Antiarrhythmic Drugs

Munir Gharaibeh MD, PhD, MHPE
Faculty of Medicine,
The University of Jordan
October 2014

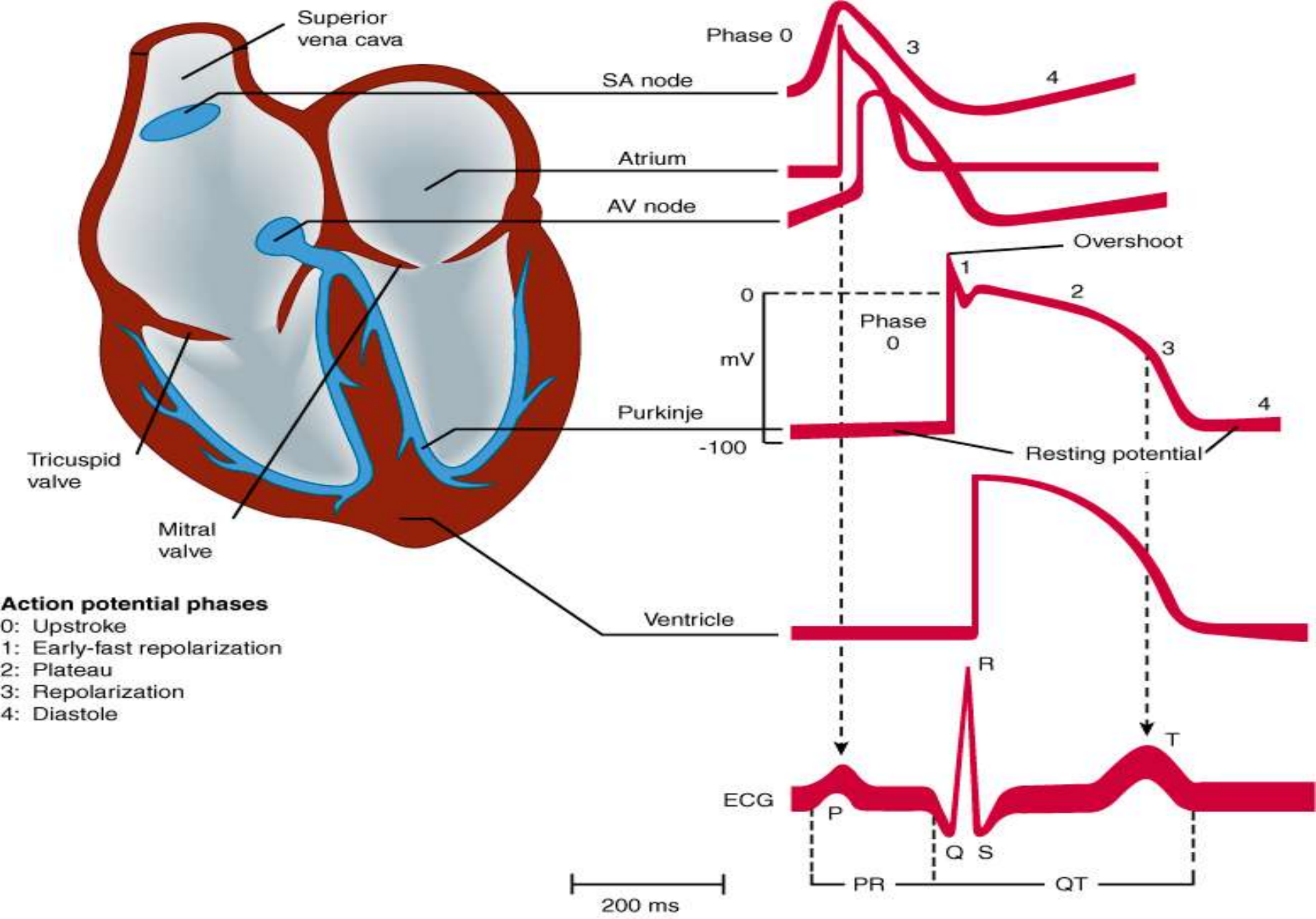
Types of Cardiac Arrhythmias

Abnormalities of Impulse Formation:

- Rate disturbances.
- Triggered automaticity.

Abnormalities of Impulse Conduction:

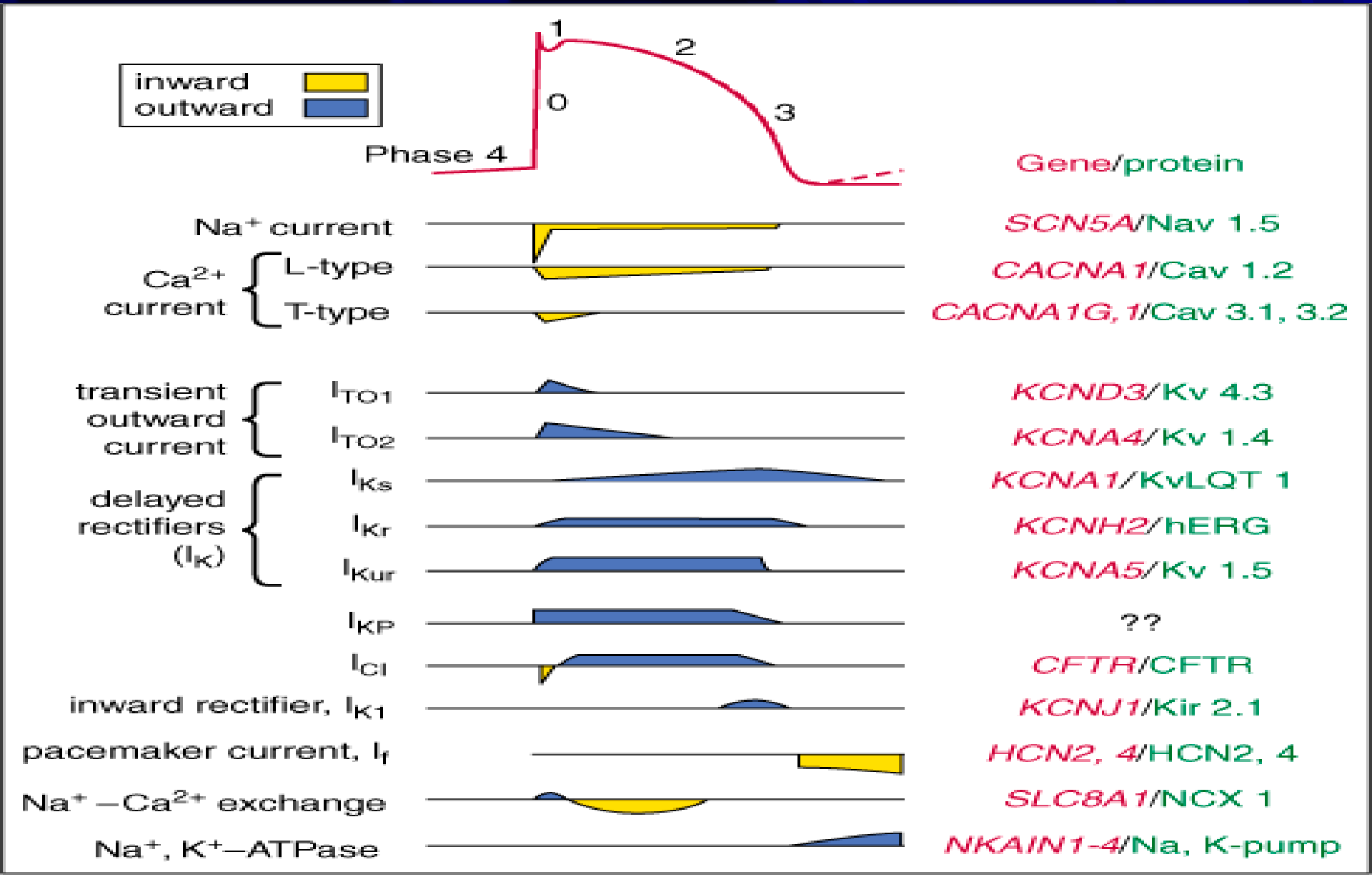
- Blocks.
- Reentry.



Action potential phases

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

Ion Permeability Changes **Potential Changes** **Genes and Proteins**



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

Causes of Cardiac Arrhythmias

Cardiac Causes:

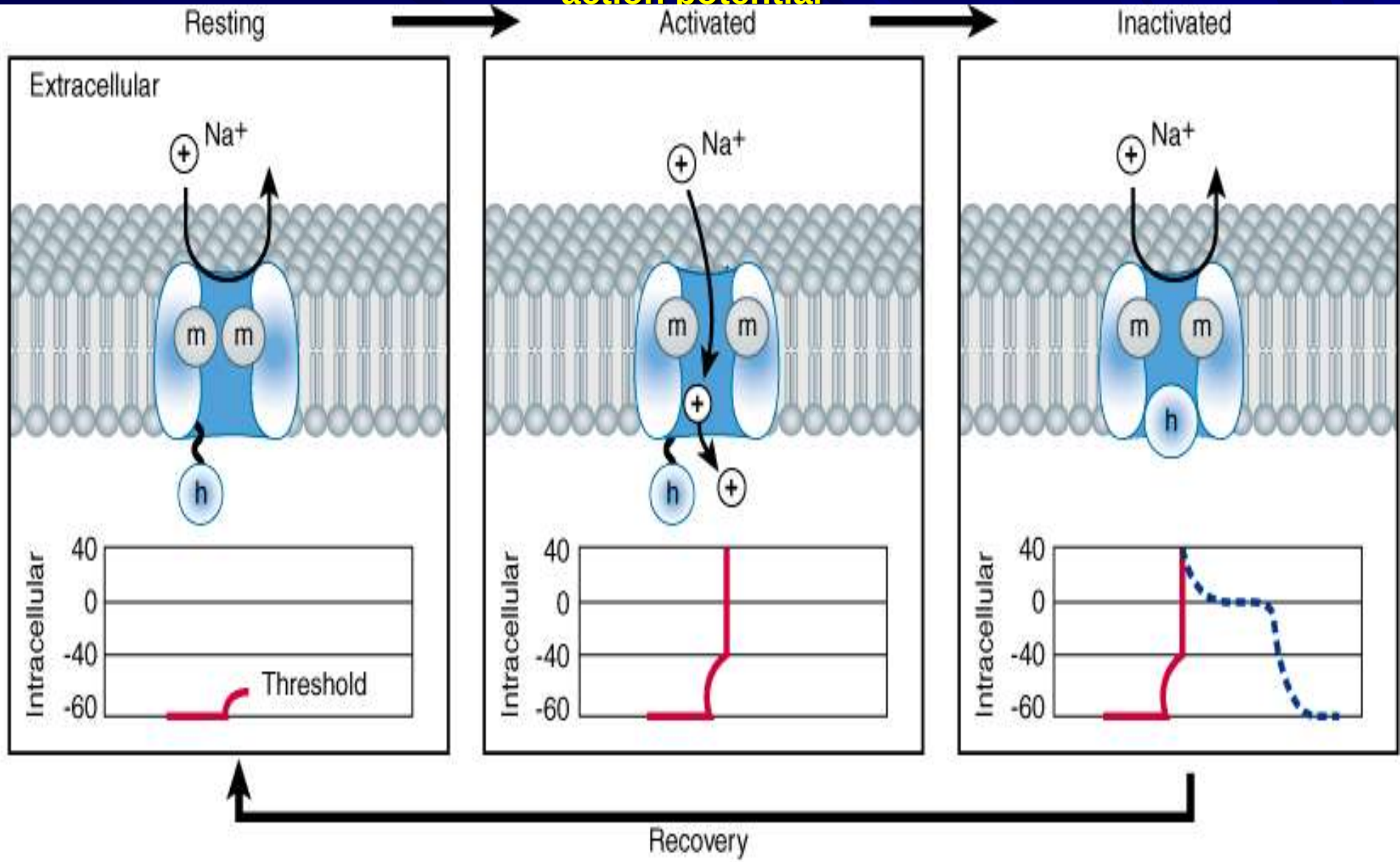
- Ischemic heart disease.
- Inflammation.
- Trauma e.g. heart surgery.
- Congestive heart failure.
- Hypotension.

Causes of Cardiac Arrhythmias

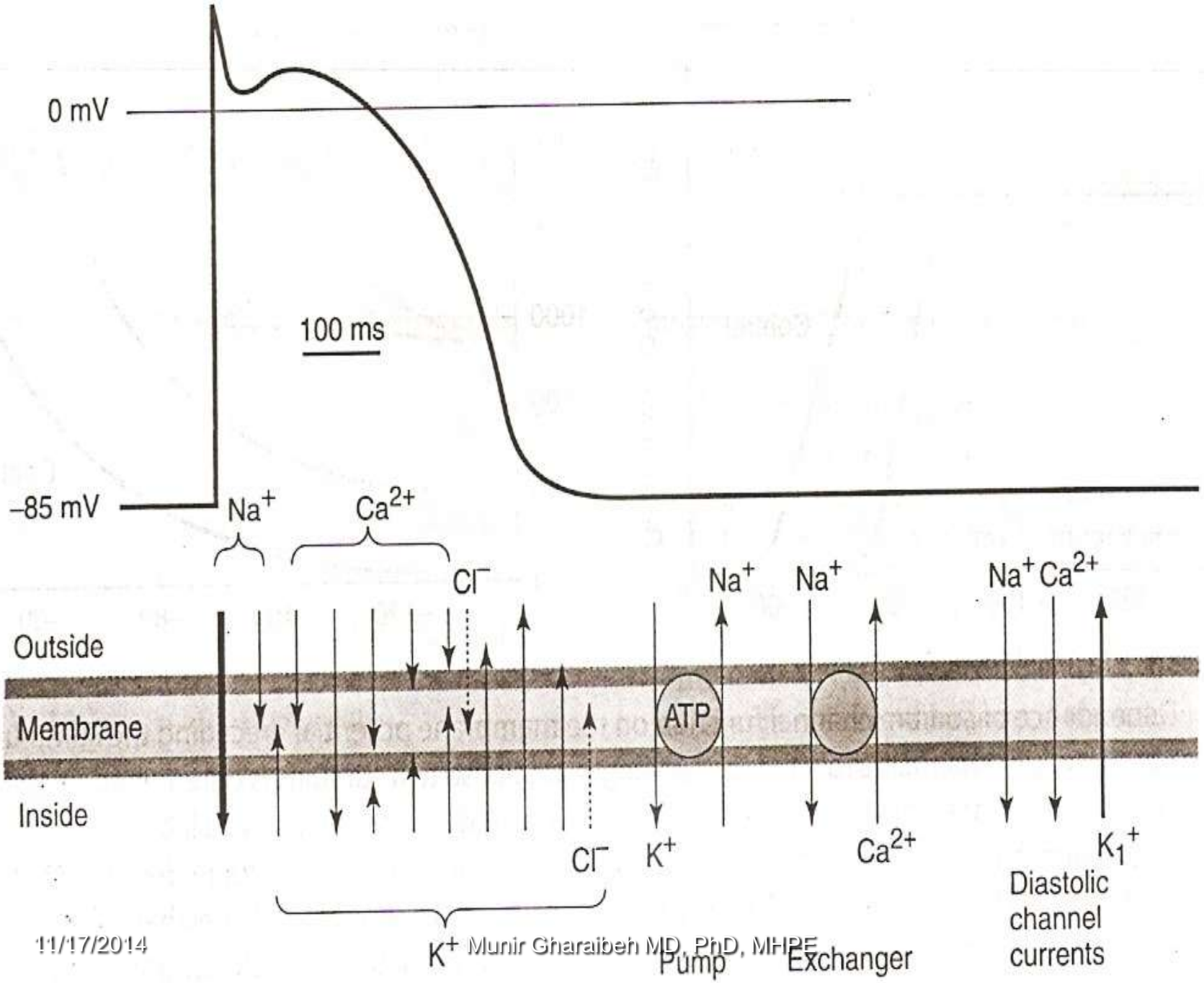
Non Cardiac Causes:

- Electrolyte imbalance.
- Acid-Base imbalance.
- Hypoxia.
- Drugs: Digitalis, Anesthetics, Tricyclic, Diuretics, Bronchodilators.
- G.I. reflexes.
- Neural reflexes.

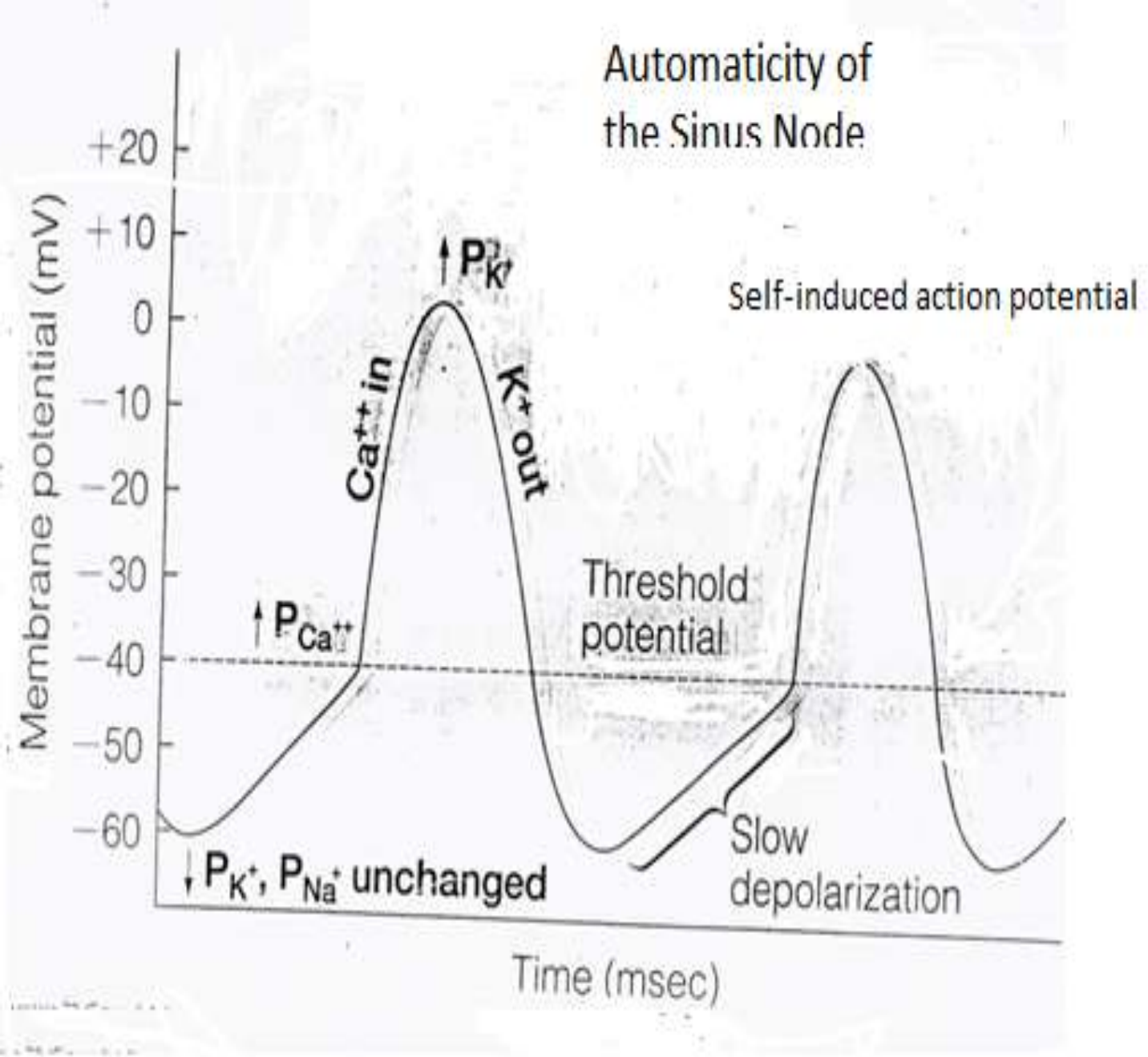
Na+ channels cycling through different conformational states during the cardiac action potential



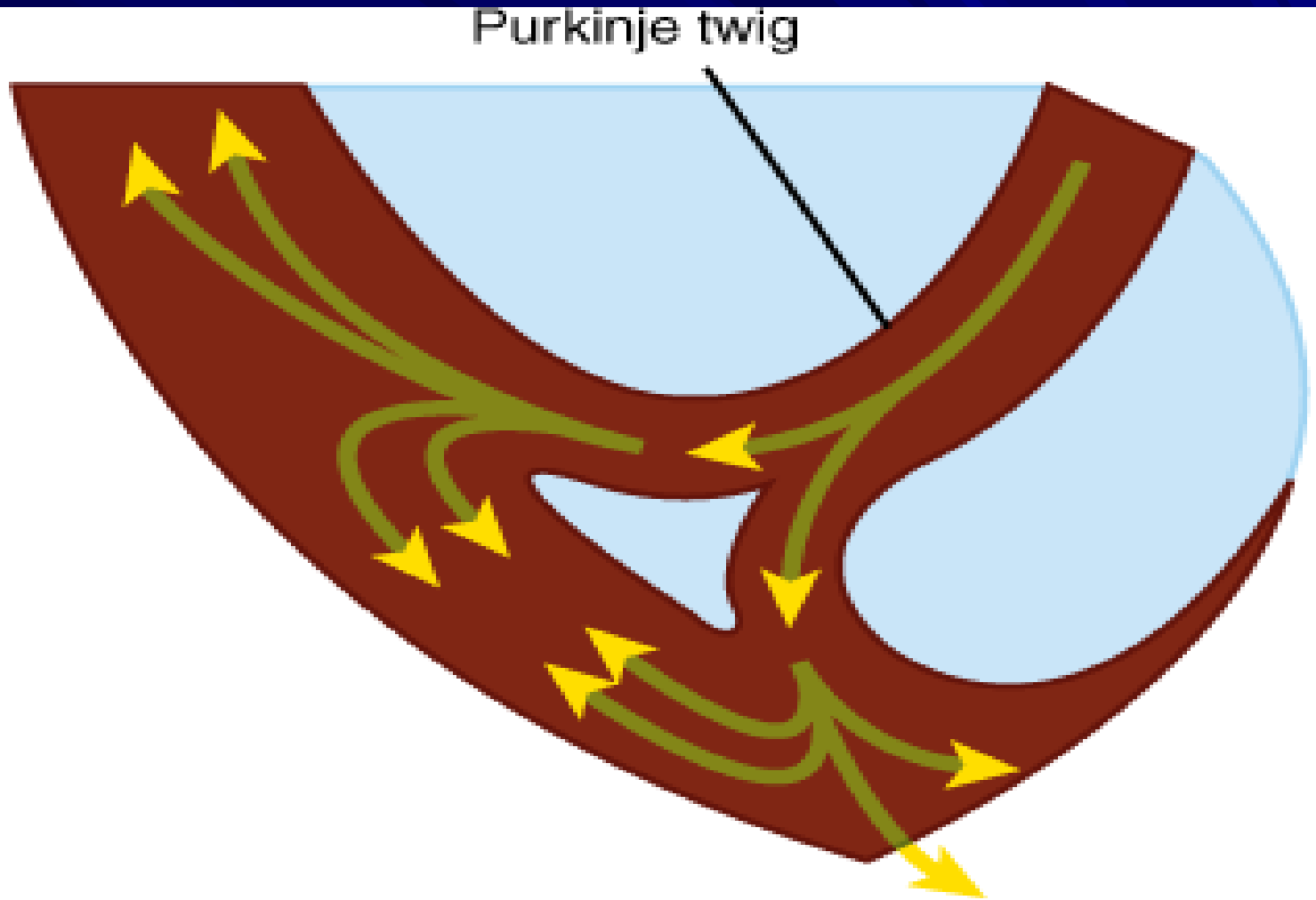
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition; http://www.accessmedicine.com


0 mV
100 ms
–85 mV
Na+
Ca2+
Cl–
Na+
Na+
Na+ Ca2+
Outside
Membrane
Inside
ATP
Cl–
K+
Ca2+
K1+
K+
Pump
Exchanger
Diastolic channel currents

Automaticity of the Sinus Node



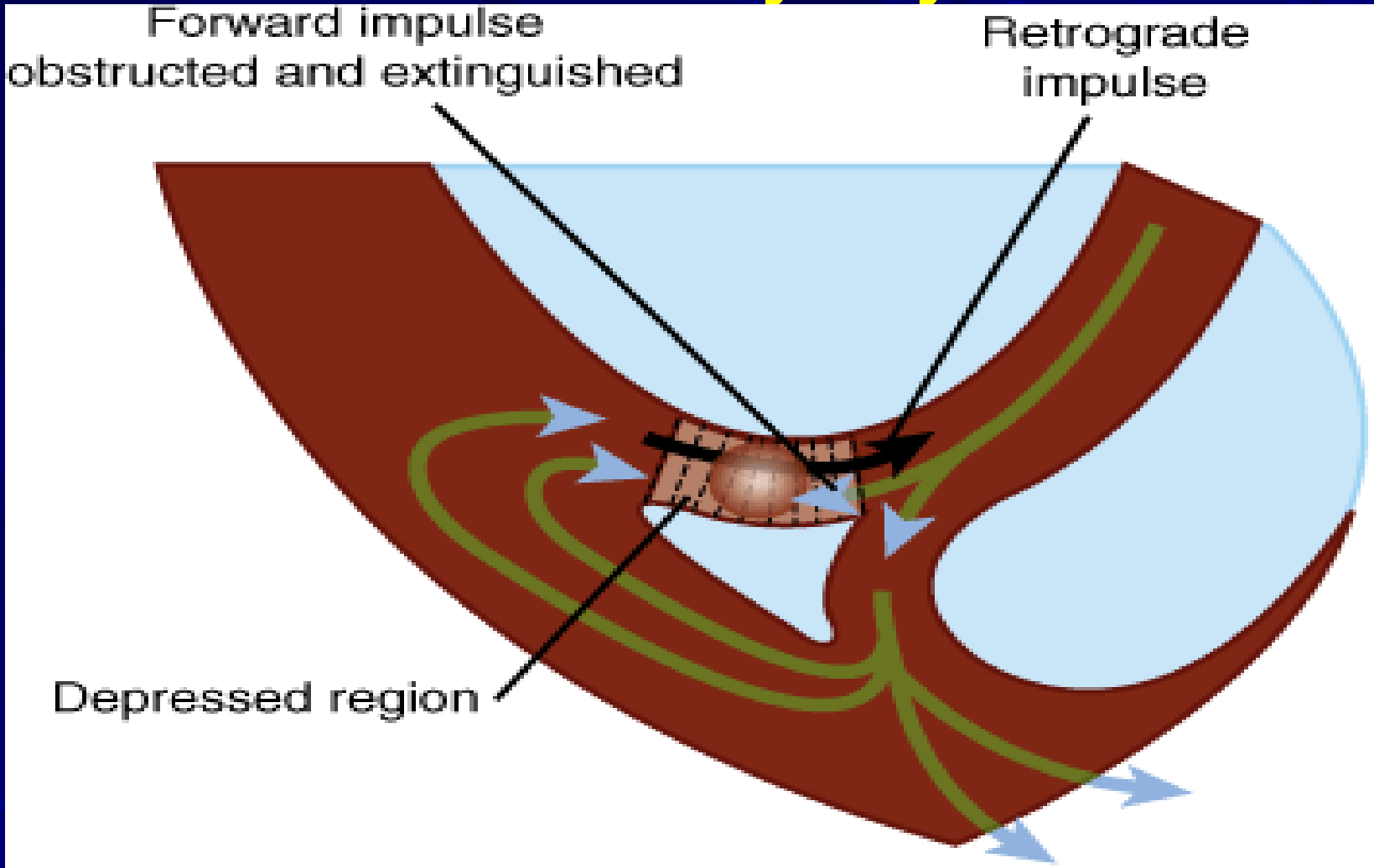
Normal Circuitry



A. Normal conduction

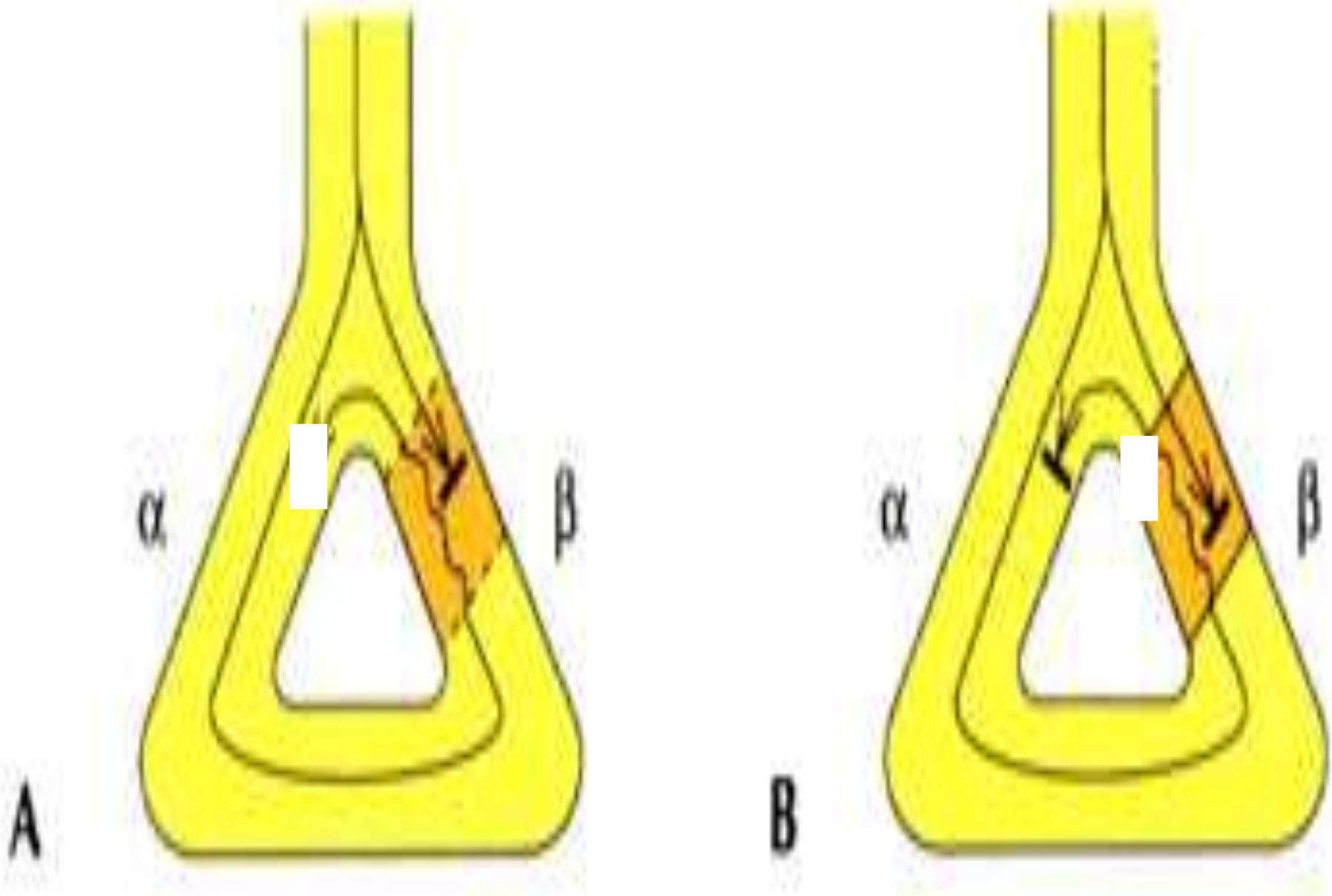
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

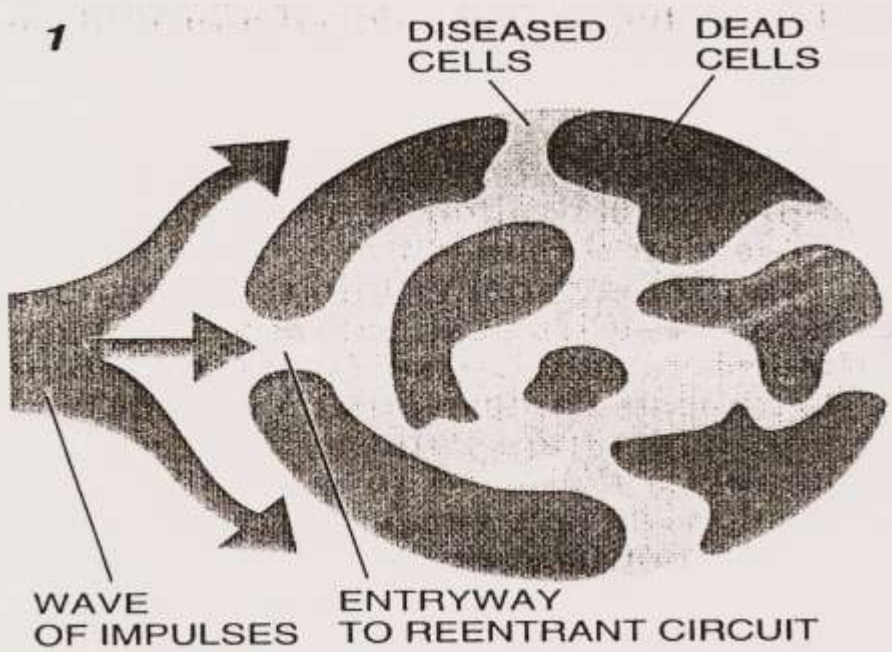
Re-entry Rhythm

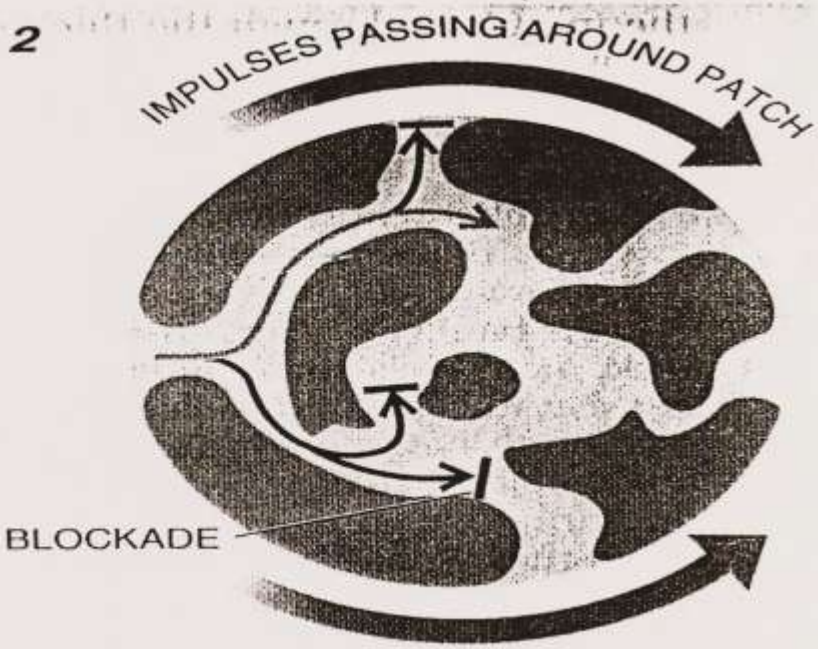


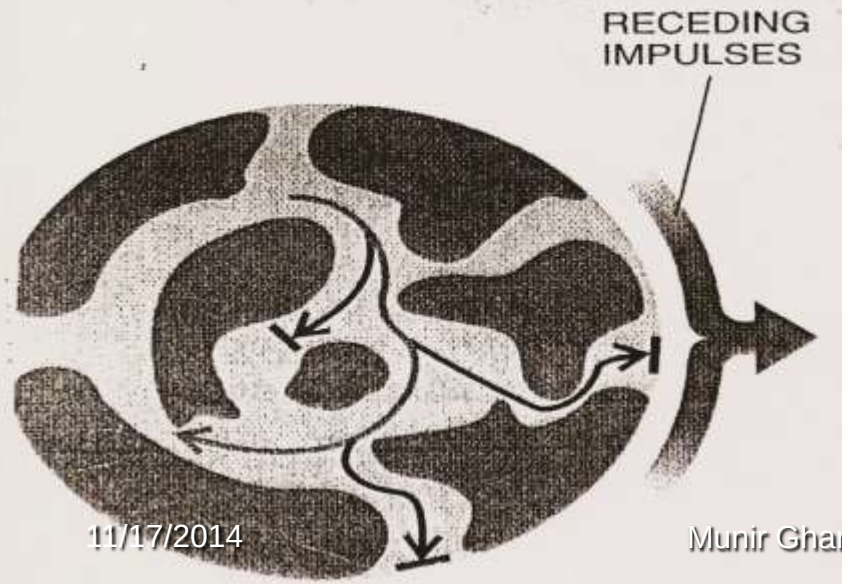
B. Unidirectional block

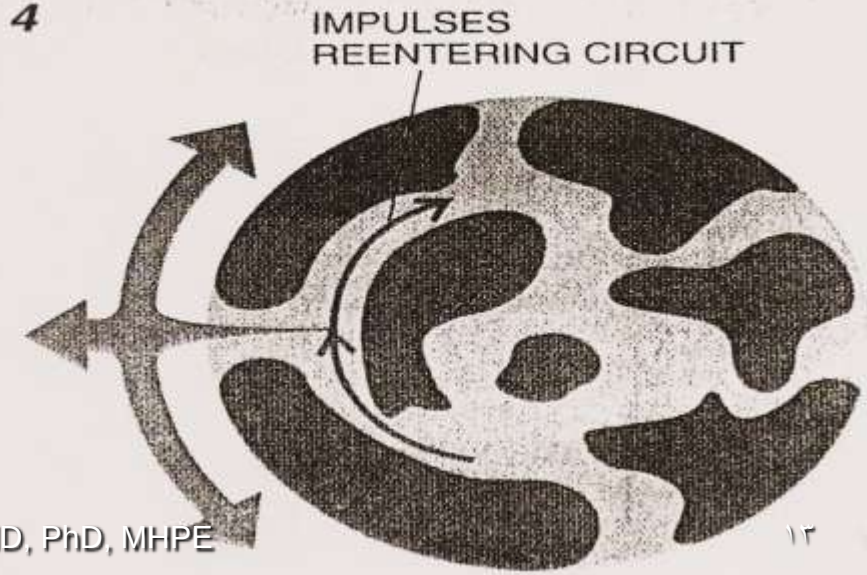
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com


α
β
A
α
β
B


1
DISEASED CELLS
DEAD CELLS
WAVE OF IMPULSES
ENTRYWAY TO REENTRANT CIRCUIT


2
IMPULSES PASSING AROUND PATCH
BLOCKADE


RECEDING IMPULSES


4
IMPULSES REENTERING CIRCUIT

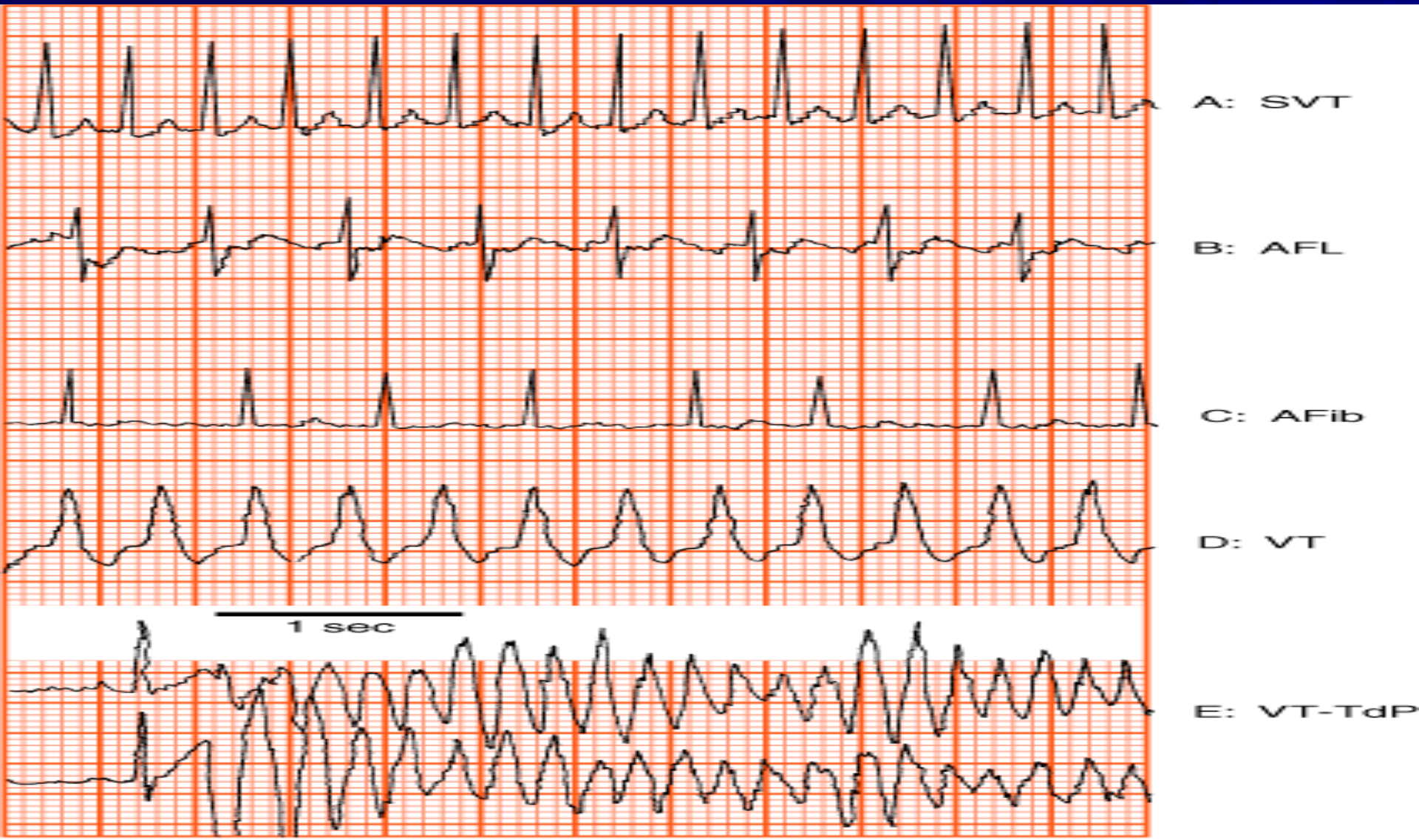
Pre-requisites for Reentry (Circus Movement)

- Anatomic or physiologic obstacle.
- Unidirectional block.
- Conduction time around the circuit must be longer than the effective refractory period.

Molecular and Genetic Basis of some Cardiac Arrhythmias

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*		LF

ECG of some Arrhythmias



Torsade de Pointes
Polymorphic Ventricular Tachycardia

LQT, syncope, and sudden death.

Causes:

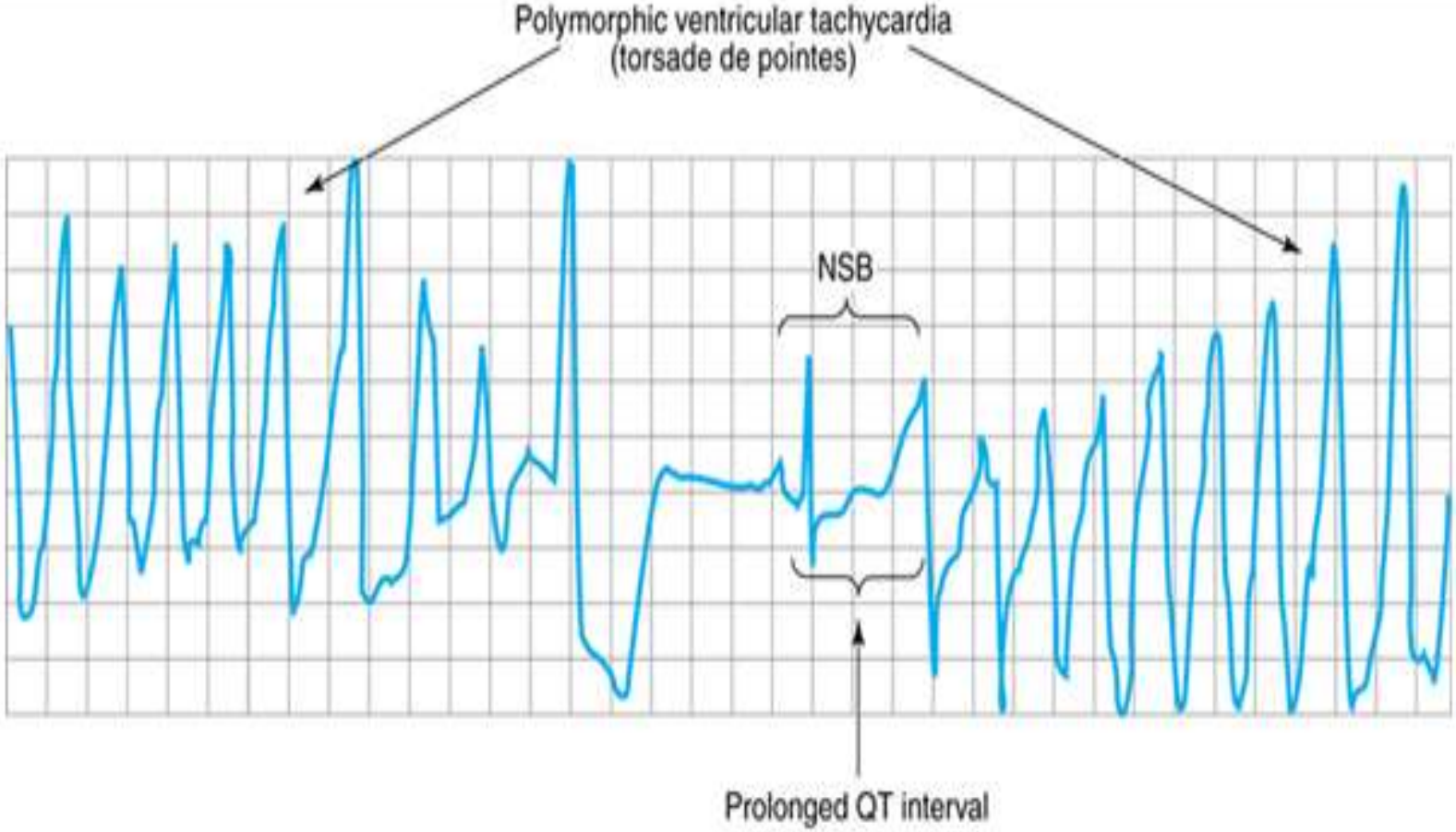
- Familial long QT interval
- Drug - Induced (drugs which prolong APD)

Mechanisms:

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

- **Genetic Studies:**
- 300 different mutations in at least 8 ion channel genes.

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

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.

Other Congenital Arrhythmias

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

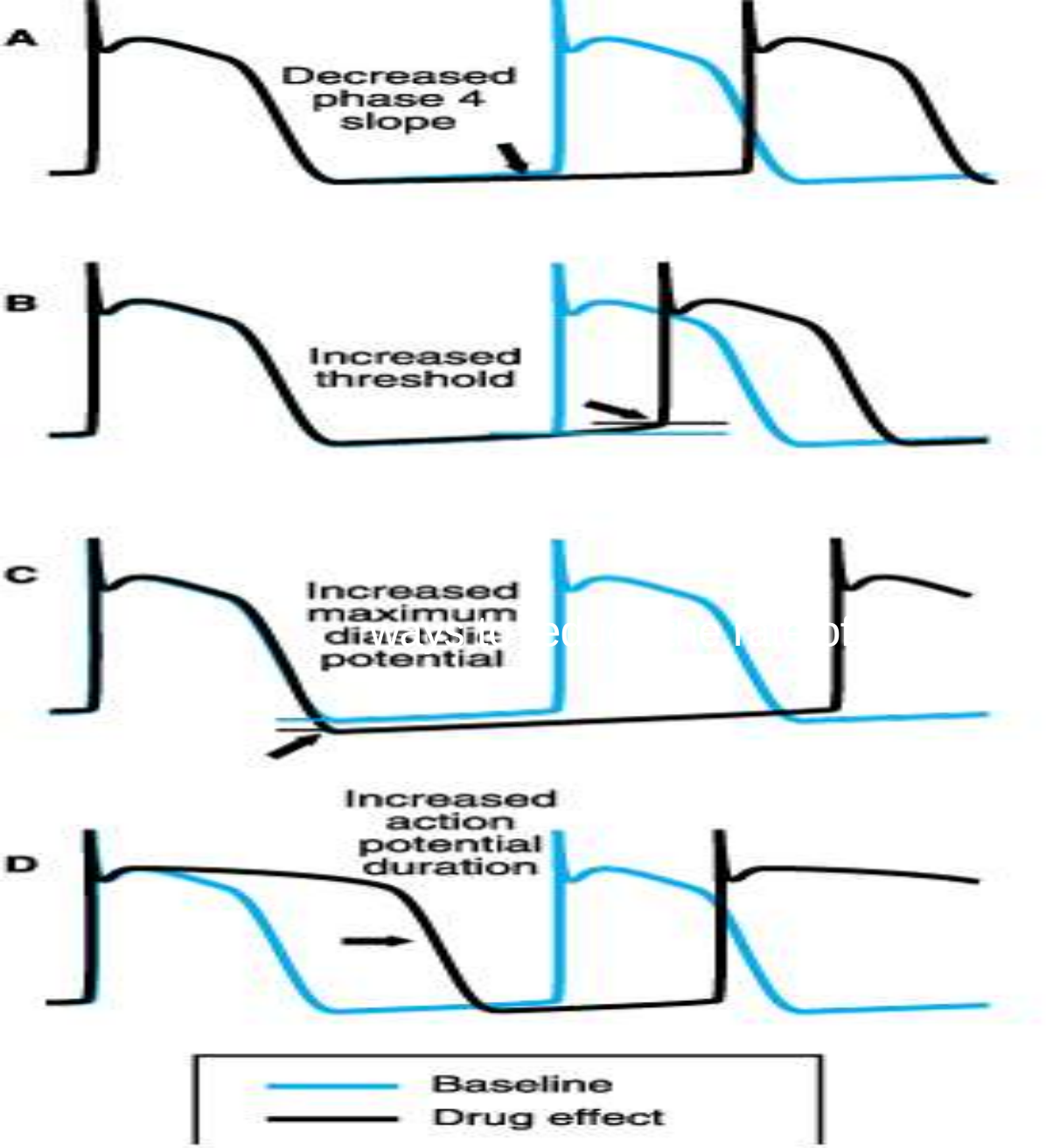
Nonpharmacologic Therapy

- Surgery.
- Radiofrequency Catheter Ablation.
- Implantable Cardioverter- Defibrillator (ICD).

Mechanism of Action of Antiarrhythmic 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.**



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Possible Effects of the Drugs on Action Potential

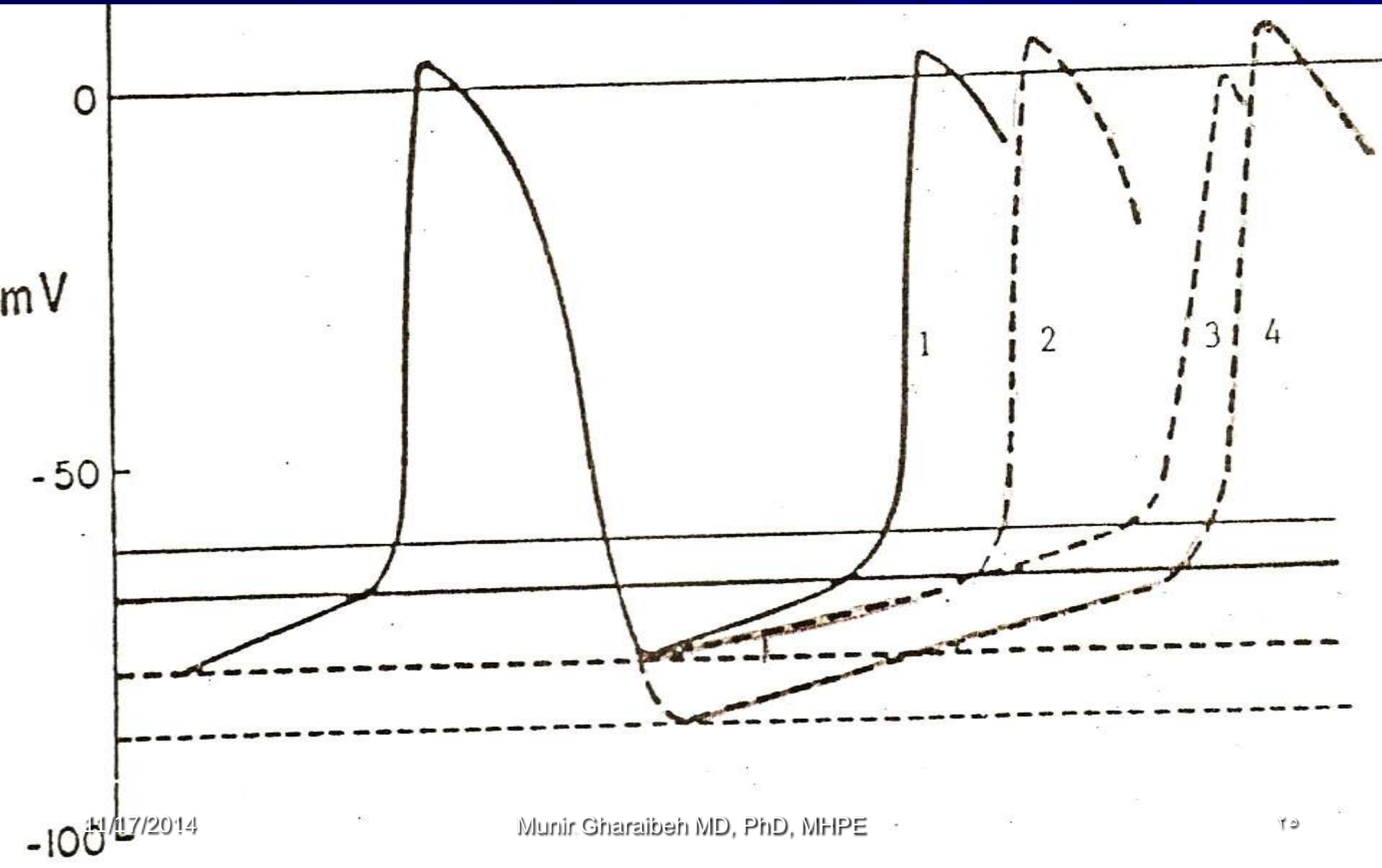
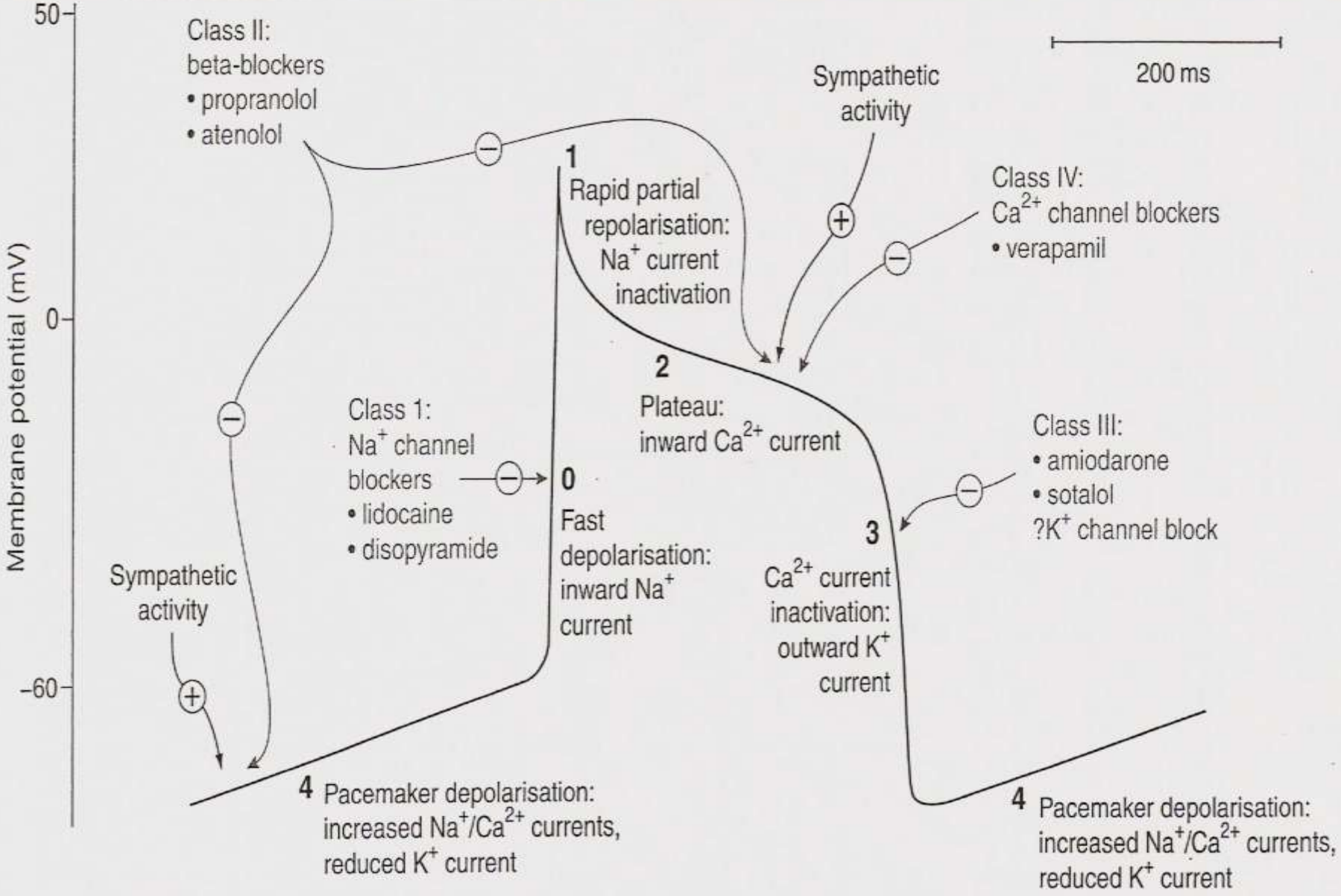


Table 17.1 **The mechanism of action, the electrophysiological actions and clinical uses of selected antidysrhythmic drugs**

		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.

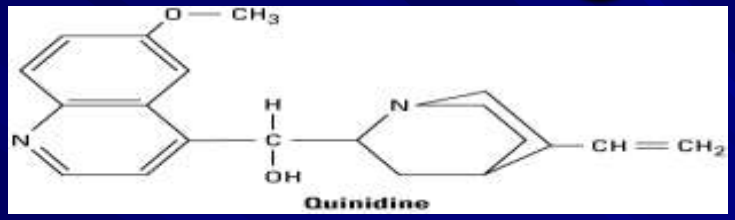


g. 17.1 An idealised action potential in a Purkinje fibre and the sites of actions of antidysrhythmic drugs. In the sinoatrial de, an action potential is triggered when the pacemaker potential reaches a critical threshold (approx. –60 mV).

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
						Supraventricular	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

Class 1A Drugs



Quinidine

Quinidine:

- Prototype, Antimalarial.
- Cinchona tree → Antipyretic.
- Inhibits α and muscarinic receptors.
- Slows upstroke, conduction, and prolongs APD and QRS duration.

Quinidine

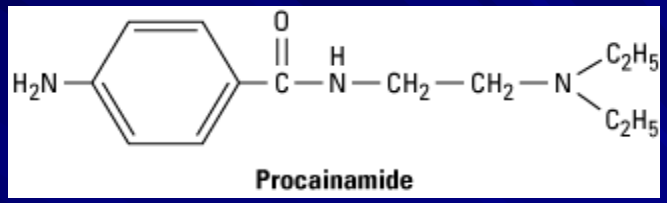
- Use restricted to patients with normal hearts(no failure, no ischemia), but have atrial or ventricular arrhythmias.
- Occasionally used in acute severe malaria.

Quinidine

Side Effects:

- Nausea (18%), Diarrhea (33%).
- Headache, Dizziness, and tinnitus= ***Cinchonism***
- Hypersensitivity, fever, rash, angioedema.
- Thrombocytopenia.
- Excessive prolongation of QT interval, slowed conduction and sudden death (TdP).
- 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 moths)
- Acetylated → NAPA (Class III) action

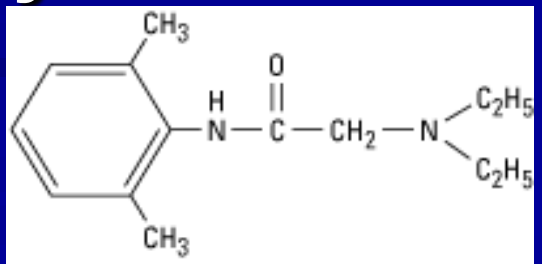
Disopyramide

- More anticholinergic effects but less diarrhea than quinidine

Class 1B Drugs

Lidocaine:

- High affinity to bind with activated and inactivated Na+ channels with rapid kinetics.
- Acts selectively on ischemic 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.
- 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: parasthesia, 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:

- Digitalis induced arrhythmias.
- Epilepsy.
- 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.
- Side Effects: Ventricular arrhythmias, CNS, and sudden death.

Class 1C Drugs

Propafenone:

- Blocks Na+ channels but also has some 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 sympathmimetic activities, has effective antiarrhythmic activity
- Very effective, well tolerated, and documented to reduce mortality after acute myocardial infarction by reducing arrhythmias.

Class II Drugs

Esmolol:

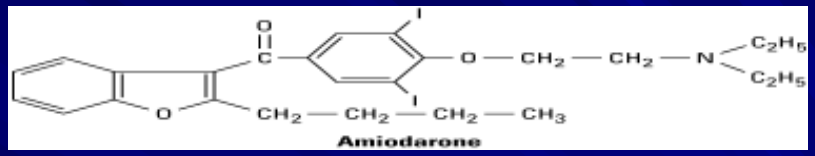
- Short acting, used in intraoperative and acute arrhythmias
- β1 selective
- No membrane stabilization effect.

Acebutolol:

- Short acting, used in intraoperative and acute arrhythmias.
- β1-selective.
- Also has direct membrane stabilizing.

Class III Drugs

Amiodarone:



Amiodarone

- Blocks K+ channels and markedly prolongs APD.
- Class I actions.
- Blocks α and β Receptors.
- Ca++ blocking actions.
- *Reserved for life-threatening atrial and ventricular arrhythmias.*
- Only 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.
- 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).
- ↑ Digoxin & Anticoagulants.
- Interactions: affected by CYP3A4 activity and can inhibit other enzymes.

Class III Drugs

Sotalol:

- Beta blocker and Class III actions.
- Atrial and ventricular arrhythmias.
- Bradycardia, HF, Prolongation of QT.

Bretylium Tosylate:

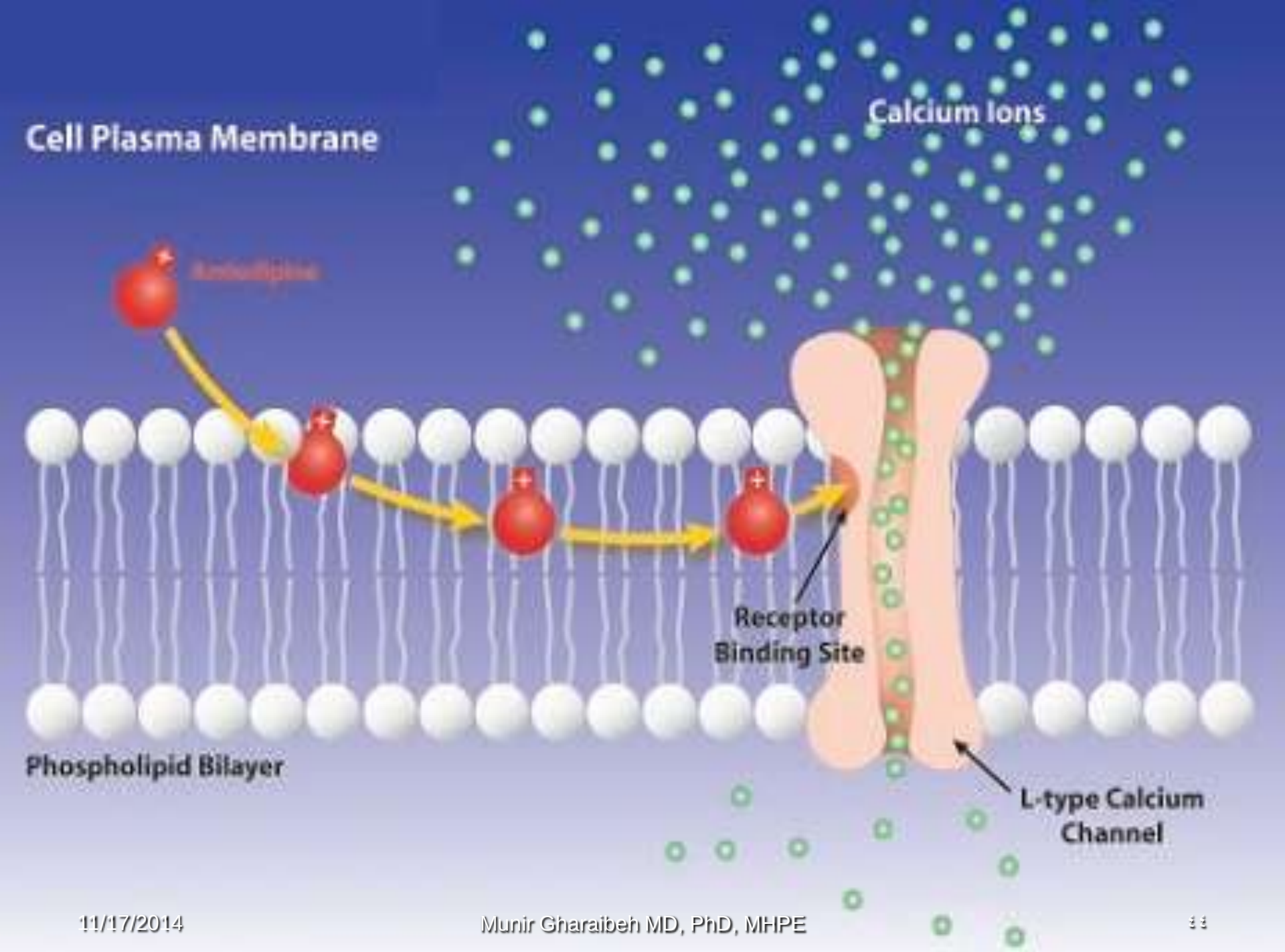
- Originally an antihypertensive, but tolerance develops.
- Releases NE, then ↓ Release / Reuptake
- Rarely used except in the prevention of ventricular fibrillation after cardiversion and lidocaine.
- Hypotension, Parotid swelling.
- **Ibutilide.**
- **Dofetilide.**

Class IV Drugs
(Ca++ Channel Blockers)

Verapamil
Diltiazem

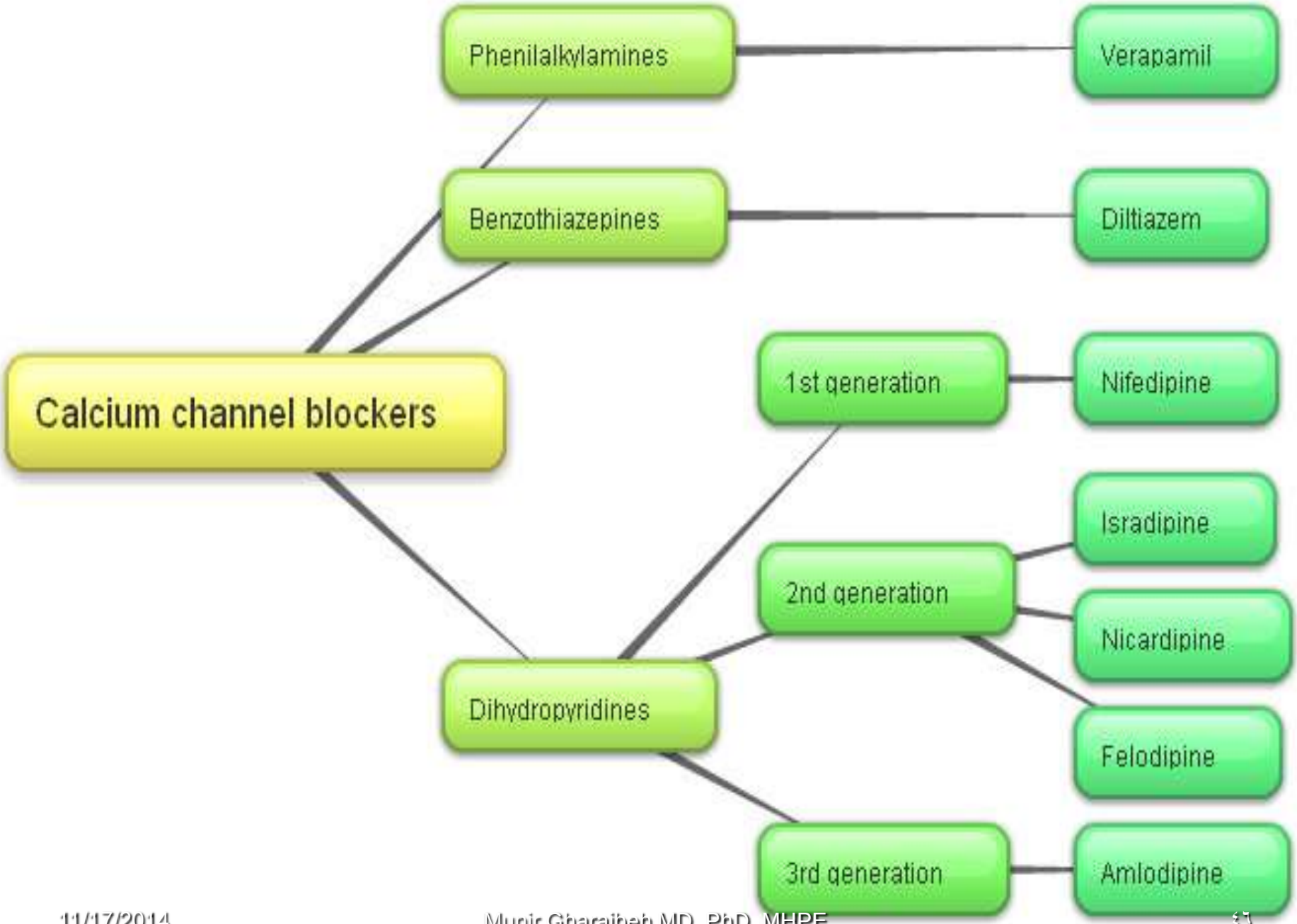
Block activated and inactivated L-type Ca++ channels.

- **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.**
- **Safe: Constipation, gastric discomfort, vertigo, headache, nervousness, pruritis.**
- **↑ Digoxin levels.**


Cell Plasma Membrane
Calcium Ions
Receptor
Binding Site
Phospholipid Bilayer
L-type Calcium
Channel

Properties of Several Recognized Voltage-Activated Calcium Channels.

Type	Channel Name	Where Found	Properties of the Calcium Current	Blocked By
L	$Ca_V1.1$–$Ca_V1.3$	Cardiac, skeletal, smooth muscle, neurons ($Ca_V1.4$ is found in retina), endocrine cells, bone	Long, large, high threshold	Verapamil, DHPs, Cd^{2+}, -aga-IIIA
T	$Ca_V3.1$–$Ca_V3.3$	Heart, neurons	Short, small, low threshold	sFTX, flunarizine, Ni^{2+}, mibefradil[1]
N	$Ca_V2.2$	Neurons, sperm[2]	Short, high threshold	Ziconotide,[3] g abapentin,[4] -CTX-GVIA, -aga-IIIA, Cd^{2+}
P/Q	$Ca_V2.1$	Neurons	Long, high threshold	-CTX-MVIIC, -aga-IVA
R	$Ca_V2.3$	Neurons, sperm[2]	Pacemaking	SNX-482, -


Calcium channel blockers
Phenilalkylamines
Verapamil
Benzothiazepines
Diltiazem
Dihydropyridines
1st generation
Nifedipine
2nd generation
Isradipine
Nicardipine
Felodipine
3rd generation
Amlodipine

Miscellaneous Drugs

Digoxin:

- Old fashioned agent for atrial arrhythmias.
- Direct Actions.
- Vagotonic Effects.
- ↑ AV refractoriness.

Miscellaneous Drugs

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.
- Also, in TdP patients even if serum Mg++ is normal.

Potassium salts:

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

Miscellaneous Drugs

Adenosine:

- Naturally occurring nucleoside.
- 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.

Miscellaneous Drugs

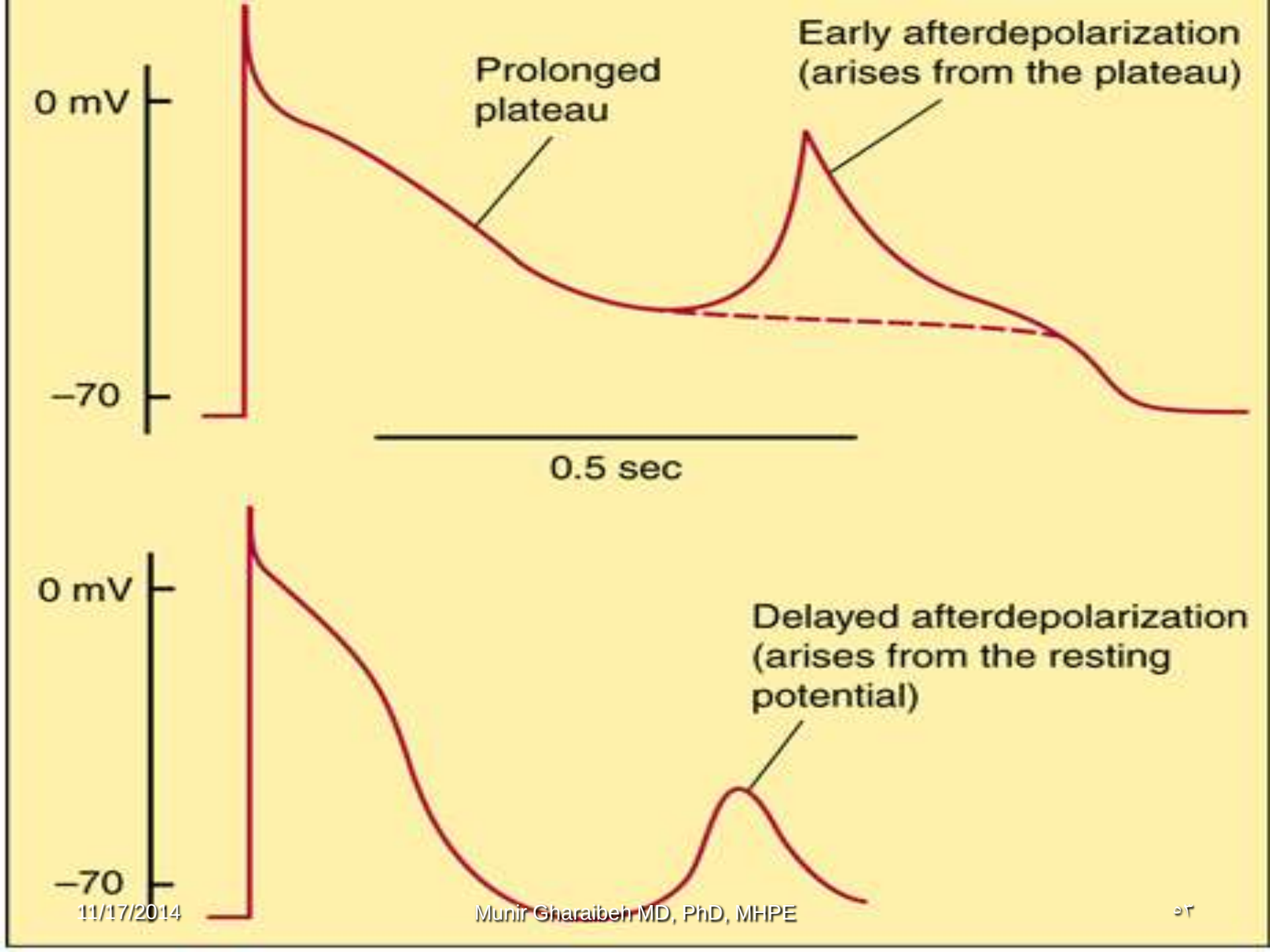
Adenosine:

- 90-95% effective in supraventricular tachycardia.
- Less effective in the presence of adenosine receptor blockers, e.g. theophylline and caffeine.
- Can cause very short –lived flushing (20%), chest tightness, AV block, headache, hypotension, nausea, and parasthesia.

Afterdepolarizations (Triggered Automaticity)

Require a normal action potential for their initiation.

- **Early Afterdepolarizations (EAD):**
  - Interrupt phase 3.
  - Exacerbated at low heart rates.
  - Contribute to development of long QT-related arrhythmias.
- **Delayed Afterdepolarizations (DAD):**
  - Occur with increased intracellular calcium.
  - Exacerbated by fast heart rates.
  - Responsible for arrhythmias of digitalis, catecholamines, and ischemia.


0 mV
−70
Prolonged plateau
Early afterdepolarization (arises from the plateau)
0.5 sec
0 mV
−70
Delayed afterdepolarization (arises from the resting potential)