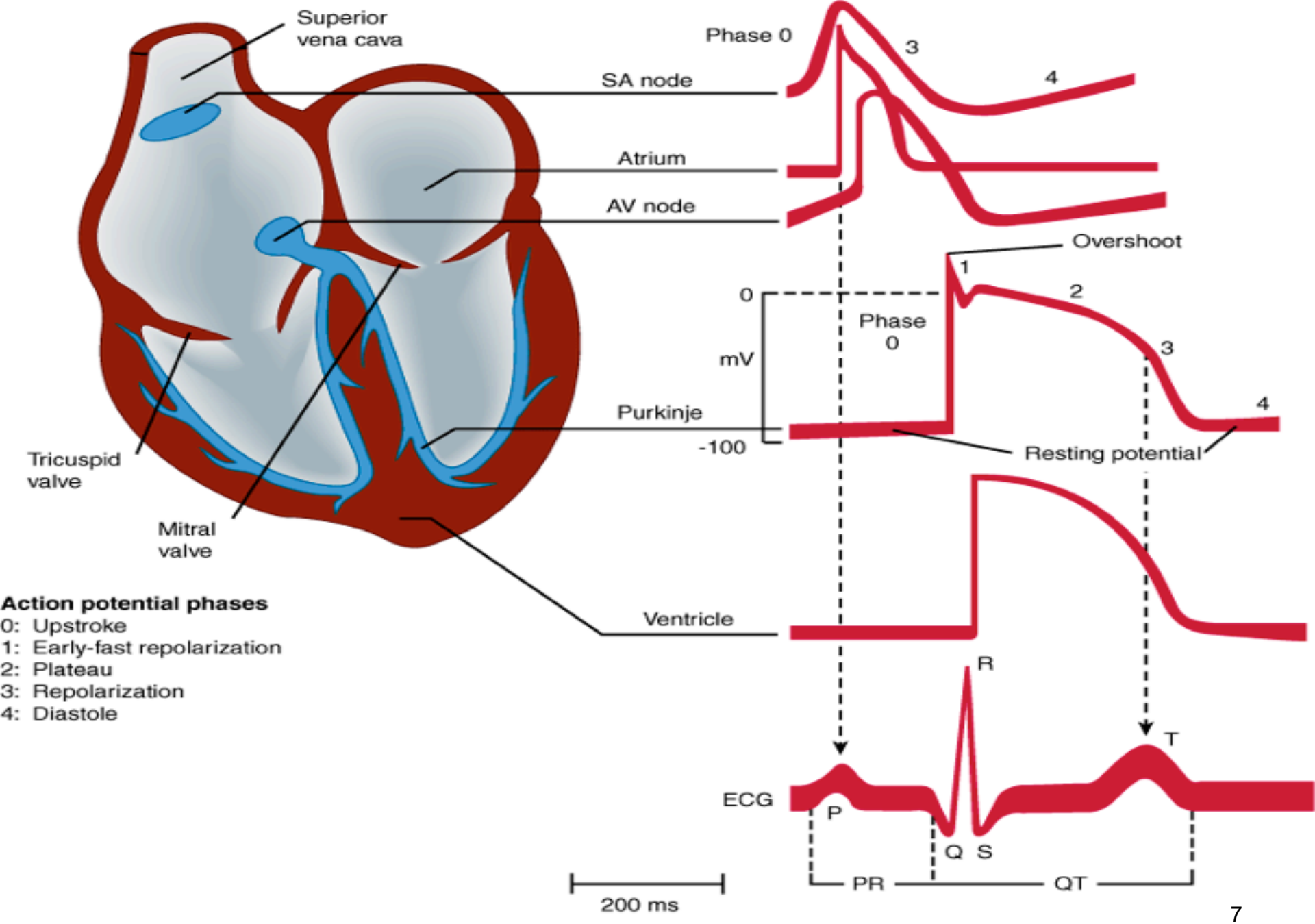
- Electrolyte imbalance.
- Acid-Base imbalance.
- Hypoxia.
- Drugs:
  - Digitalis
  - Anesthetics
  - Tricyclic
  - Diuretics
- Bronchodilators: sympathomimetic.
- Reflexes.

Non Cardiac Causes of Arrhythmias

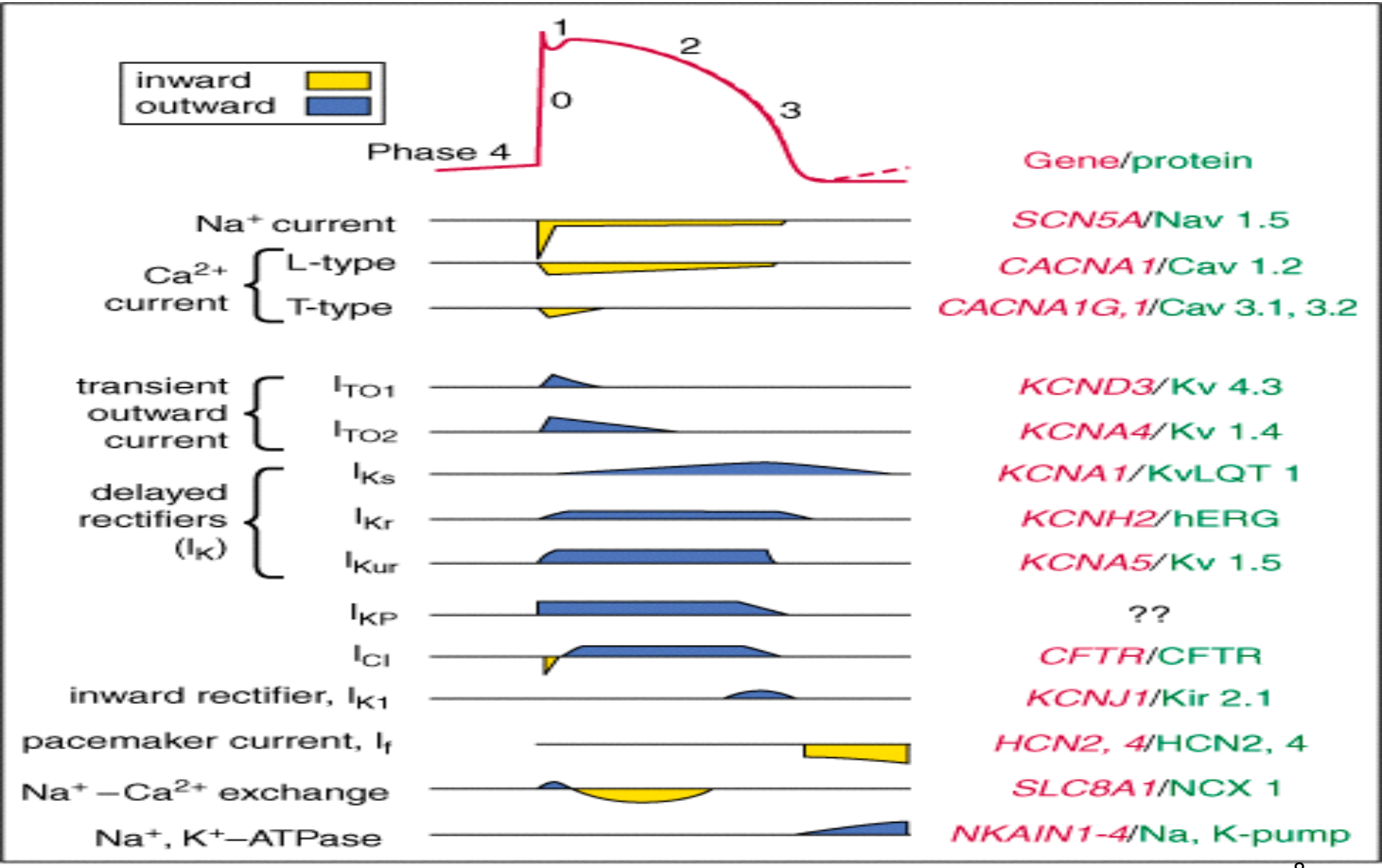
- Ischemic heart disease.
- Inflammation.
- Trauma e.g. heart surgery.
- Congestive heart failure.
- Hypotension.
- Electrolyte imbalance.
- Acid-Base imbalance.

Electrical Activity of the Heart

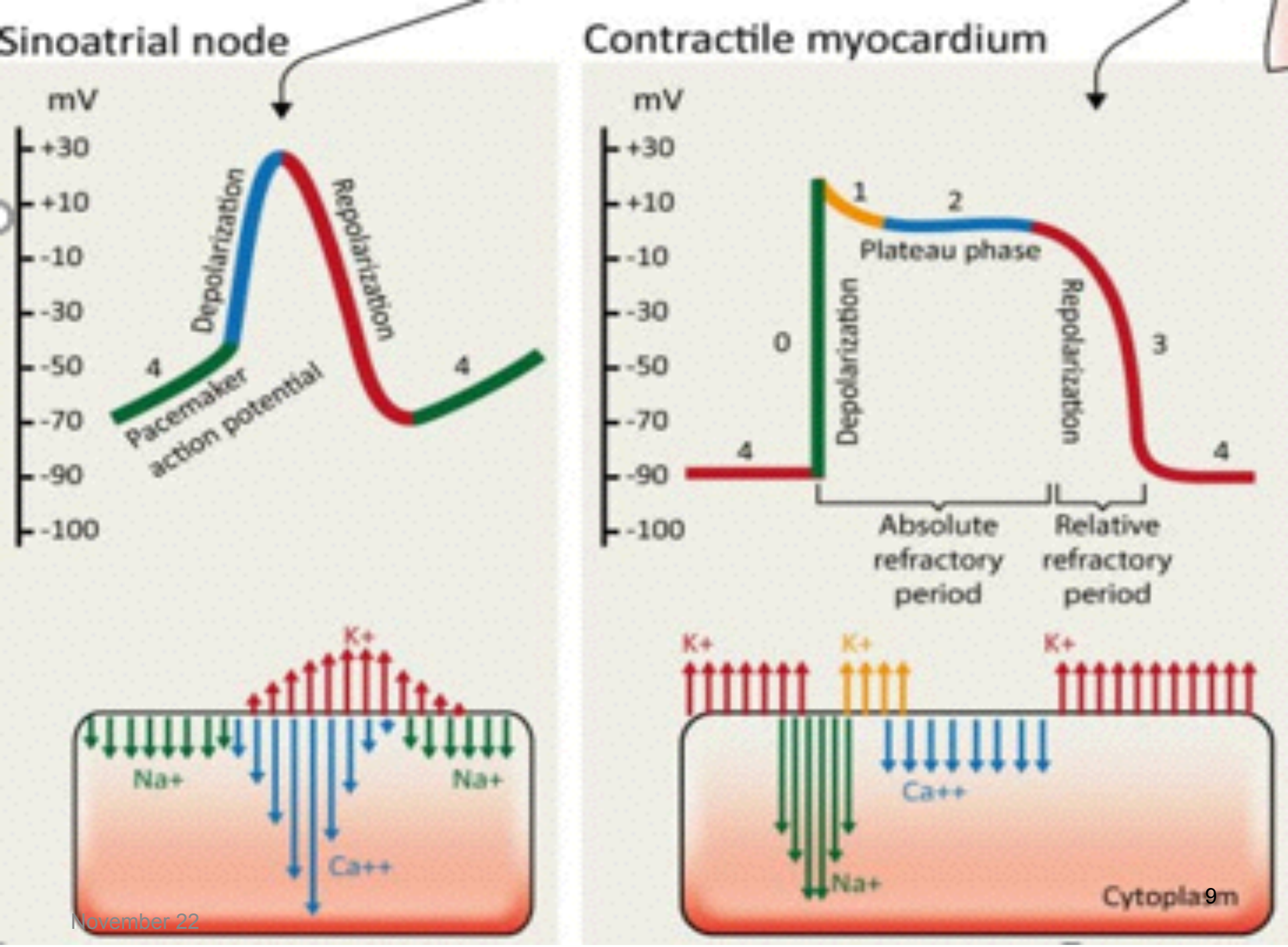
- Cardiac cells undergo depolarization and repolarization to initiate cardiac action potentials: 60 times/ minute.
- The shape and duration of each action potential are determined by the activity of ion channel protein complexes in the membranes of individual cells.
- Ion channel function can be disrupted by inherited mutation/polymorphism, acute ischemia, sympathetic stimulation, or myocardial scarring, to create arrhythmias.



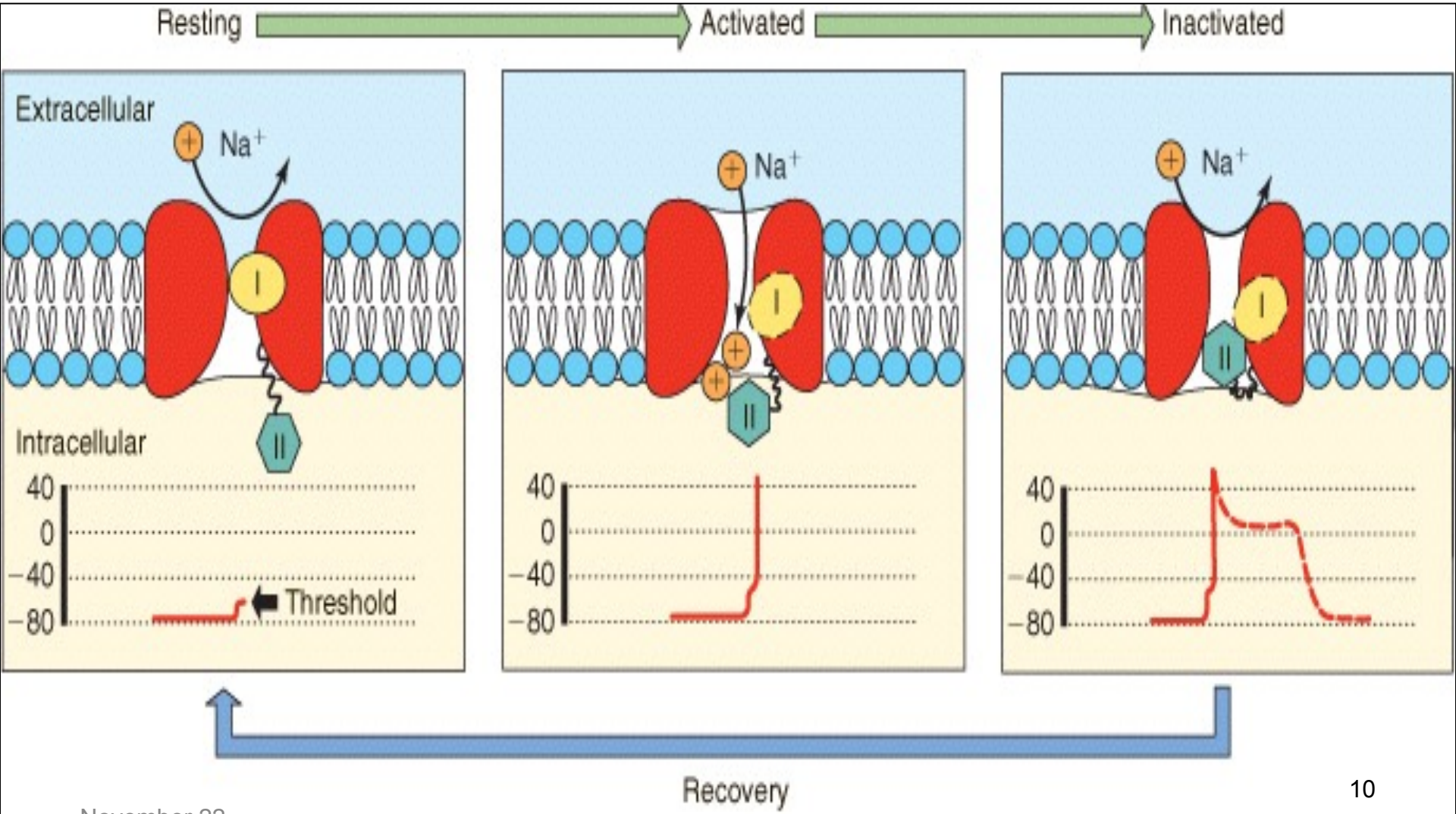
Action potential phases
0: Upstroke
1: Early-fast repolarization
2: Plateau
3: Repolarization
4: Diastole



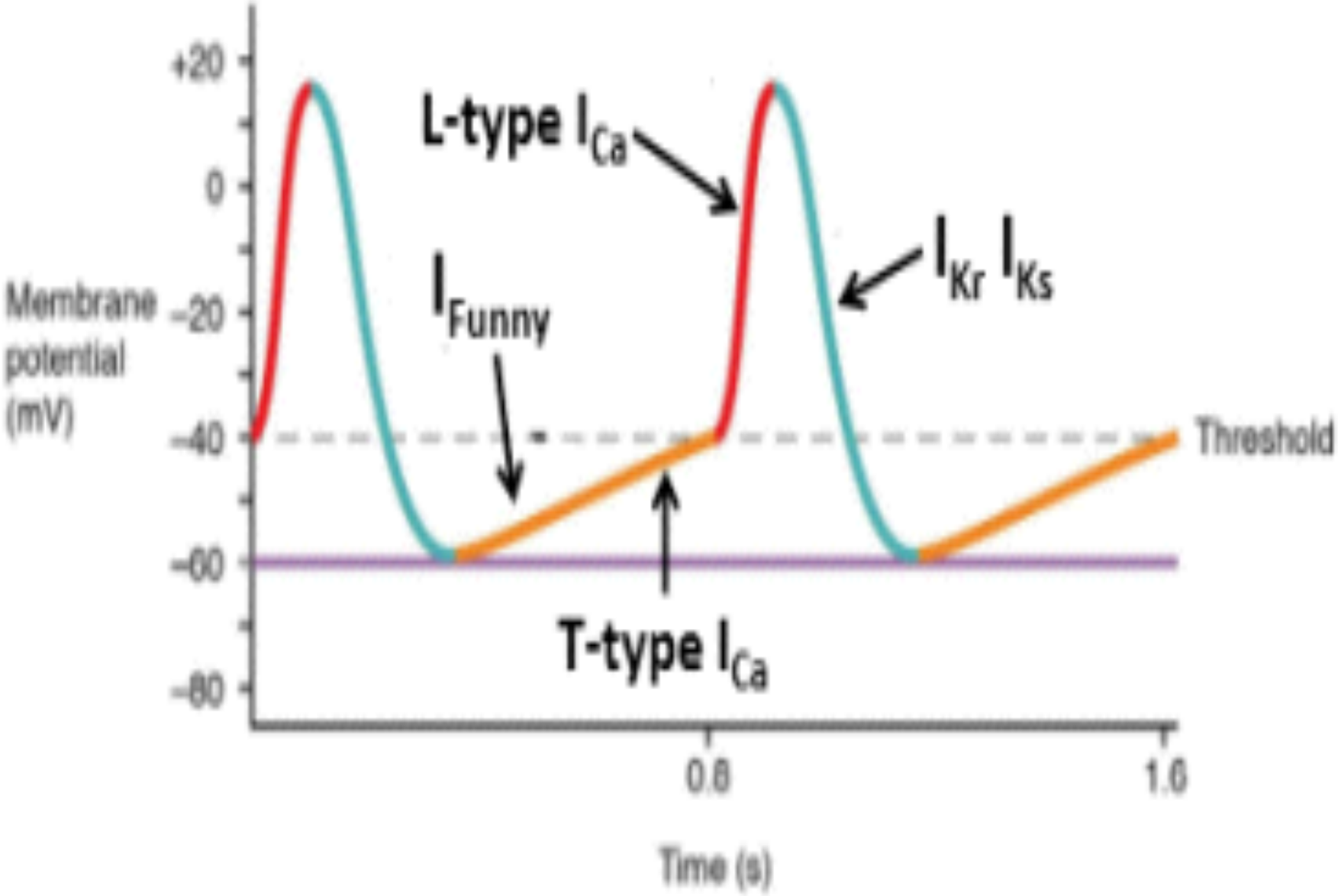
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com


Sinoatrial node
mV
+30
+10
-10
-30
-50
-70
-90
-100
Depolarization
Repolarization
4
4
Pacemaker
action potential
Contractile myocardium
mV
+30
+10
-10
-30
-50
-70
-90
-100
1
2
Plateau phase
0
Depolarization
Repolarization
3
4
4
Absolute
refractory
period
Relative
refractory
period
K+
Na+
Na+
Ca++
K+
K+
K+
Ca++
Na+
Cytoplasm

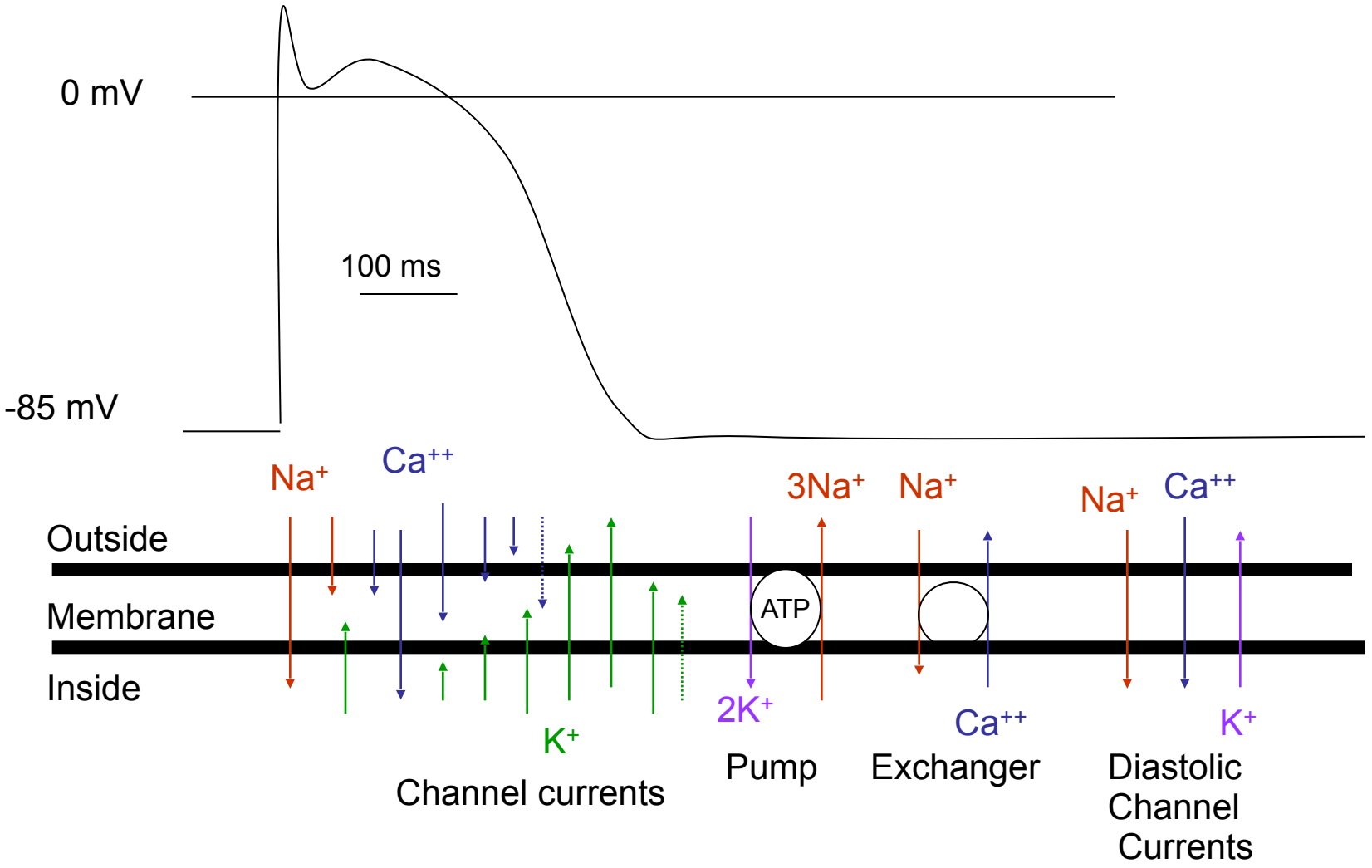
Cardiac Na+ channels



SA node automaticity



Action Potential

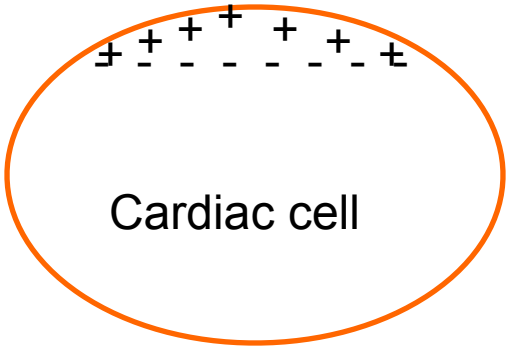


Cardiac Electrophsiology

- **A. Resting Membrane Potential (RMP)** - A voltage difference (about -90 mV) exists across the surface membrane of all cardiac cells due to uneven distribution of ions. This is created primarily by active cell membrane transport of Na+ (3 out) and K+ (2 in) by Na+, K+-ATPase.
-
- **B. Action Potential (AP)** - When cardiac cells are electrically excited, a sequence of voltage changes (depolarization and repolarization) occur as a function of time. These changes in voltage are due to changes in conductance of ions (mainly Na+, Ca++, and K+) across the cell membrane.

Distribution of ions at rest [mM]

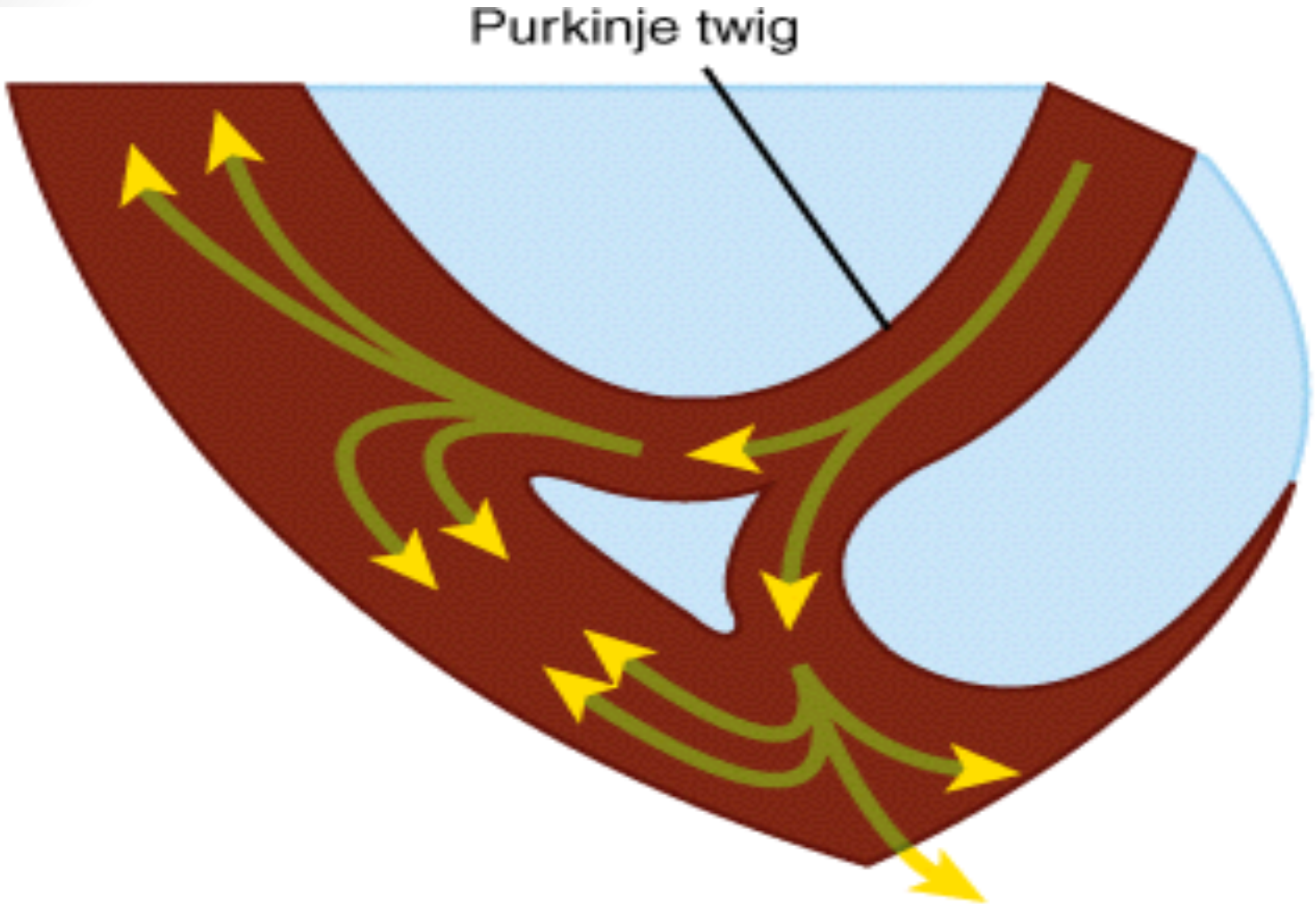
Ion	Intracellular	Extracellular
Na^+	10	145
K^+	140	4
Cl^-	4	115
Ca^{++}	<0.001	2



Action Potential

- Phase 0: rapid depolarization due to influx of Na^+ via voltage dependent sodium channels.
- Phase 1: partial repolarization due to inactivation of Na^+ channels
- Phase 2: plateau from slow Ca^{2+} influx via L-type voltage sensitive Ca^{2+} channels
- Phase 3: replolaization due to inactivation of Ca^{2+} and efflux of K^+ due to activation of K^+ channels
- Phase 4: (the pacemaker potential) inward movement of Na^+ and Ca^{2+}

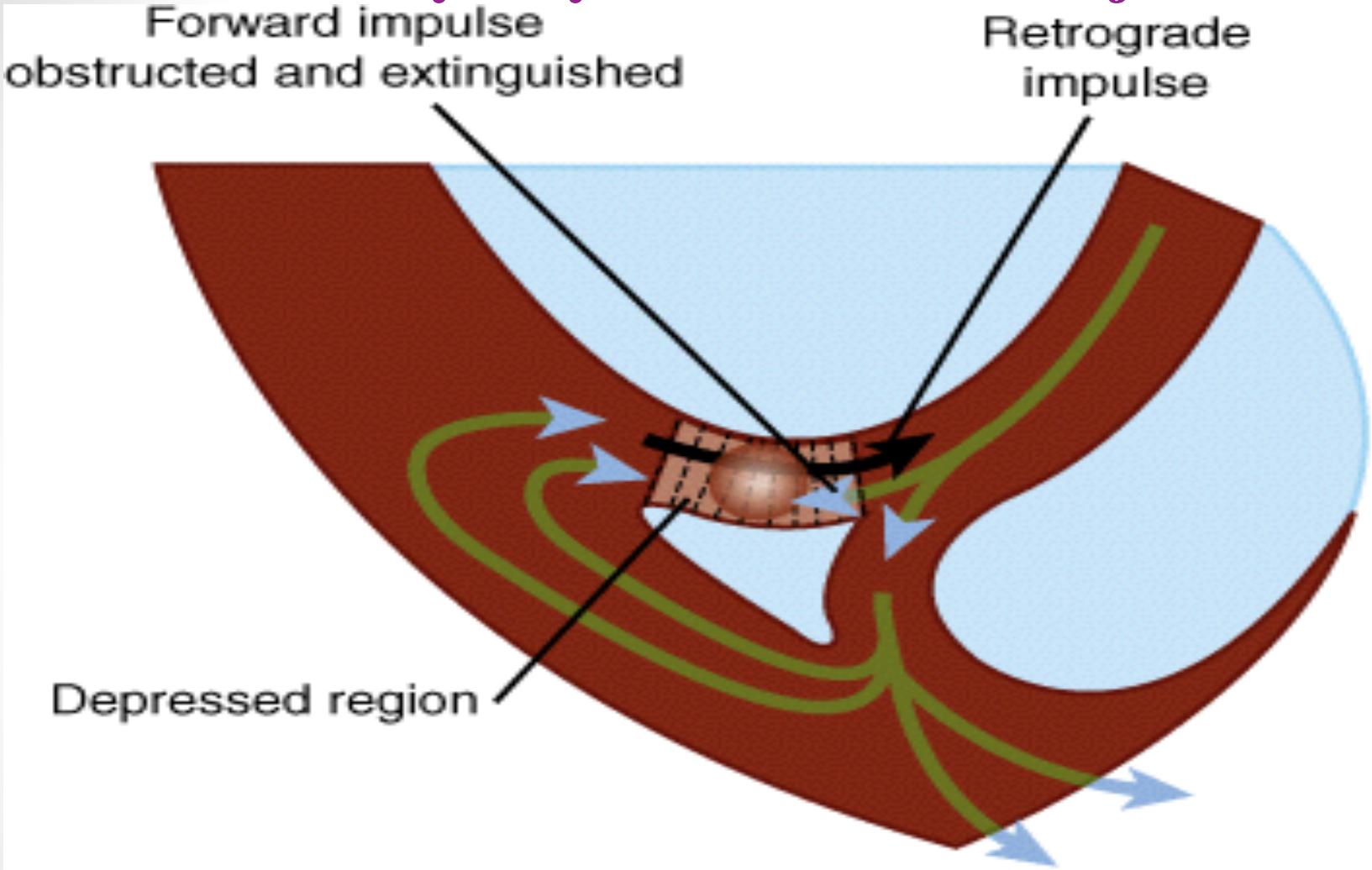
Normal Circuitry at peripheral Purkinje fiber



A. Normal conduction

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

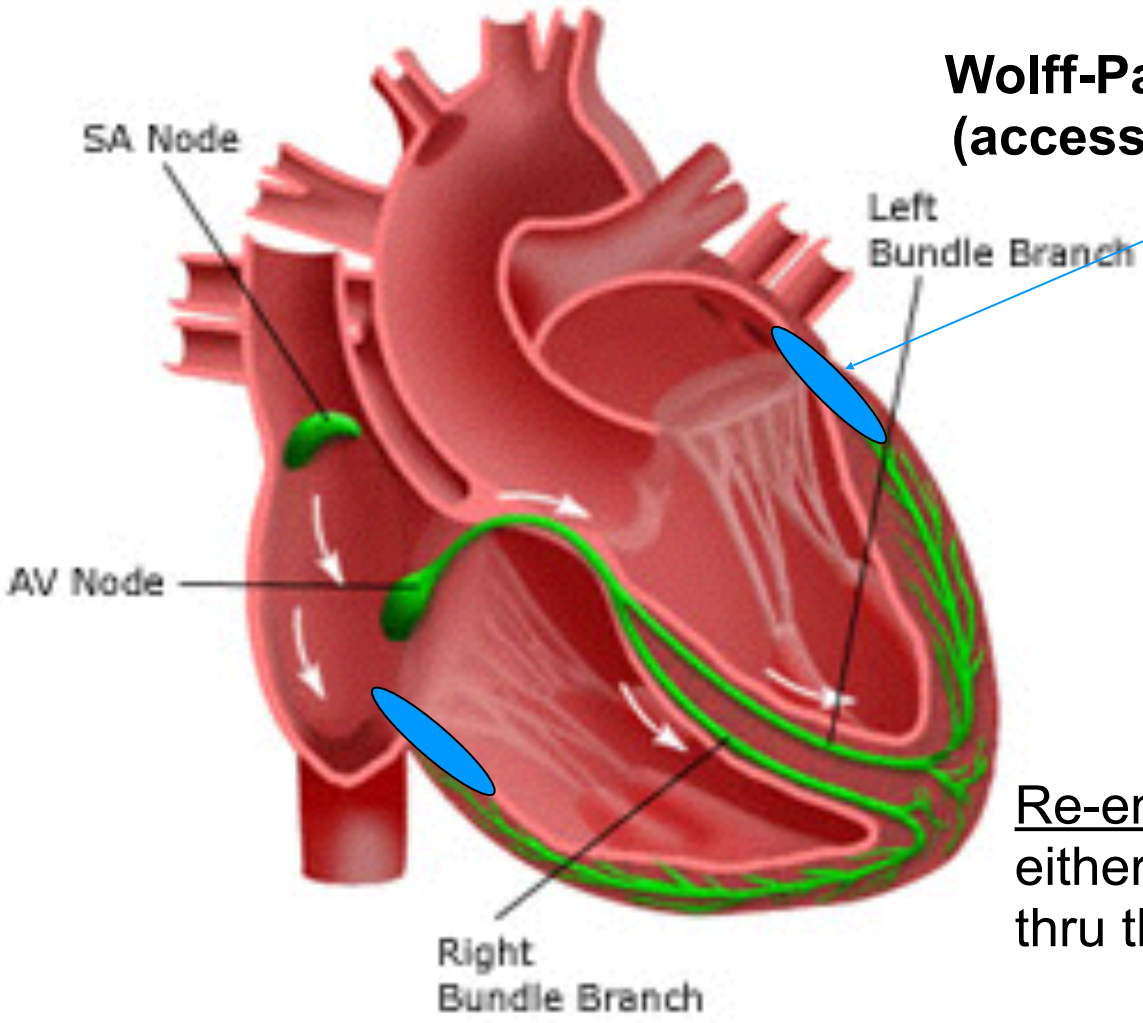
Re-entry Rhythm at the Purkinje fiber



B. Unidirectional block

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Electrical System of Heart



Wolff-Parkinson-White syndrome
(accessory conduction pathway)
bundle of Kent

<u>Re-entry arrhythmias-</u>
either antegrade conduction
thru the node or the bypass tract

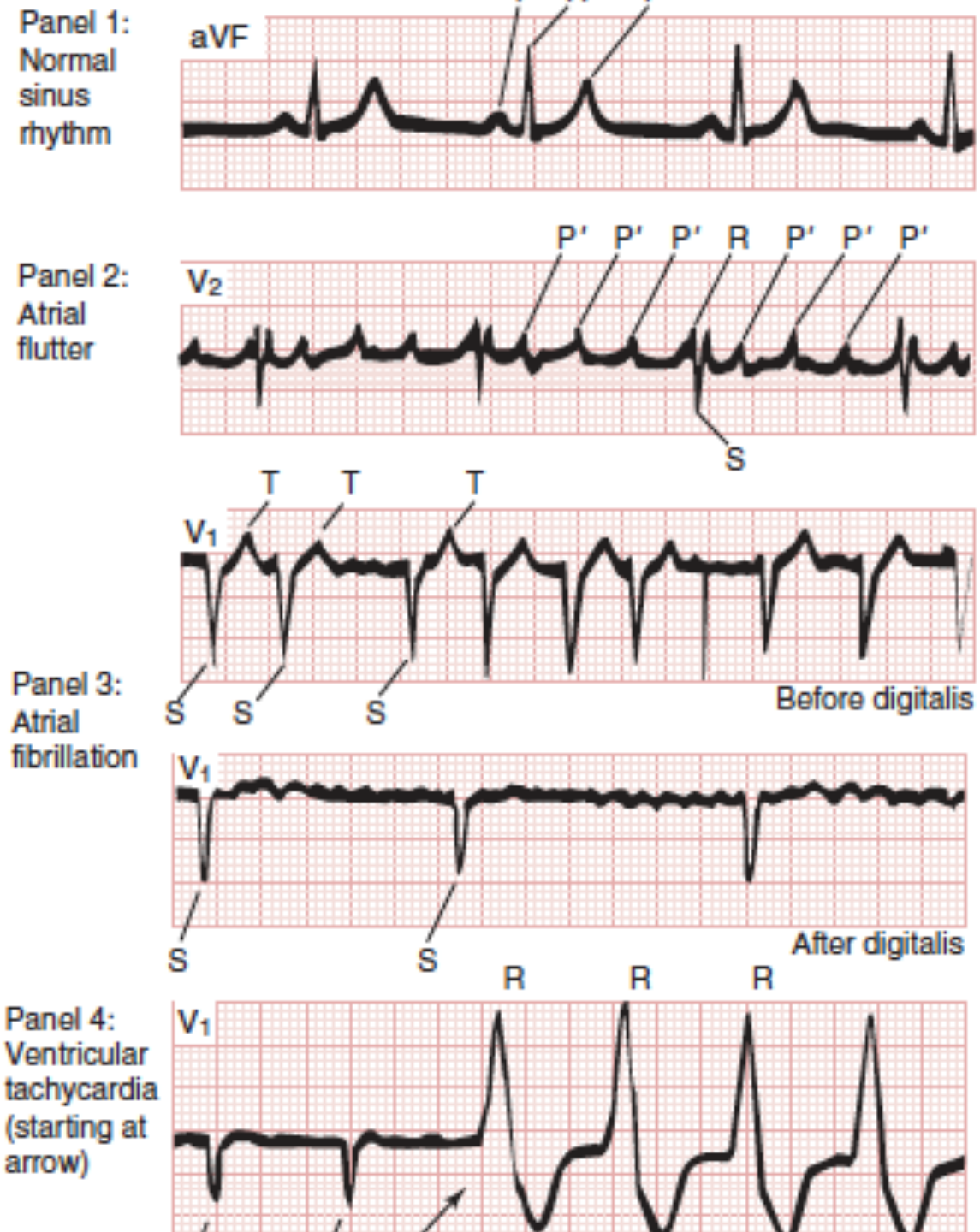
Pre-requisites for Reentry (Circus Movement)

Anatomic or physiologic obstacle.

Unidirectional block.

Conduction time around the circuit must be longer than the effective refractory period.

ECG of some Arrhythmias



Torsade de Pointes
Polymorphic Ventricular Tachycardia

LQT, syncope, and sudden death.

Causes:

- **Familial long QT interval**
- **Drug - Induced (drugs which prolong APD).**
- **Genetic mutations: 300 different mutations in at least 8 ion channel genes.**

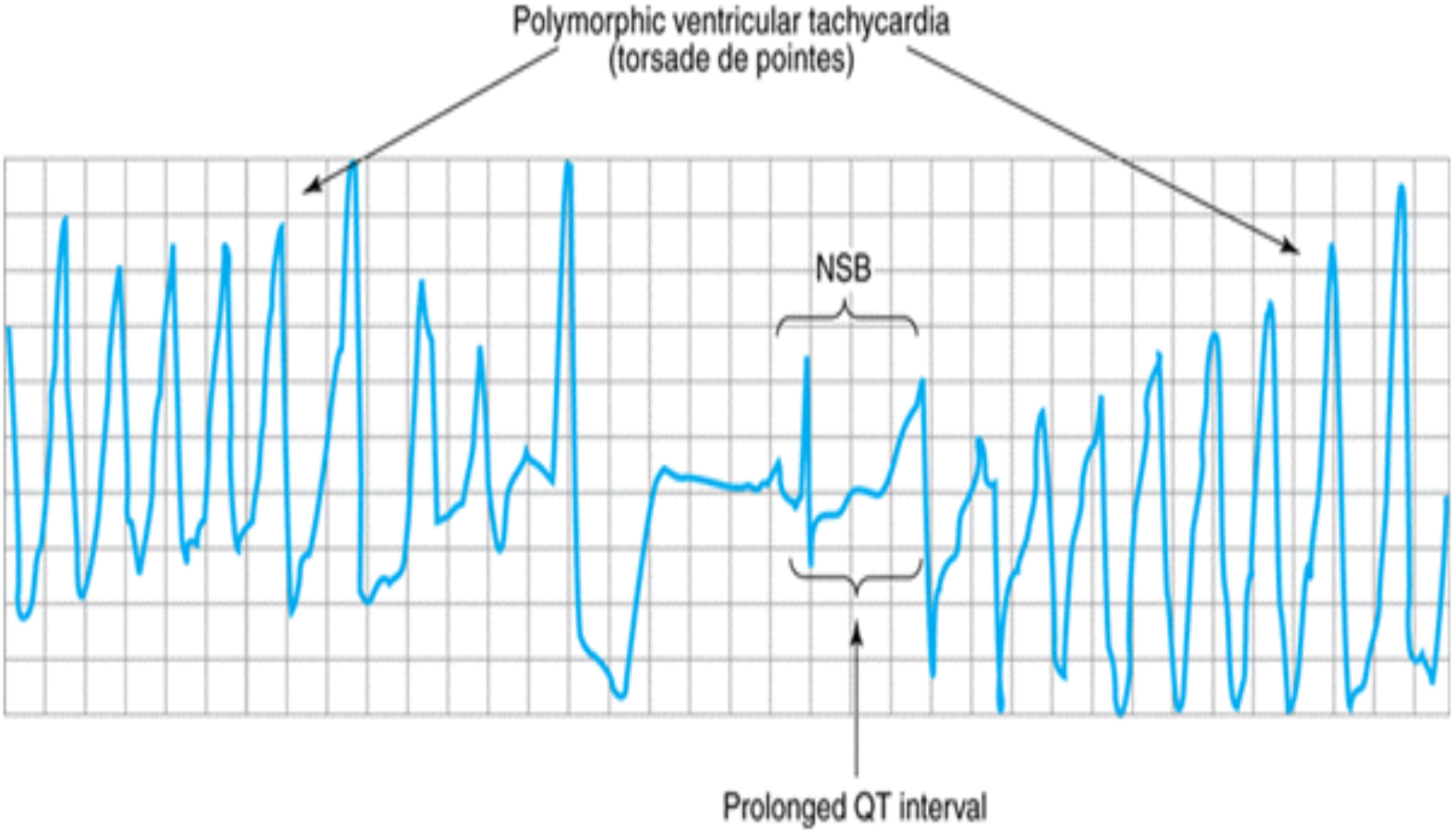
Mechanisms:

- **Increased inward current (GF), or**
- **Decreased outward current (LF) during the plateau.**

TABLE 14–1 Molecular and genetic basis of some cardiac arrhythmias.

Type	Chromosome Involved	Defective Gene	Ion Channel or Proteins Affected	Result
LQT-1	11	*KCNQ1*	I_{Ks}	LF
LQT-2	7	*KCNH2 (HERG)*	I_{Kr}	LF
LQT-3	3	*SCN5A*	I_{Na}	GF
LQT-4	4	Ankyrin-B[1]		LF
LQT-5	21	*KCNE1 (minK)*	I_{Ks}	LF
LQT-6	21	*KCNE2 (MiRP1)*	I_{Kr}	LF
LQT-7[2]	17	*KCNJ2*	I_{KIr}	LF
LQT-8[3]	12	*CACNA1c*	I_{Ca}	GF
SQT-1	7	*KCNH2*	I_{Kr}	GF
SQT-2	11	*KCNQ1*	I_{Ks}	GF
SQT-3	17	*KCNJ2*	I_{KIr}	GF
CPVT-1[4]	1	*hRyR2*	Ryanodine receptor	GF
CPVT-2	1	*CASQ2*	Calsequestrin	LF
Sick sinus syndrome	15 or 3	*HCN4 or SCN5A*[5]		LF
Brugada syndrome	3	*SCN5A*	I_{Na}	LF
PCCD	3	*SCN5A*	I_{Na}	LF
Familial atrial fibrillation	11	*KCNQ1*	I_{Ks}	GF

Figure 14-8



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Electrocardiogram from a patient with the long QT syndrome during two episodes of torsades de pointes. The polymorphic ventricular tachycardia is seen at the start of this tracing and spontaneously halts at the middle of the panel. A single normal sinus beat (NSB) with an extremely prolonged QT interval follows, succeeded immediately by another episode of ventricular tachycardia of the torsades type. The usual symptoms include dizziness or transient loss of consciousness. (Reproduced, with permission, from *Basic and Clinical Pharmacology*, 10th edition, McGraw-Hill, 2007.)

Torsade de Pointes

Risk Factors:

- Bradycardia.
- Hypokalemia.
- Triggered upstrokes.
- Drugs which ↑ APD.

Treatment:

- K+
- ↓ Triggered upstrokes (β Blockers or Mg++)
- ↓ APD (Pacemaker or isoproterenol).

www.sads.org= sudden arrhythmia death syndrome foundation

Other Congenital Arrhythmias

- **Short QT Syndrome:**
  - GF mutations in three potassium channel genes(KCNH2, KCNQ1, and KCNJ2).

- **Chatecholaminergic Polymorphic Ventricular Tachycardia (CPVT):**
  - Stress or emotion-induced syncope.
  - Caused by mutations in sarcoplasmic proteins that control calcium.
  - Inhibiting RyR2 channels with flecainide appears to prevent CPVT.

Other Congenital Arrhythmias

- **Sick Sinus Syndrome:**
  - Mutations in HCN4 and SCN5A
- **Brugada Syndrome:**
  - Ventricular fibrillation, persistent ST elevation, and BBB(5 in 10,000).
  - Linked to LF mutations in SCN5A
- **Familial Atrial Fibrillation:**
  - Linked to GF mutation in the potassium channel gene, KCNQ1.

Nonpharmacologic Therapy

- Surgery.
- Radiofrequency Catheter Ablation(إستئصال).
- Cryoablation(الاستئصال بالتبريد).
- Implantable Cardioverter- Defibrillator (ICD).
- Gene therapy!!!!.

Anti-arrhythmias Drugs

- **Effect of drugs on automaticity**

  Most of the arrhythmic agents suppress automaticity by blocking either sodium or calcium channels to reduce the ratio of these ions to potassium,

  thus result in a reduction in the depolarization or diastolic and raises the threshold of discharge to a less negative voltage.

- **Effect of drugs on conduction abnormalities**

  Prevent reentry by slowing conduction and/or increasing the refractory period.

Anti-arrhythmias Drugs

- Available anti-arrhythmic drugs suppress arrhythmias by blocking flow through specific ion channels or by altering autonomic function.

- Anti-arrhythmic drug therapy can have two goals: Termination of an ongoing arrhythmia or Prevention of an arrhythmia.

- Anti-arrhythmic drugs, might help control arrhythmias, but; unfortunately, also might cause them, especially during long-term therapy.

Principle of Mechanism of action of Anti-arrhythmias Drugs

- **Readily bind to activated channels or inactivated channels but bind poorly to rested channels. i.e.: *Use -Dependent or State-Dependent*.**
- **Channels in normal cells will rapidly lose the drug from the receptors during the resting portion of the cycle.**
- **This selectivity is lost with increasing doses, leading to drug-induced arrhythmias.**
- **Also, these drugs may become" *Proarrhythmic or Arrhythmogenic"* during fast heart rates, acidosis, hyperkalemia, or ischemia.**

Table 21.2 Summary of antidysrhythmic drugs (Vaughan Williams classification)

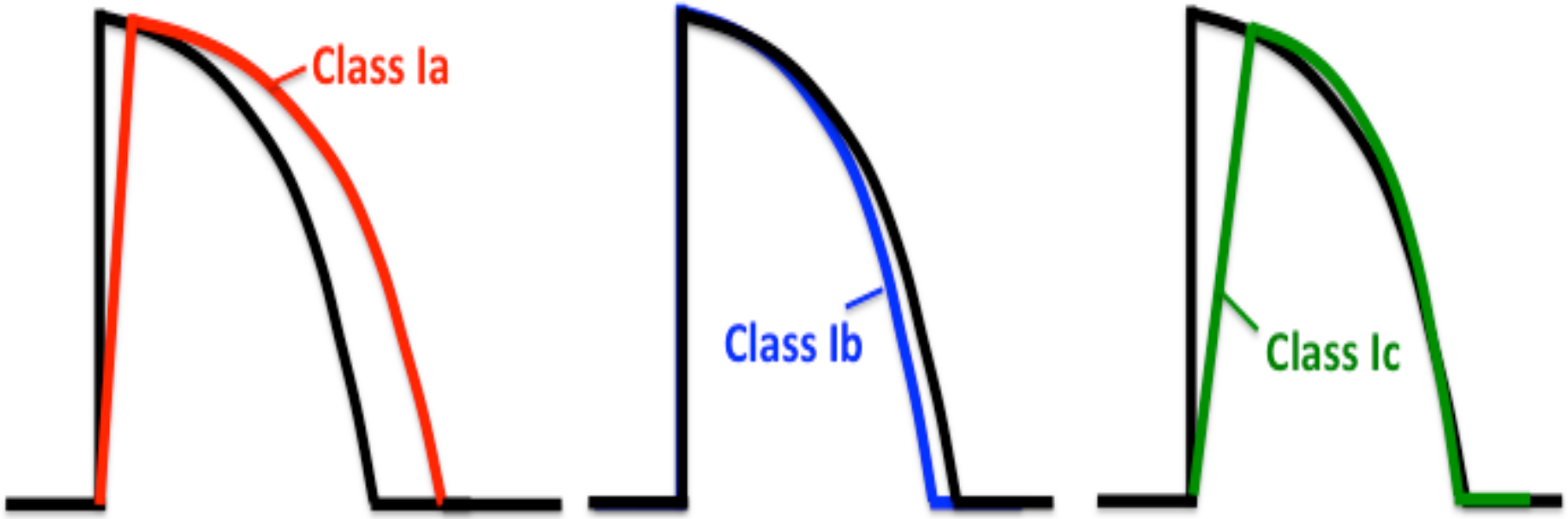
Class	Example(s)	Mechanism
Ia	Disopyramide	Sodium-channel block (intermediate dissociation)
Ib	Lidocaine	Sodium-channel block (fast dissociation)
Ic	Flecainide	Sodium-channel block (slow dissociation)
II	Propranolol	β-Adrenoceptor antagonism
III	Amiodarone, sotalol	Potassium-channel block
IV	Verapamil	Calcium-channel block

classification of antiarrhythmic drugs

- Class 1 action is sodium channel blockade. Subclasses of this action reflect effects on the action potential duration (APD) and the kinetics of sodium channel blockade.
- Class 1A action prolong the APD and dissociate from the channel with intermediate kinetics.
- Class 1B action shorten the APD in some tissues of the heart and dissociate from the channel with rapid kinetic.
- Class 1C action have minimal effects on the APD and dissociate from the channel with slow kinetics.

Class I Antiarrhythmic Drug Effects

On the Ventricular Action Potential:



On the ECG:

↑QRS & ↑QT

↓QT

↑↑QRS

classification of antiarrhythmic drugs

- Class 2 action is sympatholytic. Drugs with this action reduce ß-adrenergic activity in the heart.

- Class 3 action manifests as prolongation of the APD. Most drugs with this action block the rapid component of the delayed rectifier potassium current, I Kr .
- Class 4 action is blockade of the cardiac calcium current. This action slows conduction in regions where the action potential

TABLE 14–2 Membrane actions of antiarrhythmic drugs.

Drug	Block of Sodium Channels		Refractory Period		Calcium Channel Blockade	Effect on Pacemaker Activity	Sympatholytic Action
	Normal Cells	Depolarized Cells	Normal Cells	Depolarized Cells			
Adenosine	0	0	0	0	+	0	+
Amiodarone	+	+++	↑↑	↑↑	+	↓↓	+
Diltiazem	0	0	0	0	+++	↓↓	0
Disopyramide	+	+++	↑	↑↑	+	↓	0
Dofetilide	0	0	↑	?	0	0	0
Dronedarone	+	+	na	na	+	na	+
Esmolol	0	+	0	na	0	↓↓	+++
Flecainide	+	+++	0	↑	0	↓↓	0
Ibutilide	0	0	↑	?	0	0	0
Lidocaine	0	+++	↓	↑↑	0	↓↓	0
Mexiletine	0	+++	0	↑↑	0	↓↓	0
Procainamide	+	+++	↑	↑↑↑	0	↓	+
Propafenone	+	++	↑	↑↑	+	↓↓	+
Propranolol	0	+	↓	↑↑	0	↓↓	+++
Quinidine	+	++	↑	↑↑	0	↓↓	+
Sotalol	0	0	↑↑	↑↑↑	0	↓↓	++
Verapamil	0	+	0	↑	+++	↓↓	+
Vernakalant	+	+	+	+	na	0	na

na, data not available.

TABLE 14–3 Clinical pharmacologic properties of antiarrhythmic drugs.

Drug	Effect on SA Nodal Rate	Effect on AV Nodal Refractory Period	PR Interval	QRS Duration	QT Interval	Usefulness in Arrhythmias		Half-Life
						Supra-ventricular	Ventricular	
Adenosine	↓↑	↑↑↑	↑↑↑	0	0	++++	?	< 10 s
Amiodarone	↓↓[1]	↑↑	Variable	↑	↑↑↑↑	+++	+++	(weeks)
Diltiazem	↑↓	↑↑	↑	0	0	+++	–	4–8 h
Disopyramide	↑↓[1,2]	↑↓[2]	↑↓[2]	↑↑	↑↑	+	+++	7–8 h
Dofetilide	↓(?)	0	0	0	↑↑	++	None	7 h
Dronedarone					↑	+++	–	24 h
Esmolol	↓↓	↑↑	↑↑	0	0	+	+	10 min
Flecainide	None,↓	↑	↑	↑↑↑	0	+[3]	++++	20 h
Ibutilide	↓ (?)	0	0	0	↑↑	++	?	6 h
Lidocaine	None[1]	None	0	0	0	None[4]	+++	1–2 h
Mexiletine	None[1]	None	0	0	0	None	+++	12 h
Procainamide	↓[1]	↑↓[2]	↑↓[2]	↑↑	↑↑	+	+++	3–4 h
Propafenone	0, ↓	↑	↑	↑↑↑	0	+	+++	5–7 h
Propranolol	↓↓	↑↑	↑↑	0	0	+	+	5 h
Quinidine	↑↓[1,2]	↑↓[2]	↑↓[2]	↑↑	↑↑	+	+++	6 h
Sotalol	↓↓	↑↑	↑↑	0	↑↑↑	+++	+++	7 h
Verapamil	↓↓	↑↑	↑↑	0	0	+++	–	7 h
Vernakalant		↑	↑			+++	–	2 h

[1] May suppress diseased sinus nodes.

[2] Anticholinergic effect and direct depressant action.

[3] Especially in Wolff-Parkinson-White syndrome.

[4] May be effective in atrial arrhythmias caused by digitalis.

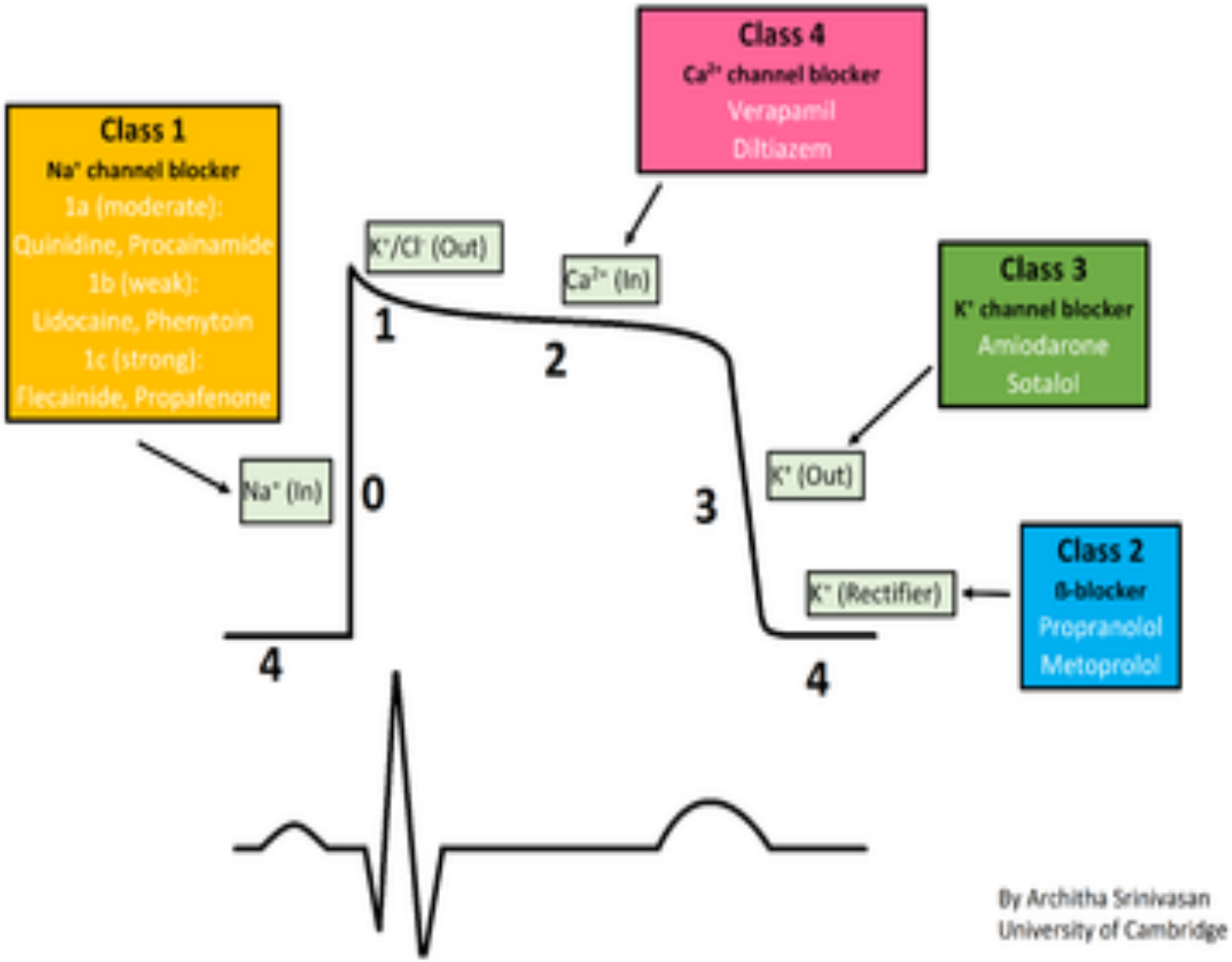
[5] Half-life of active metabolites much longer.

Table 17.1 The mechanism of action, the electrophysiological actions and clinical uses of selected antidysrhythmic drugs

		Example	Mechanism of action	Electrophysiological actions	Clinical use
Vaughan Williams classification	Class Ia	Disopyramide	Na^+ channel block	Reduced rate of depolarisation of action potential, increased ERP, decreased AV conduction	Ventricular fibrillation, especially associated with myocardial infarction
	Class Ib	Lidocaine			
	Class II	Propranolol, atenolol	β-Adrenoceptor antagonism	Slowed pacemaker activity, increased AV refractory period	Dysrhythmia prevention in myocardial infarction; paroxysmal atrial fibrillation due to sympathetic activity
	Class III	Amiodarone, sotalol	K^+ channel block	Increased action potential duration and increased ERP	Atrial fibrillation; ventricular fibrillation
	Class IV	Verapamil	Ca^{2+} channel block	Decreased APD, slowed AV conduction	Supraventricular tachycardias; atrial fibrillation
Not classified by system		Adenosine	K^+ channel activation	Slowed pacemaker activity, slowed AV conduction	Given i.v. for supraventricular tachycardias
		Digoxin	K^+ channel activation (vagal action)	Slowed AV conduction (block)	Atrial fibrillation
		Magnesium chloride	? Ca^{2+} channel block		Ventricular fibrillation; digoxin toxicity

APD, action potential duration; AV, atrioventricular; ERP, effective refractory period.

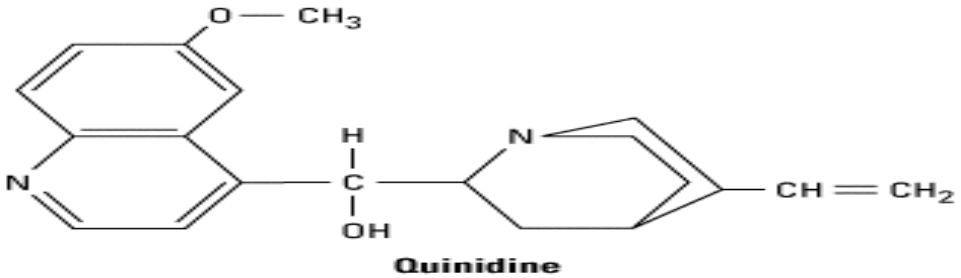
Drugs Affecting the Cardiac Action Potential



By Architha Srinivasan
University of Cambridge

Class 1A Drugs

Quinidine:



Quinidine

- Prototype, related to quinine.
- Cinchona tree → Antipyretic → Quinine = Antimalarial.
- Inhibits Na channels.
- Also, inhibits α and muscarinic receptors.
- Slows upstroke, conduction, and prolongs APD and QRS duration.

Quinidine

- Quinidine Bind to sodium channels and prevent sodium influx, and so slower the rapid depolarization.

- Inhibit arrhythmias, which caused by increased automoticity, and also prevent reentry arrhythmias by producing bidirectional block.

- Use nowadays restricted to patients with “normal hearts”(no failure, no ischemia), but have atrial or ventricular arrhythmias.

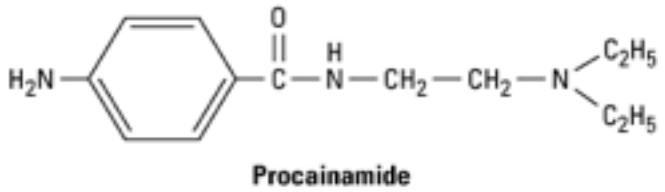
Quinidine

Side Effects: Toxic

- Nausea (18%), Diarrhea (33%).
- Headache, Dizziness, and tinnitus= *Cinchonism*
- Hypersensitivity, fever, rash, angioedema.
- Thrombocytopenia.
- Excessive prolongation of QT interval, slowed conduction.
- Hypotension.
- ↑Serum Digoxin levels.
- ↑ Warfarin effects.
- Sudden death.

Class 1A Drugs

Procainamide:



Procainamide

- Oral, but has short t½.
- L.E. (30% of patients Tx over 6 months).
- Acetylated → NAPA (has Class III actions)

Disopyramide

PROCAINAMIDE

- structurally related to the local anesthetic procaine

---

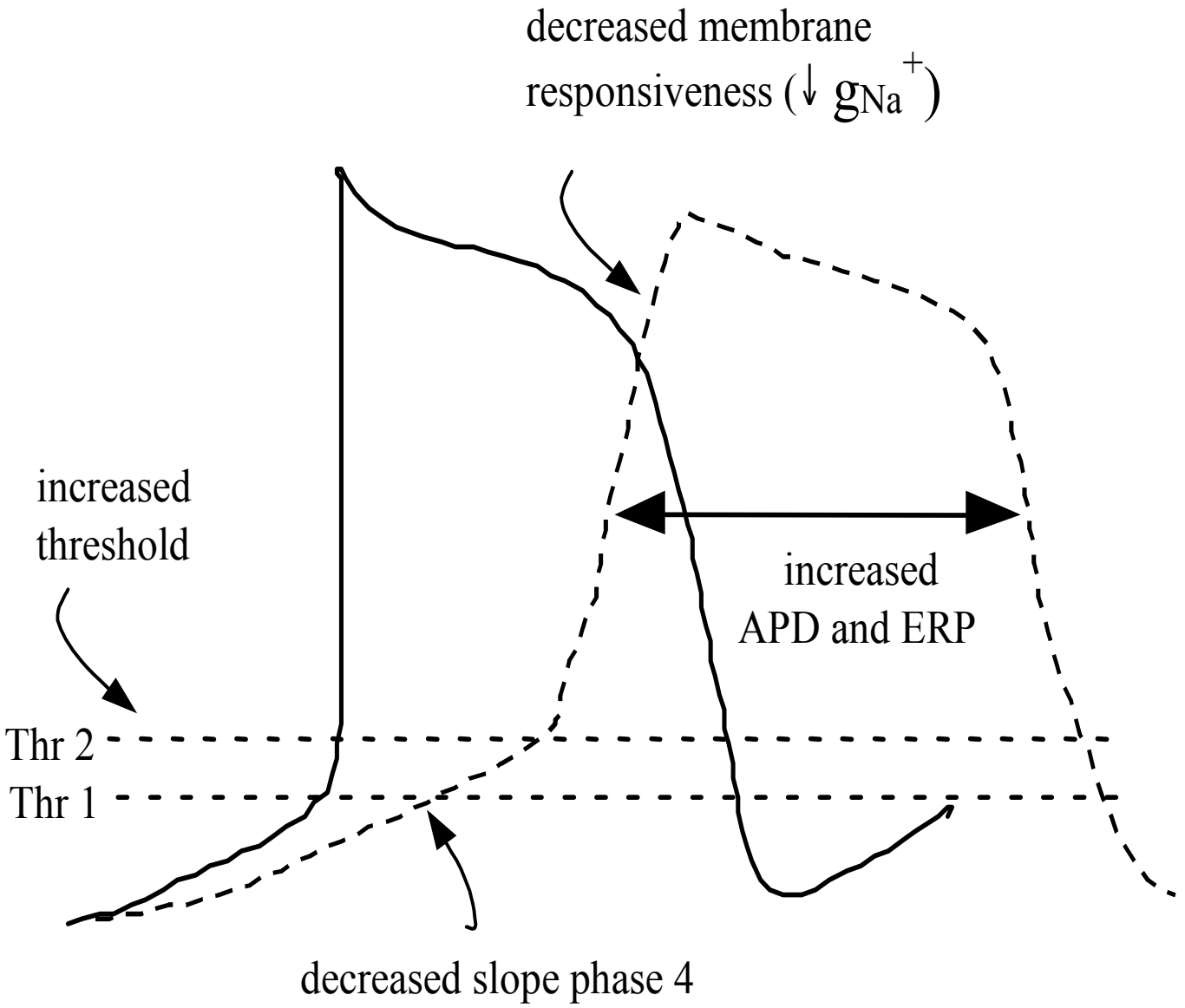
1. Major electrophysiological effects in heart:

   a. Decrease automaticity - decrease phase 4 spontaneous depolarization and increase threshold.

   b. Decrease conduction velocity throughout heart due to decrease in membrane responsiveness (Vmax).

   c. Increase in action potential duration and refractory period in atrial and ventricular cells - blocks K^+ efflux

Effect of Procainamide (Quinidine) on action potential



PROCAINAMIDE

2. Other Cardiac Effects
   a. ECG may be greatly altered; P-R, QRS and Q –T intervals are prolonged.
   b. Possible excessive slowing of conduction.

3. Adverse Effects
   a. Hypotension with large i.v. doses
   b. Lupus erythematosis-like (auto-immune) syndrome may occur.
   c. Prolongs QT interval, possible “torsades de pointe”

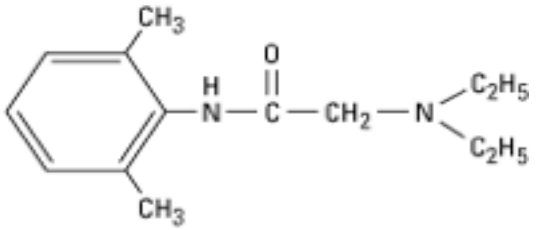
4. Pharmacokinetics
   a. Can be given orally, I.V., or I.M.
   b. Has short T1/2 (3-4 hrs); frequent administration or use sustained release formulation.
   c. Some individuals rapidly acetylate procainamide (NAPA - cardioactive metabolite).

Uses – atrial and ventricular arrhythmias (acute MI)

Class 1B Drugs

Lidocaine(Lignocaine, or Xylcaine):

- High affinity to bind with activated and inactivated Na+ channels with rapid kinetics.
- Acts selectively in ischemic ventricular tissue to promote conduction & block reentry.
- More effective with ↑ K+.
- Not effective in atrial arrhythmias.



Lidocaine

Class 1B Drugs

Lidocaine:

Kinetics:

- Well absorbed, but ineffective orally, due to first pass effect, so given IV.
- Well distributed, including the brain.

Side Effects:

- Least cardiotoxic of the class, except for hypotension with high doses due to depression of the myocardium.
- CNS: paresthesia, tremor, nausea, slurred speech, and convulsions.
- *Was routinely given to all MI patients to prevent ventricular arrhythmias*.

Class 1B Drugs

Tocainide:

- Oral analog of lidocaine.
- CNS, GI and blood dyscrasia.

Mexiletine:

- Oral analog of lidocaine.
- Neurologic side effects.

Phenytoin:

- Antiepileptic.
- Useful in:
  - Digitalis- induced arrhythmias.
  - Arrhythmias after congenital heart surgery.
  - Congenital prolonged QT interval.

Class 1C Drugs

Flecainide:

- Potent blocker of Na + and K+ channels.
- Negative inotropic effect.
- Proarrhythmic → ventricular.
- Effective in supra ventricular tachycardia with normal hearts.

Class IC – Flecainide

General Properties:

a. **Marked affinity for and blockade of Na^+ channels.**
b. **Marked slowing of conduction velocity (shallow phase 0 slope).**
c. **Little change in AP duration**
d. **Useful in resistant, life-threatening ventricular arrhythmias.**

Toxicity:

a. **Proarrhythmic, particularly in MI patients.**
b. **Blurred vision &CNS side effects**
c. **Ventricular arrhythmias and sudden death.**

Class 1C Drugs

Propafenone:

- Blocks Na+ channels but also has beta blocking and Ca++ blocking activity.
- No effect on QT interval.
- Used for supraventricular arrhythmias.
- Side effects: metallic taste, constipation, and arrhythmias.

Class II Drugs

Propranolol

- Besides beta blocking, membrane stabilization, and intrinsic sympathomimetic activities, has effective antiarrhythmic activity
- Very effective, well tolerated, and documented to reduce mortality after acute myocardial infarction by reducing arrhythmias, besides reducing myocardial oxygen requirements.

CLASS II
β- ADRENERGIC BLOCKING AGENTS
Propranolol

1. <u>Cardiac action</u> – blocks effects of catecholamines on:
   a. Automaticity (S-A node and elsewhere; heart rate)
   b. A-V conduction
   c. Refractory period

2. <u>Electrophysiological effects (other)</u>
   a. Quinidine-like effects on membranes
   b. Depression of conduction velocity

Beta-Adrenergic Blockers

USES

a. Paroxysmal atrial tachycardia
b. Arrhythmias associated with hydrocarbon anesthetics
c. Arrhythmias resulting from tricyclic antidepressants or L-dopa
d. Pheochromocytoma

ADVERSE EFFECTS

a. Negative inotropic action on heart
b. Bronchospasm
c. Depression and nightmares (lipid-soluble agent)
d. Rebound increase in sensitivity to ß-adrenergic agonists on withdrawal
e. A-V block

Carvedilol – β and α adrenergic blocking agent

Class II Drugs

Acebutolol

Metoprolol

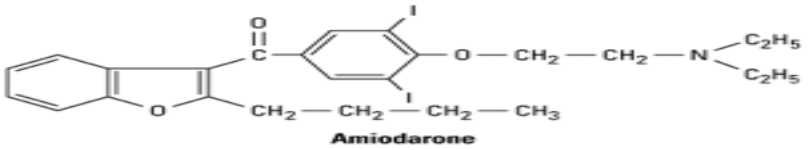
β1 selective drugs.

- **Esmolol: Short acting, used in intraoperative and acute arrhythmias**

- **Salotol : non selective B blocker(prolong action potential)**

Class III Drugs

Amiodarone:



- Blocks K+ channels and markedly prolongs APD.

Also:

- Class I actions.
- Blocks α and β Receptors.
- Ca++ blocking actions.
- *Effect is due to alteration of lipid membrane.*
- *Reserved for life-threatening atrial and ventricular arrhythmias.*
- Slows heart rate and AV conduction.
- Low incidence of TdP despite significant QT prolongation.
- Peripheral vasodilator (only with IV).

Class III Drugs

Amiodarone:

- Given IV (Loading dose 10gm) and orally.
- Has slow kinetics (t½ 25-110 days), metabolized by CYP3A4 enzymes.

Toxicity: ***mainly extracardiac and dose related.***

- Lung fibrosis (1%).
- CNS.
- Thyroid(hypo and hyper).
- GI and liver.
- Corneal deposits,
- Skin: photodermatitis and discoloration (Figure).
- ↑ Digoxin & Anticoagulants.
- Interactions: affected by CYP3A4 activity.

Blue-man Syndrome

Class III Drugs

Bretylium Tosylate:

- Originally an antihypertensive, but tolerance develops.
- Releases NE, then ↓ Release / Reuptake
- Rarely used, except for prevention of ventricular fibrillation after failure of cardioversion and lidocaine.
- Hypotension, Parotid swelling.

Class III Drugs

Sotalol:

- Beta blocker but has Class III actions.
- For atrial and ventricular arrhythmias.
- Causes bradycardia, HF, and Prolongation of QT.
- Ibutilide.
- slows cardiac depolarization by blockadeof the rapid component (I Kr) of the delayed rectifier potassium current.
- Dofetilide.

Ibutilide

- Slows cardiac depolarization by blockade of the rapid component (I_{Kr}) of the delayed rectifier potassium current.
- **Activation of slow inward sodium current has also been suggested as an additional mechanism of action potential prolongation.**
- Intravenous ibutilide is used for the acute conversion of atrial flutter and atrial fibrillation to normal sinus rhythm.
- More effective in atrial flutter
- Most important adverse effect is excessive QT-interval prolongation and torsades de pointes.
- Patients require continuous ECG monitoring for 4 hours until QTc returns to baseline.

Class IV Drugs
(Ca++ Channel Blockers)

Verapamil
Diltiazem

Block activated and inactivated L-type Ca++ channels.

- **Effects more marked in tissues that fire frequently, less completely polarized at rest, and those dependant on Ca++ (SA node and AV node).**
- ***Paroxysmal Supraventricular Tachycardia*.**
- **Vasodilators, and have negative inotropic effects.**
- **Can cause severe AV block in diseased hearts.**
- **Relatively safe: Constipation, gastric discomfort, vertigo, headache, nervousness, pruritis.**
- **↑ Digoxin levels.**

Table 21.1 Antidysrhythmic drugs unclassified in the Vaughan Williams system

Drug	Use
Atropine	Sinus bradycardia
Adrenaline (epinephrine)	Cardiac arrest
Isoprenaline	Heart block
Digoxin	Rapid atrial fibrillation
Adenosine	Supraventricular tachycardia
Calcium chloride	Ventricular tachycardia due to hyperkalaemia
Magnesium chloride	Ventricular fibrillation, digoxin toxicity

Magnesium:

- Works on Na+/K+ ATPase, Na+ channels, certain K+ channels and Ca++ channels.
- Effective IV in refractory digitalis- induced ventricular arrhythmias only in hypomagnesemic patients.
- Effective in TdP patients even if serum Mg++ is normal.

Potassium salts:

- For digitalis- induced arrhythmias with hypokalemia.
- Depress ectopic pacemakers and slow conduction.

Miscellaneous Agents -

Digitalis - sensitizes baroreflexes to increase vagal tone and depress sympathetic activity to heart.

Adenosine brief slowing of AV conduction

Digoxin

Digoxin:

- **Old fashioned agent for heart failure and atrial arrhythmias.**
- **Direct Actions.**
- **Vagotonic Effects.**
- **↑ AV refractoriness.**

DIGOXIN drug for treatment of atrial fibrillation and flutter

1. **Electrophysiological actions**

   A. Prolong A-V refractory period

   B. Effect largely through sensitization of baroreflex receptors; Enhancement of vagal tone and withdrawal of sympathetic nerve activity.

2. **Therapeutic action:**

   Reduces ventricular rate by making A-V node more refractory to the numerous atrial impulses.

3. **Adverse actions:**

   Arrhythmias (PVCs, AV conduction block), nausea, and blurred vision – often with halos.

Adenosine

Naturally occurring nucleoside.

- Stimulates purinergic(P1) receptors.
- Activates inward rectifier K+ current and inhibits Ca++ current.
- Very short acting (t 1/2 10 seconds).
- ↓ Phase 4 depolarization in SA node.
- ↓ AV conduction.
- No effect on ventricles.

Adenosine

90-95% effective in supraventricar tachycardia, replaced verapamil.

- Less effective in the presence of adenosine receptor blockers, e.g. theophylline and caffeine.
- Can cause transient flushing (20%), chest tightness, AV block, headache, hypotension, nausea, and paresthesia.

ADENOSINE

Concentration of adenosine rises with hypoxia as ATP production is reduced. Use in paroxysmal supraventric tachycardias (PSVT).

1. Major actions:
   a. Acts on A_1 receptors to inhibit adenylate cyclase (↓cAMP).
   b. Activates K+ currents and hyperpolarizes nodes
   c. Slows conduction in AV node.

2. Pharmacokinetics:
   a. rapid onset of action, i.v. - 10-20 seconds
   b. very short half life - 10 seconds

3. Adverse Effects:
   a. hypotension, facial flushing, headache
   b. Possible "symptoms" of angina
   c. bronchoconstriction, arrhythmias

Uses: Treatment of PSVT (nodal reentry) / diagnosis of supraventricular vs ventricular tachycardia.