Antiarrhythmic Drugs

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Cardiac Arrhythmias

Definition.

Etiology:

- Hereditary
- Acquired

Types:

Abnormalities of Impulse Formation:

- Rate disturbances.
- Triggered automaticity.

Abnormalities of Impulse Conduction:

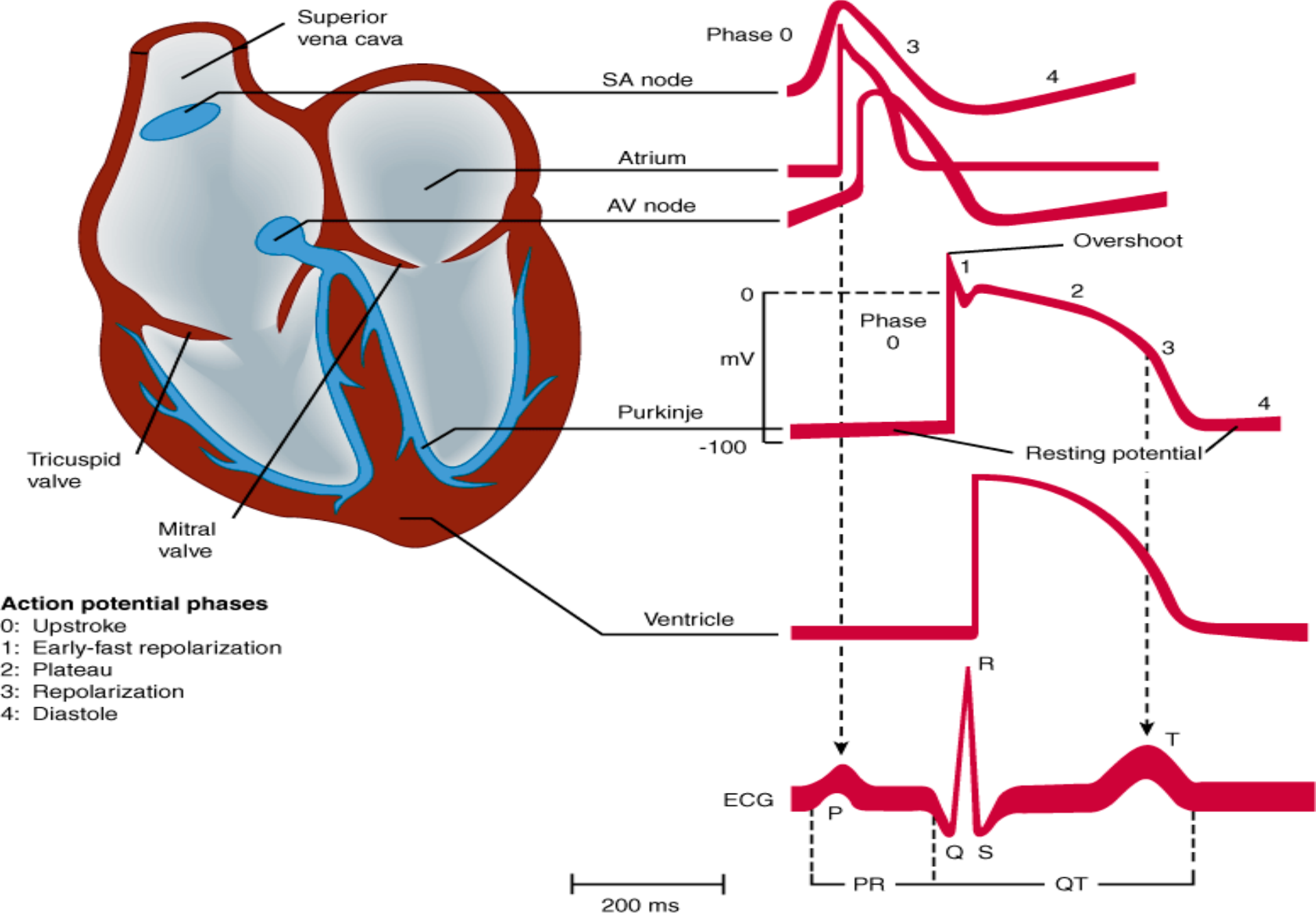
- Blocks.
- Reentry.

Cardiac Causes of Arrhythmias

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

Non Cardiac causes Arrhythmias

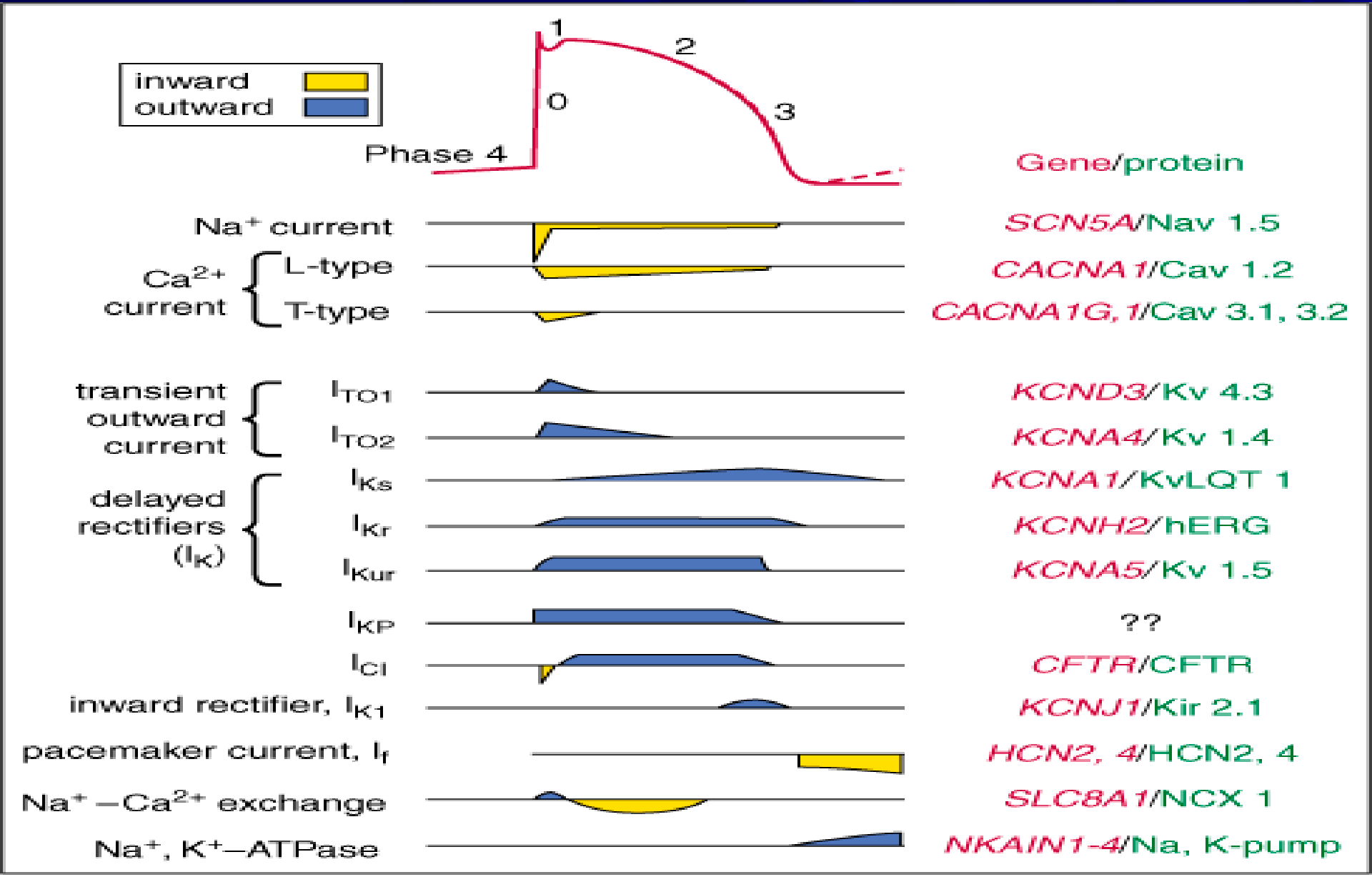
- Electrolyte imbalance.
- Acid-Base imbalance.
- Hypoxia.
- Drugs:
  - Digitalis
  - Anesthetics
  - Tricyclic
  - Diuretics
  - Bronchodilators: sympathomimetic.
- Reflexes.



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



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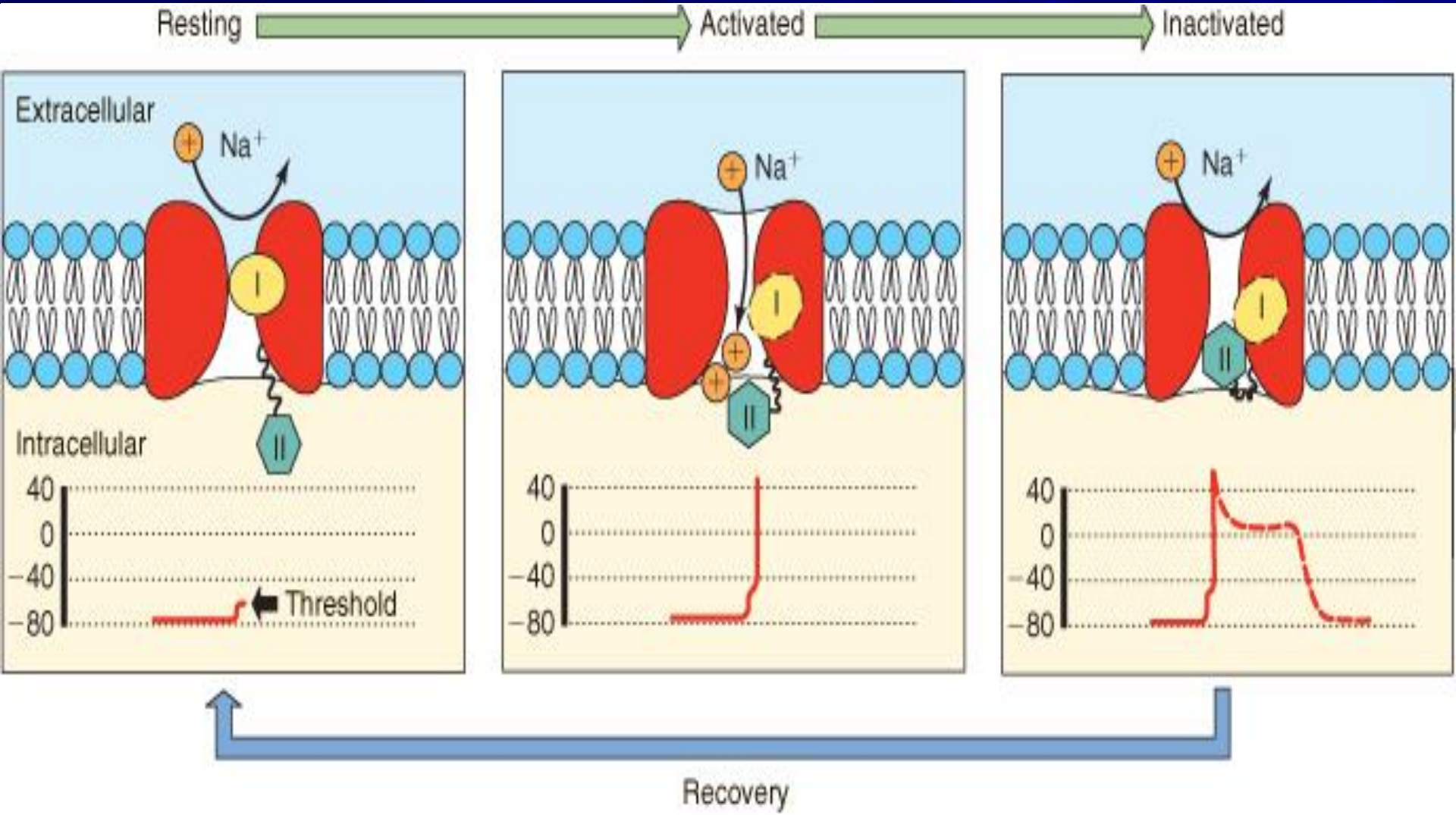
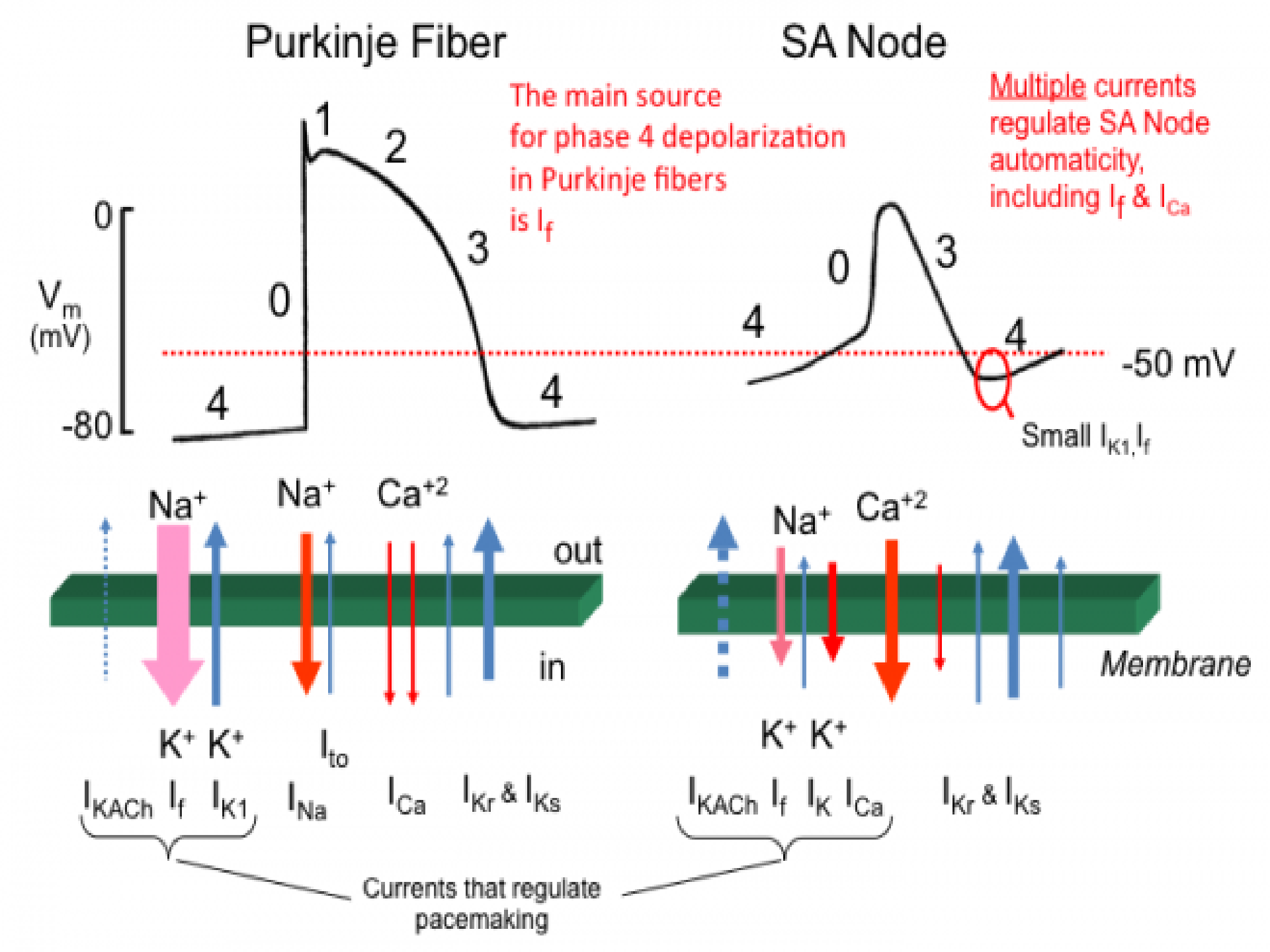
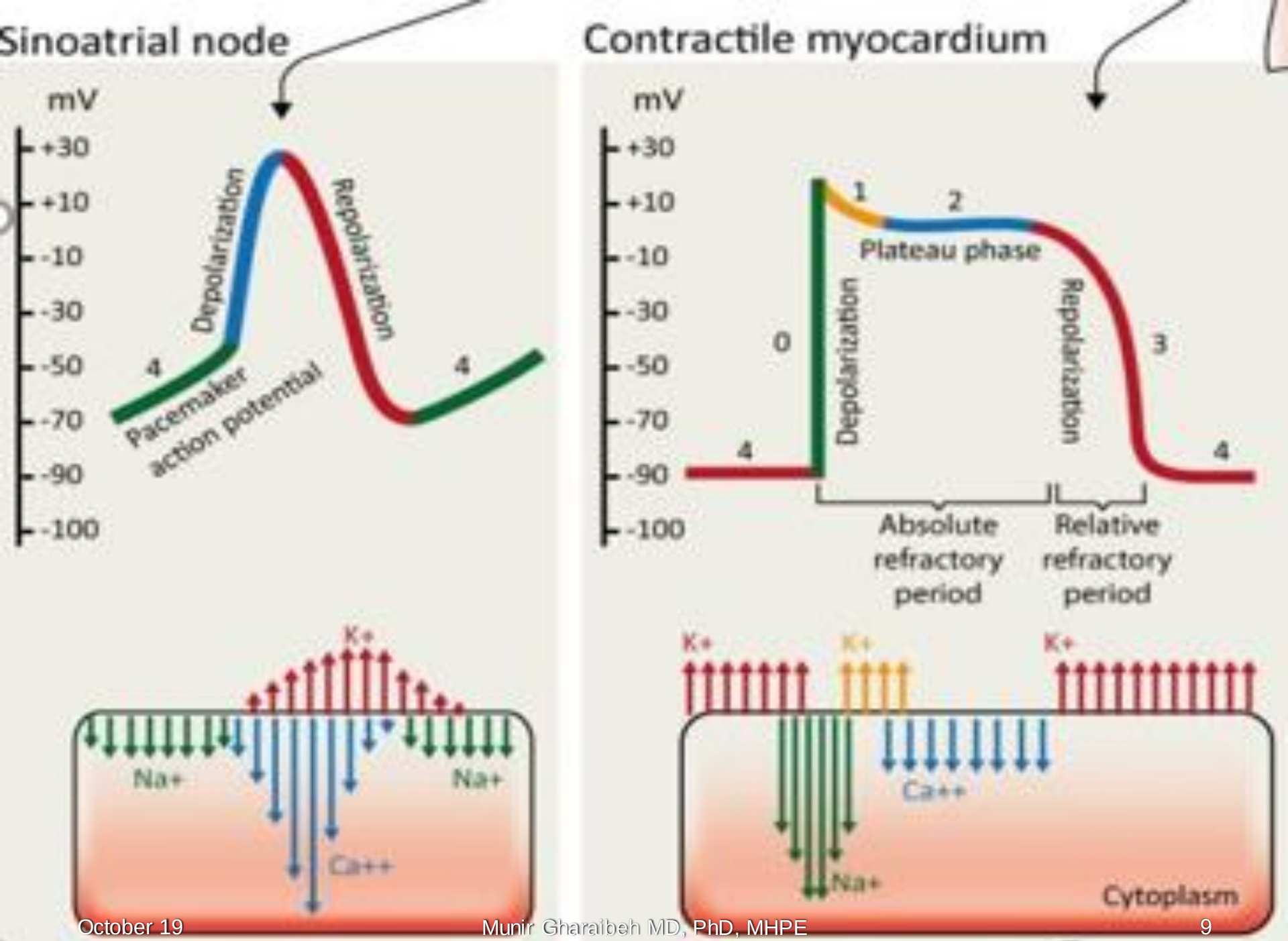
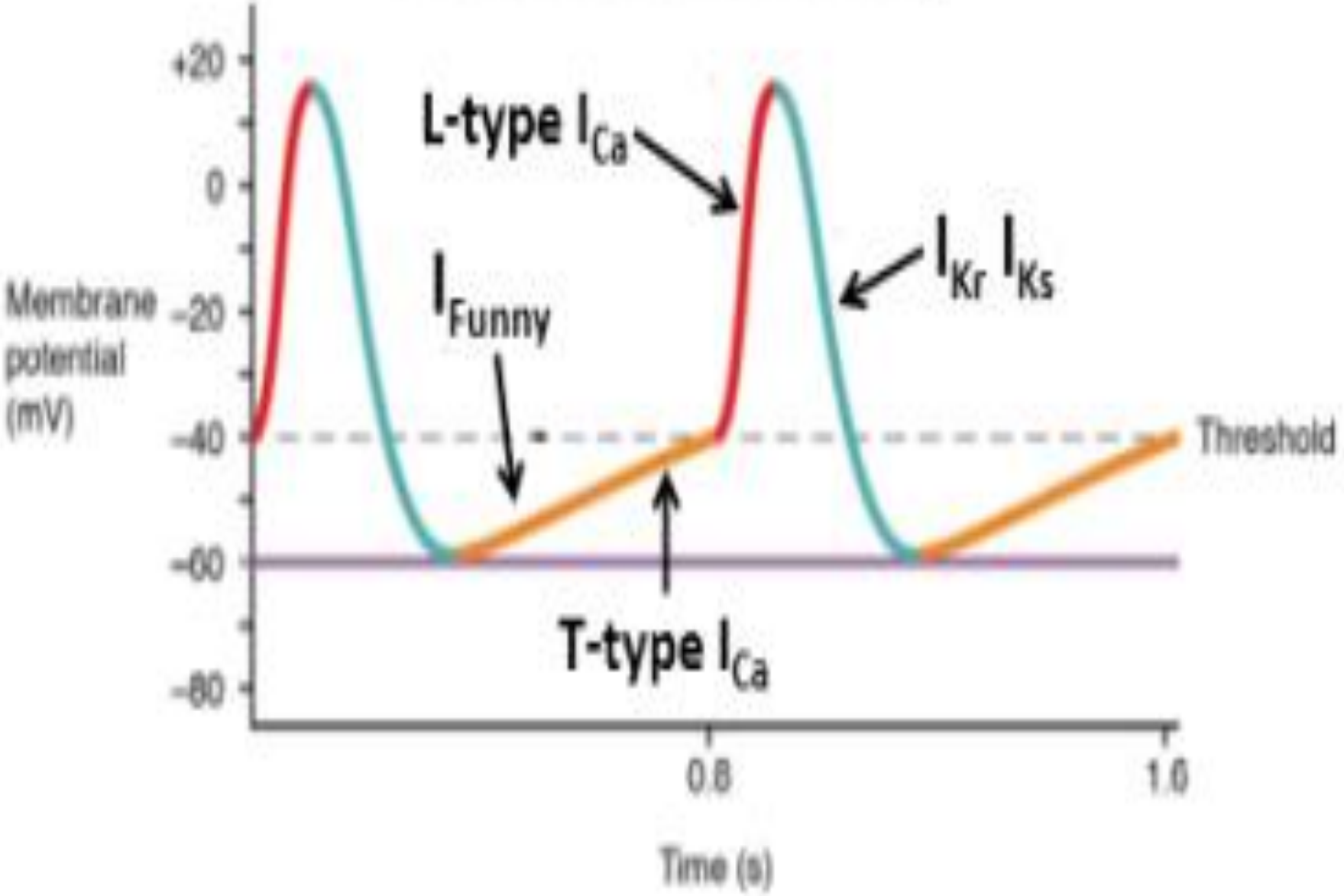
Cardiac Na+ channels



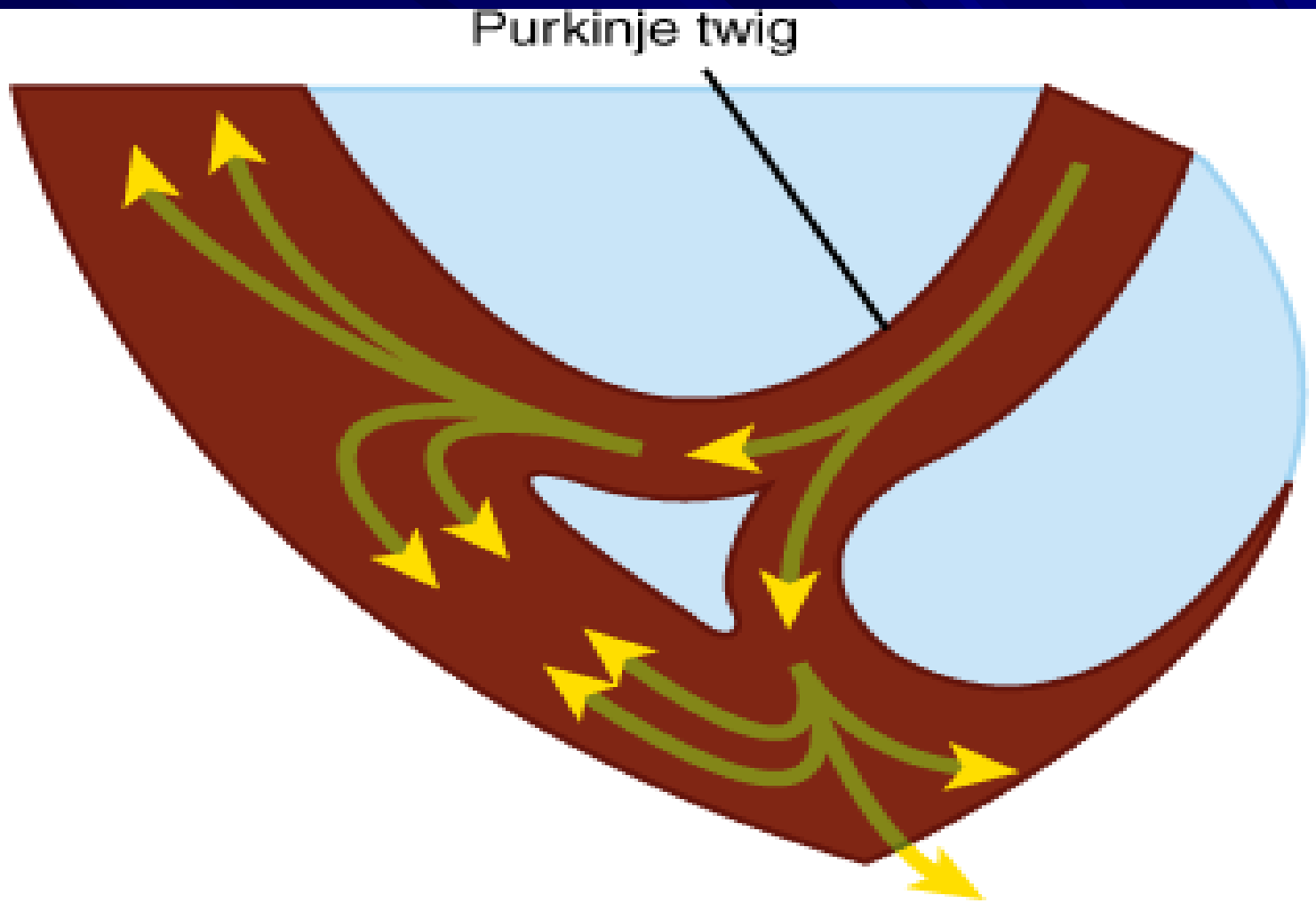

Purkinje Fiber
SA Node
The main source for phase 4 depolarization in Purkinje fibers is I_f
Multiple currents regulate SA Node automaticity, including I_f & I_{Ca}
V_m (mV)
0
-80
1
2
3
0
4
4
0
3
4
4
-50 mV
Small I_{K1}, I_f
Na^+
Na^+
Ca^{+2}
out
in
K^+ K^+
I_{to}
I_{KACh} I_f I_{K1}
I_{Na}
I_{Ca}
I_{Kr} & I_{Ks}
Na^+
Ca^{+2}
Membrane
K^+ K^+
I_{KACh} I_f I_K I_{Ca}
I_{Kr} & I_{Ks}
Currents that regulate pacemaking


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

SA node automaticity



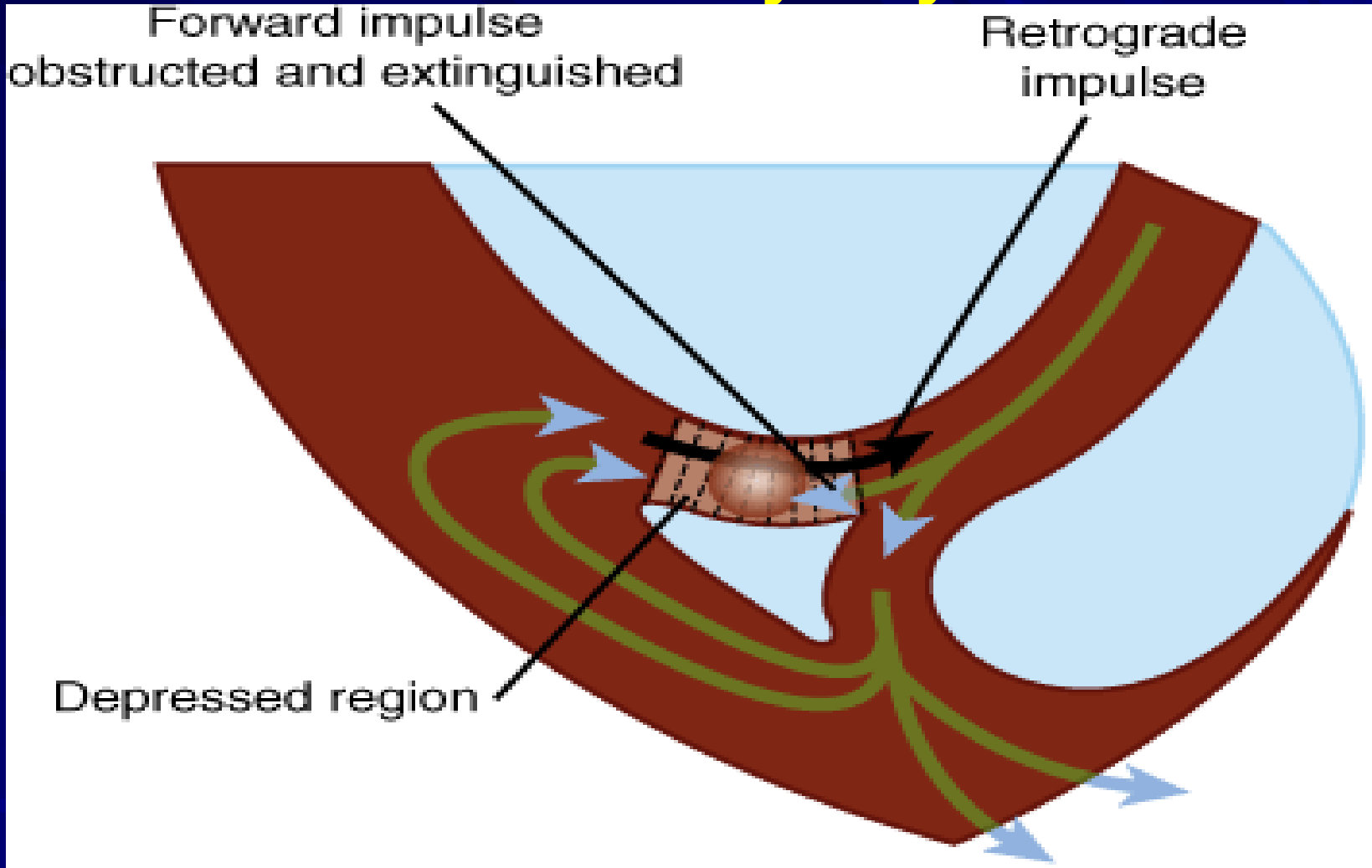
Normal Circuitry



A. Normal conduction

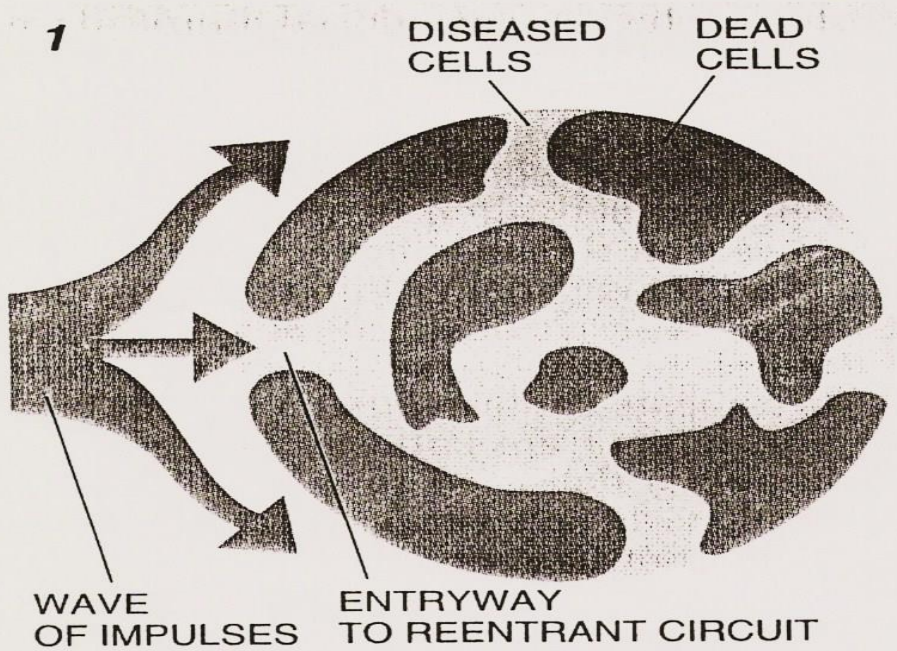
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

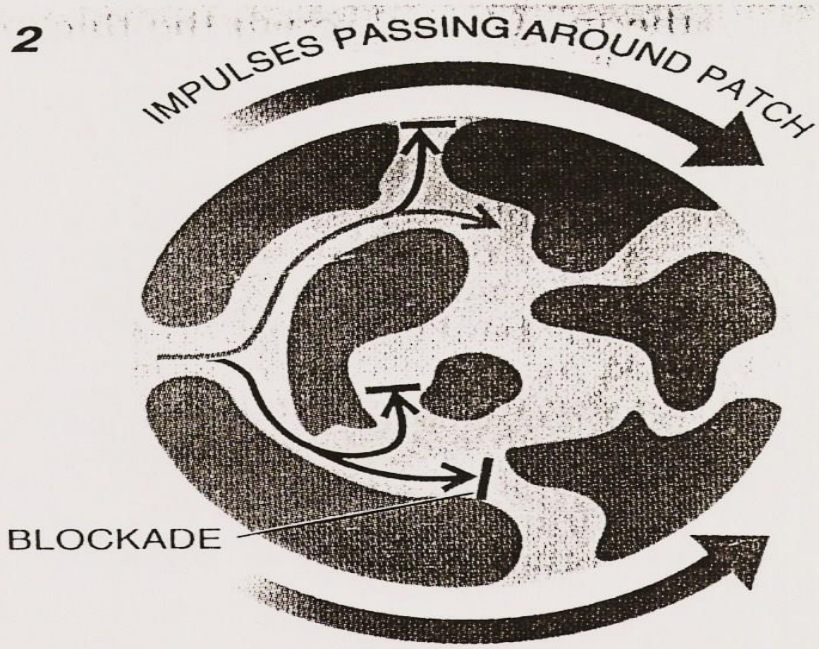
Re-entry Rhythm

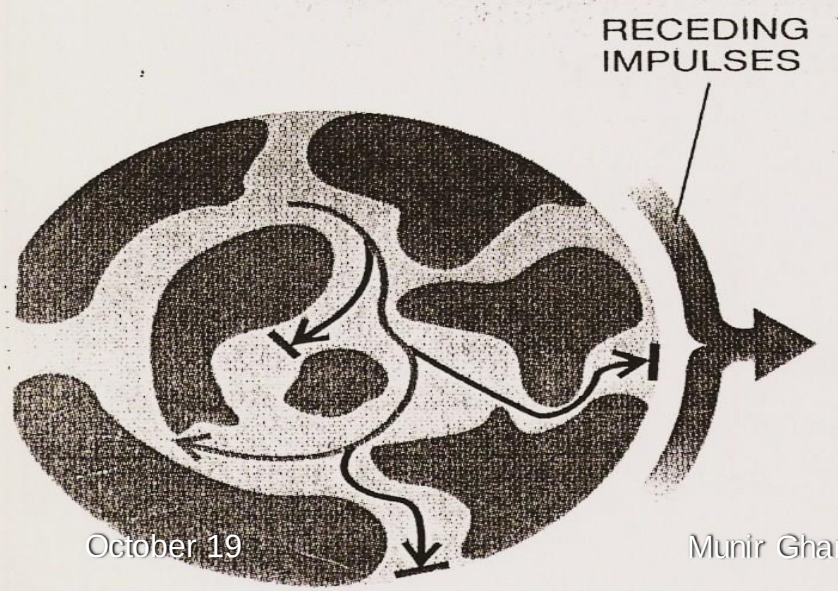


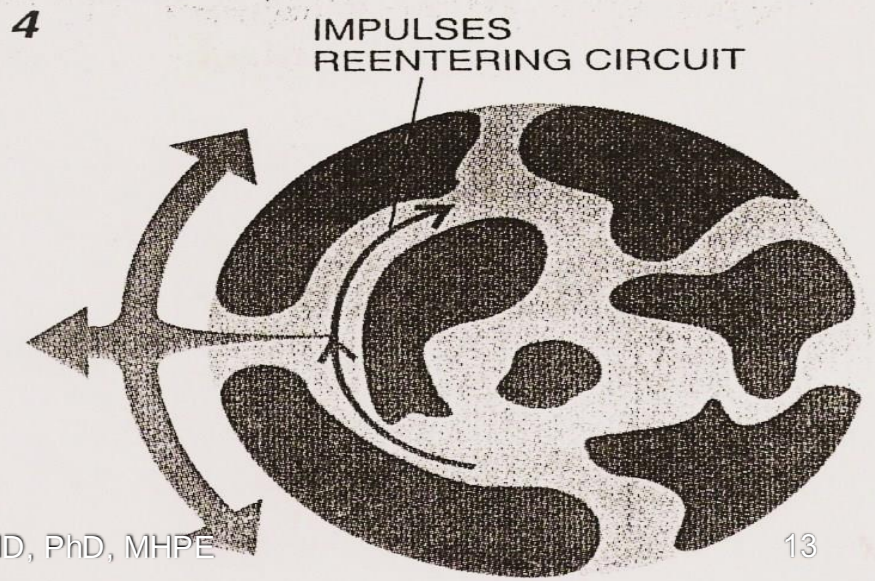
B. Unidirectional block

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


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


2
IMPULSES PASSING AROUND PATCH
BLOCKADE


RECEDING IMPULSES


4
IMPULSES REENTERING CIRCUIT

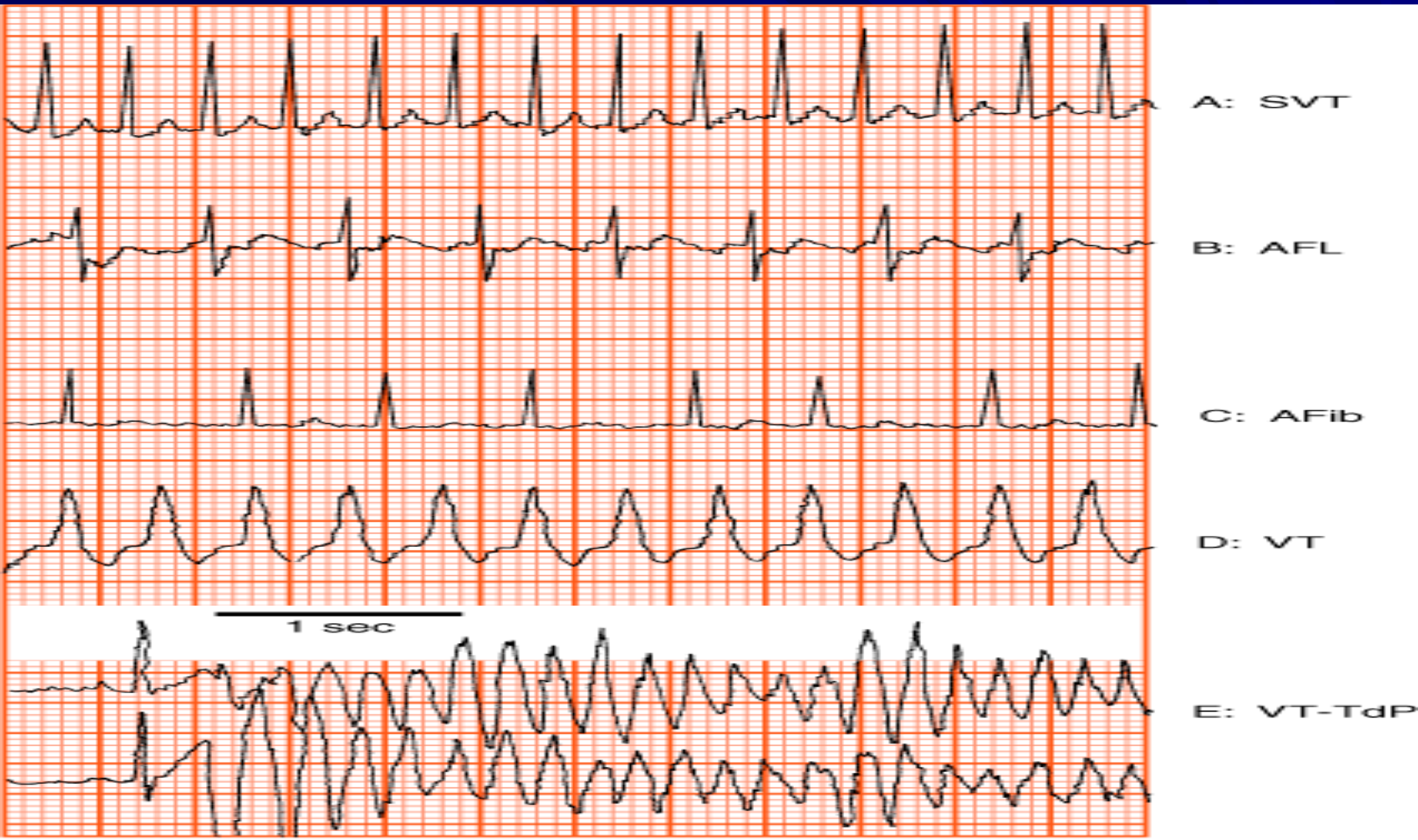
Pre-requisites for Reentry (Circus Movement)

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

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

ECG of some Arrhythmias



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

Torsade de Pointes
Polymorphic Ventricular Tachycardia

LQT, syncope, and sudden death.

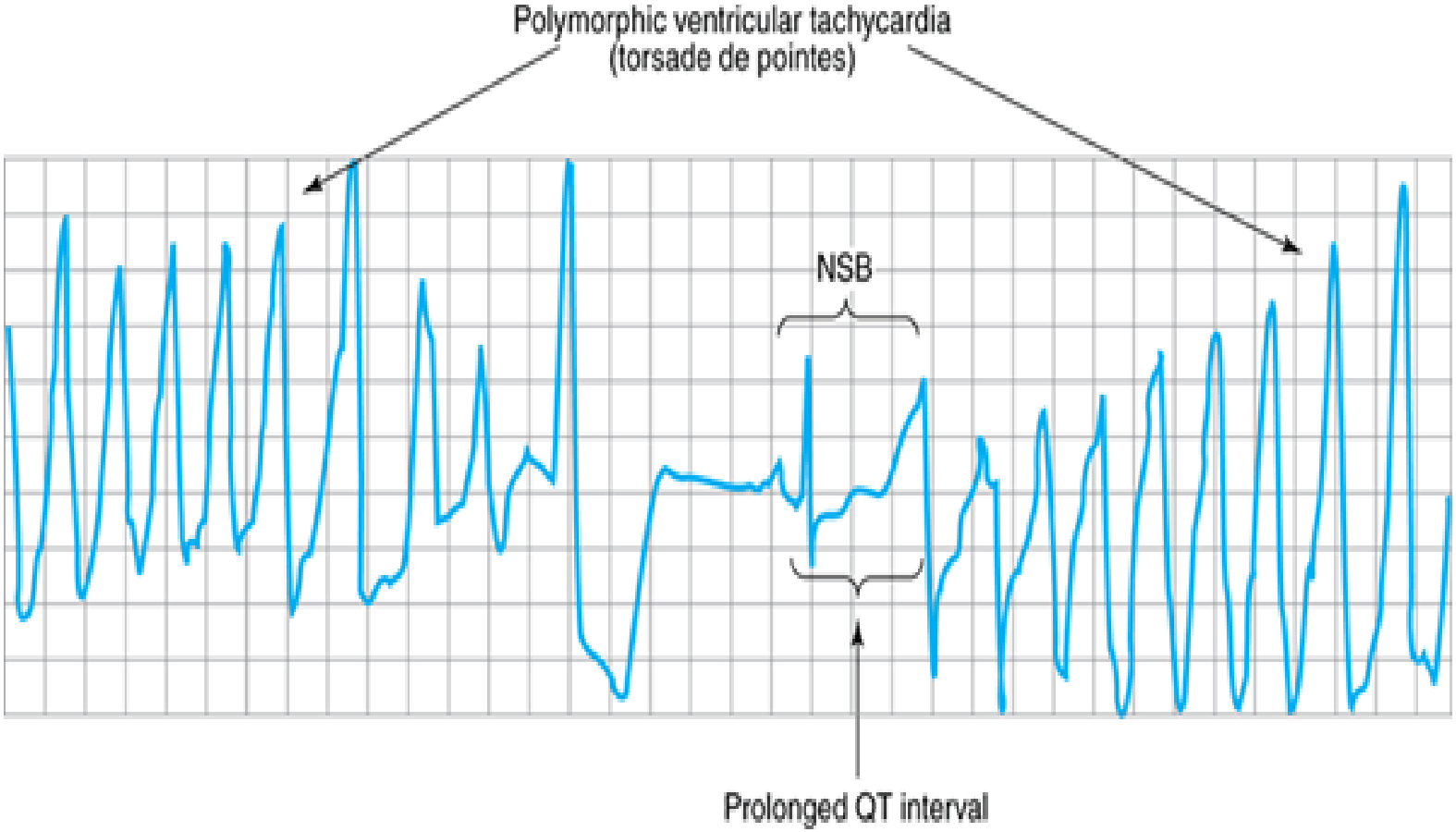
Causes:

- 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.

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

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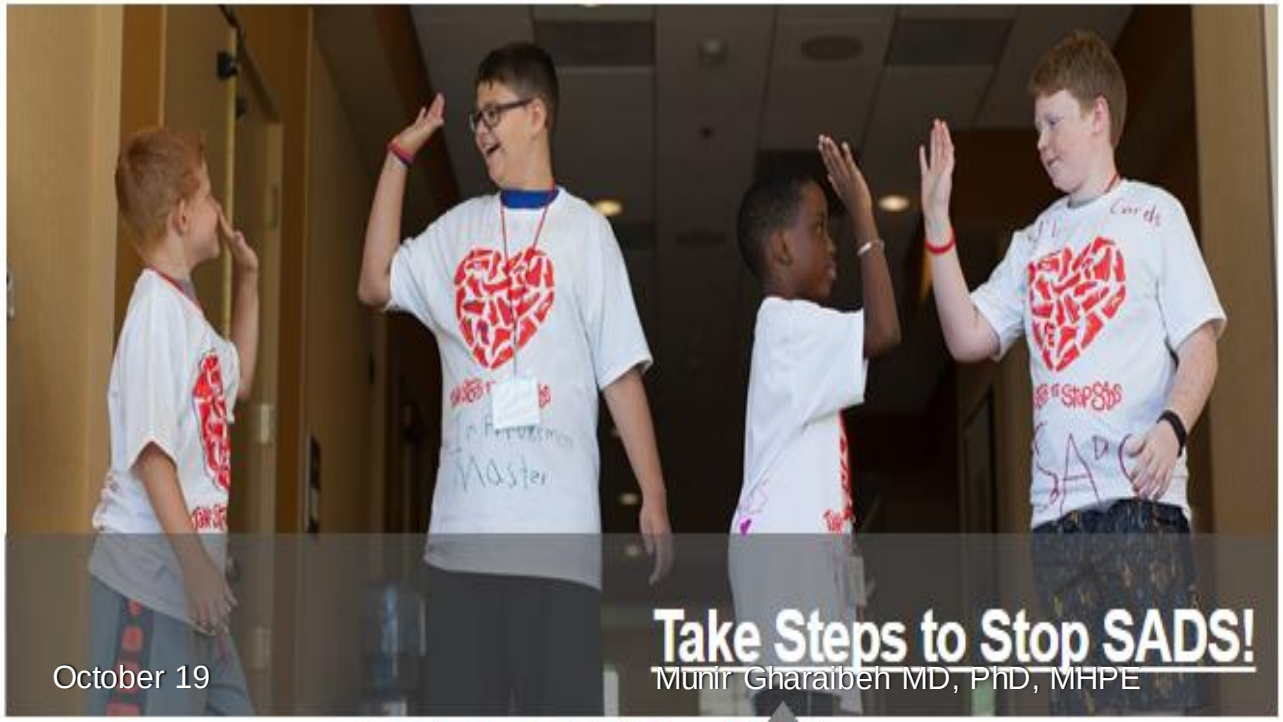

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Other Congenital Arrhythmias

- **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(5 in 10,000).
  - Linked to LF mutations in SCN5A
- **Familial Atrial Fibrillation:**
  - Linked to GF mutation in the potassium channel gene, KCNQ1.

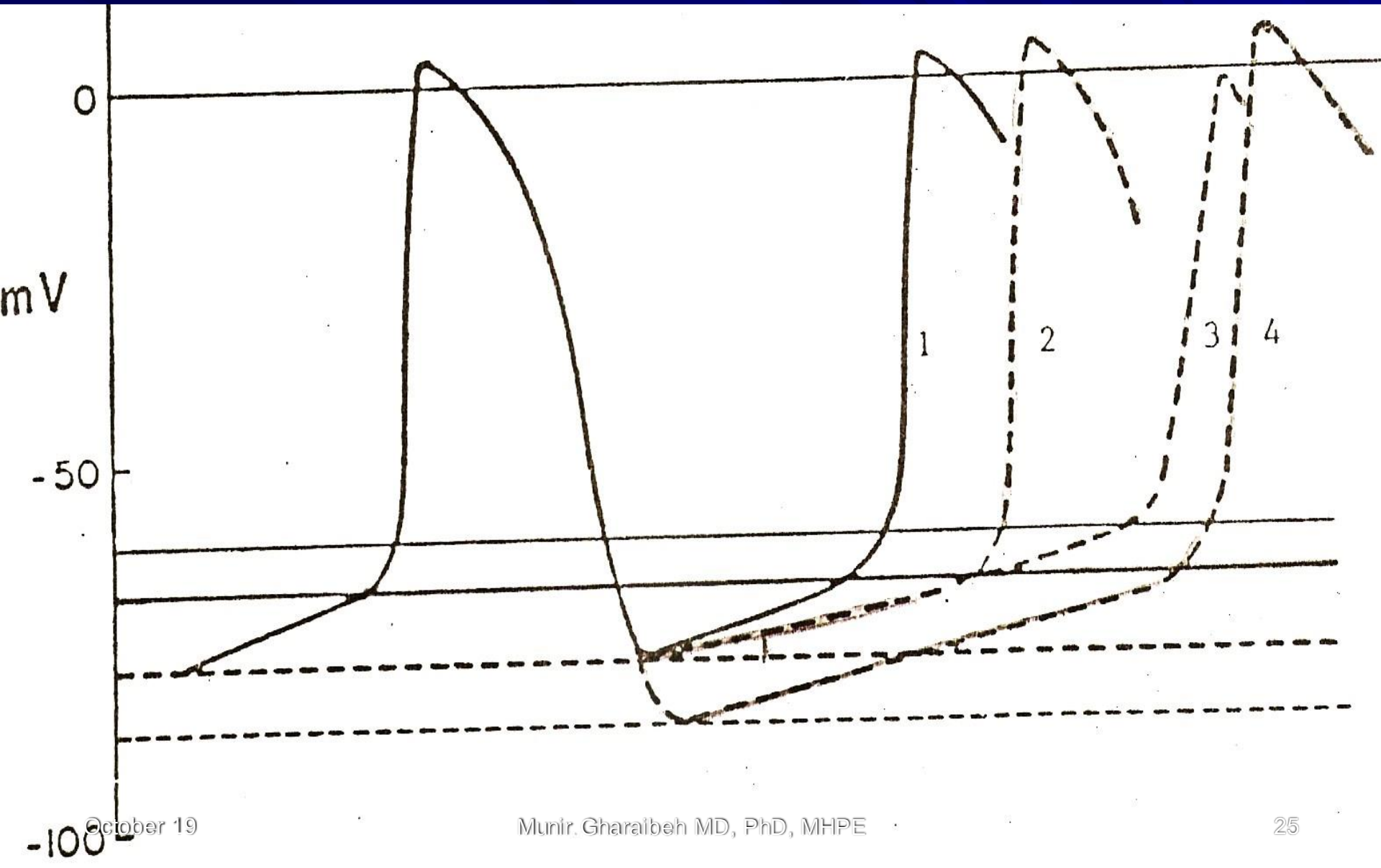
Nonpharmacologic Therapy

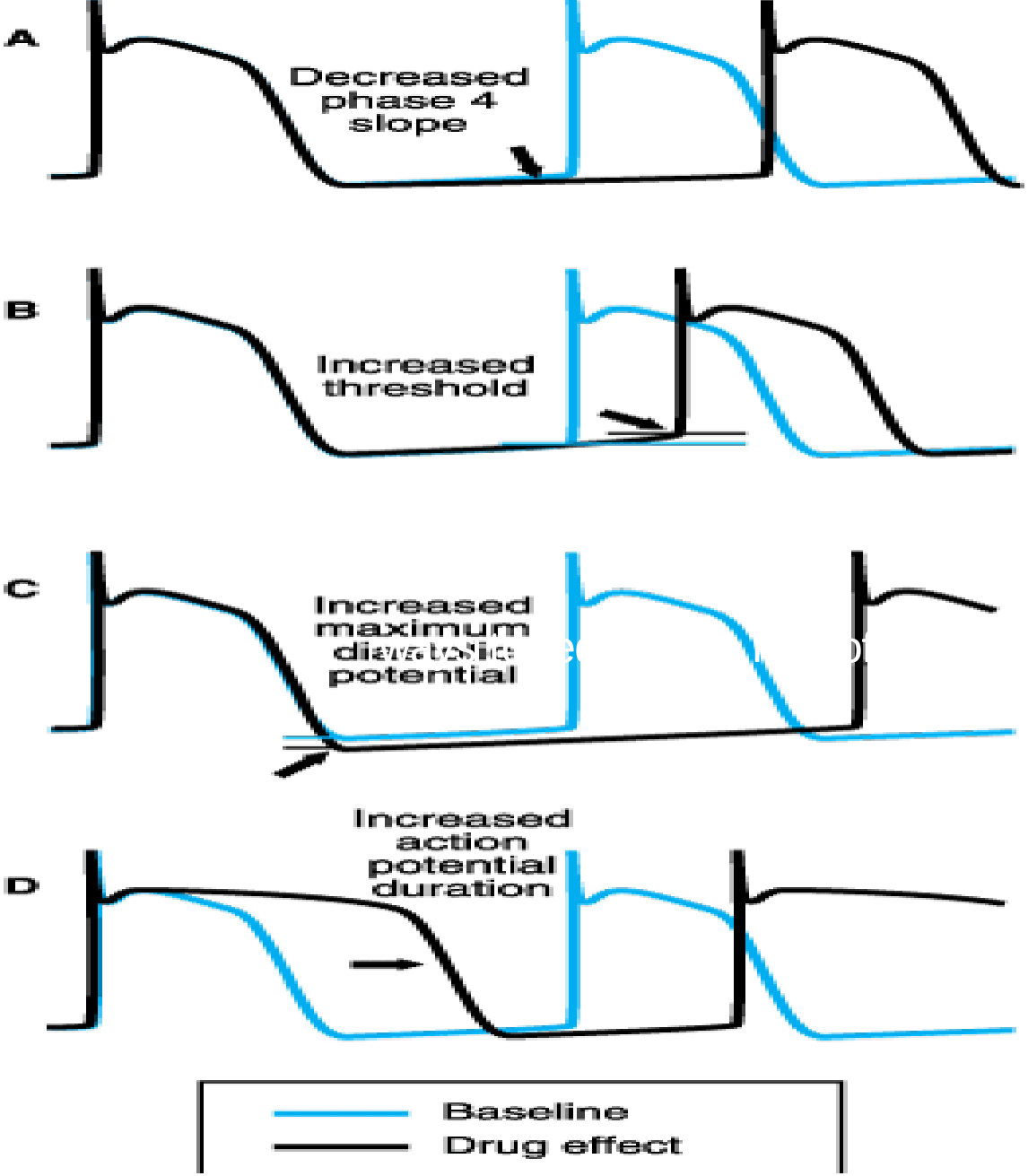
- Surgery.
- Radiofrequency Catheter Ablation(إستئصال).
- Cryoablation.
- Implantable Cardioverter- Defibrillator (ICD).
- Gene therapy!!!!.

Principles of Mechanisms 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.**

Possible Effects of Drugs on Action Potential





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

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.

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

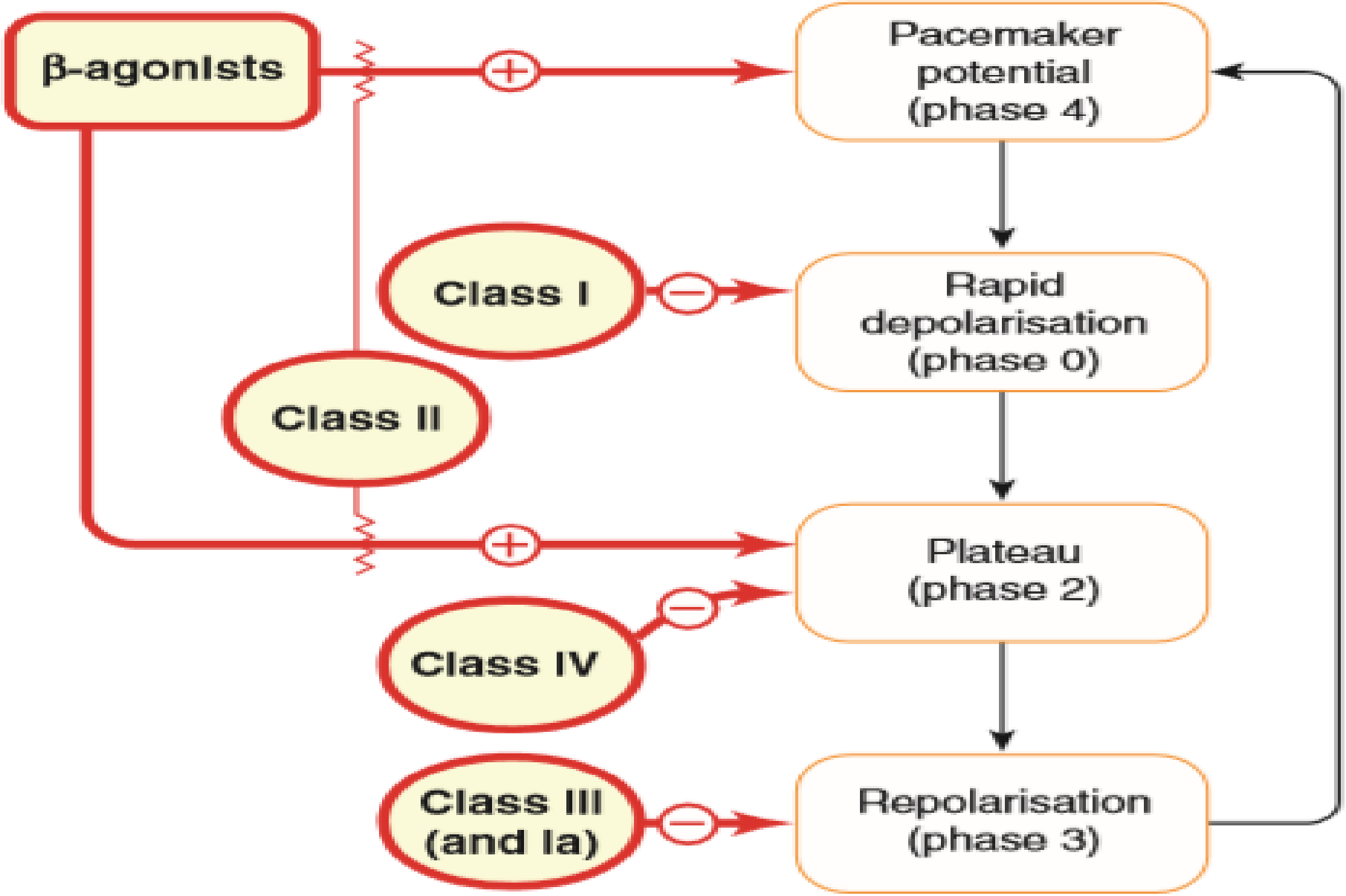
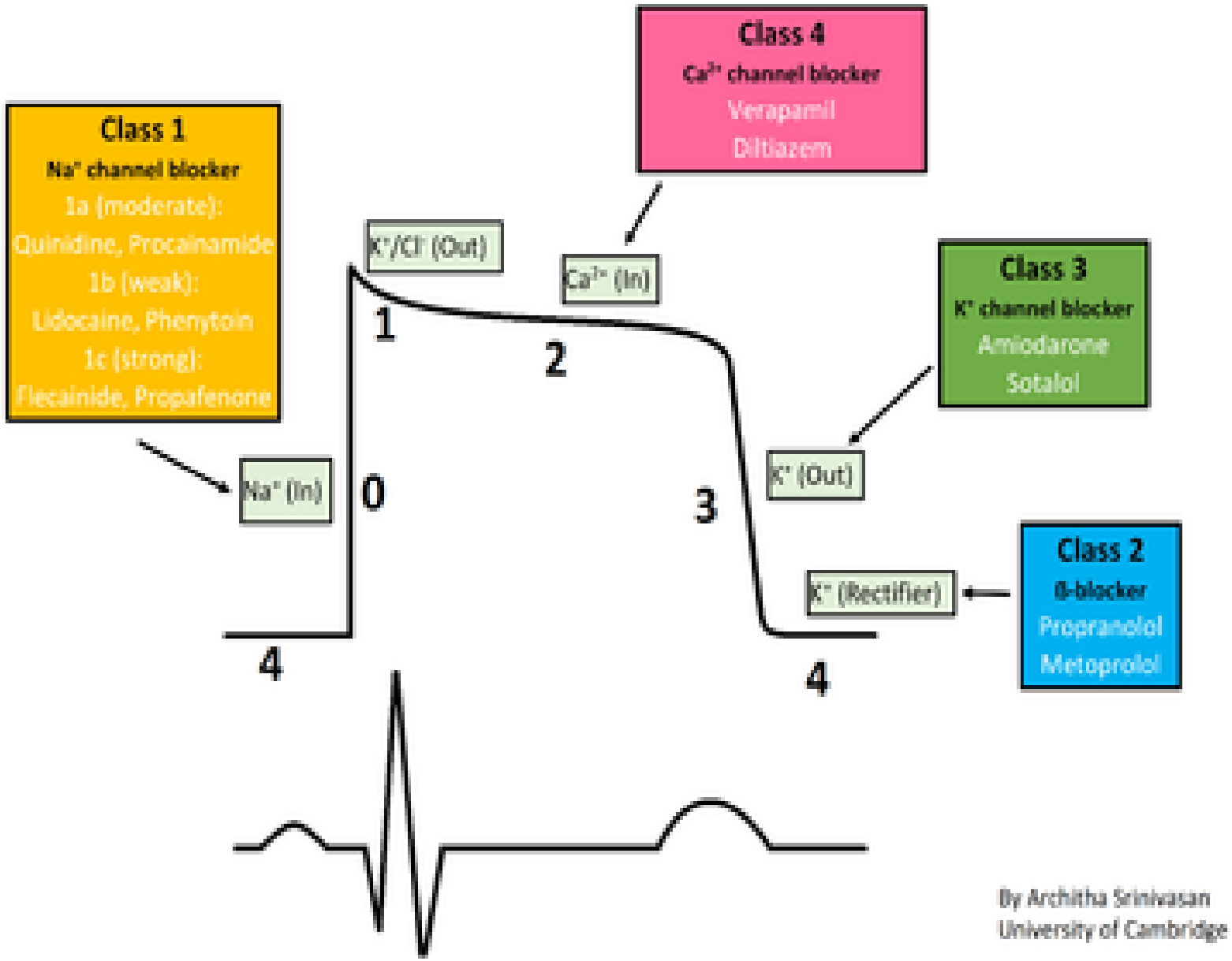


Fig. 21.9 Effects of antidysrhythmic drugs on the different phases (as defined in Fig. 21.1) of the cardiac action potential.

Drugs Affecting the Cardiac Action Potential



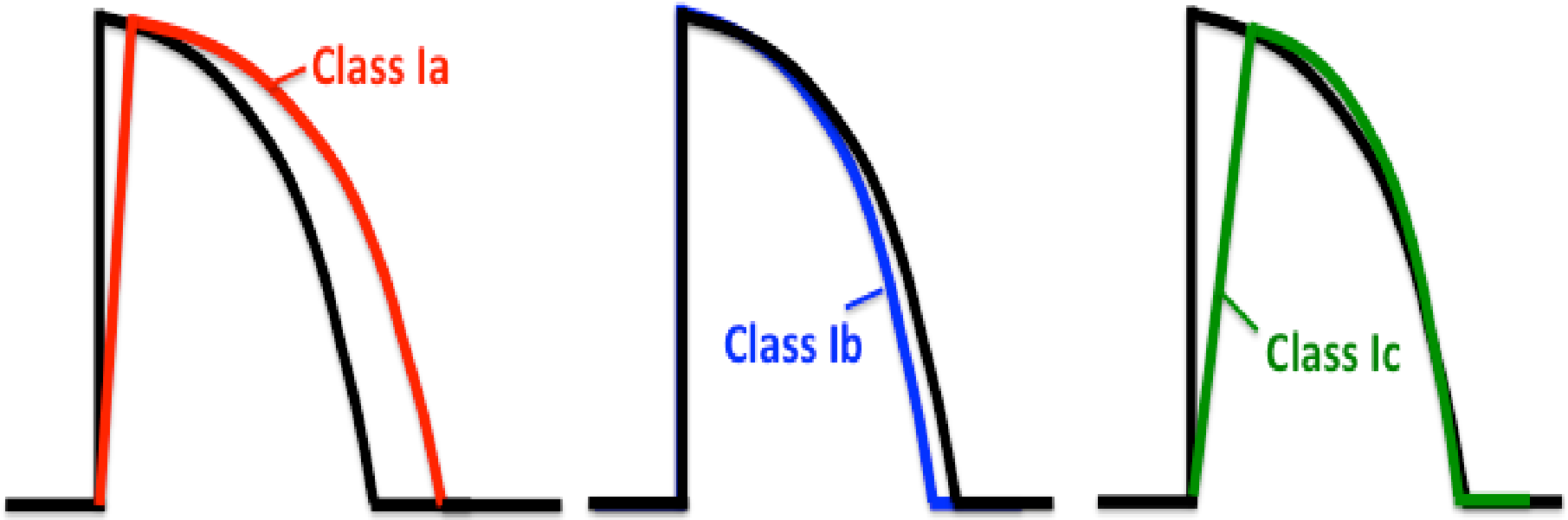
By Architha Srinivasan
University of Cambridge

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: Supraventricular	Usefulness in Arrhythmias: Ventricular	Half-Life
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 I Antiarrhythmic Drug Effects

On the Ventricular Action Potential:



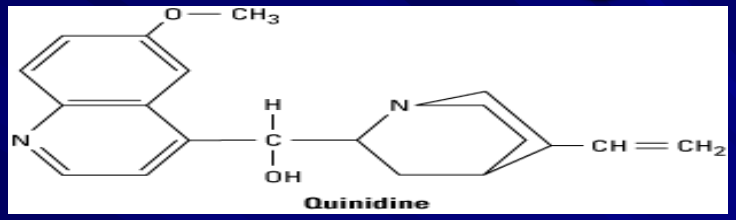
On the ECG:

↑QRS & ↑QT

↓QT

↑↑QRS

Class 1A Drugs



Quinidine:

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

Quinidine

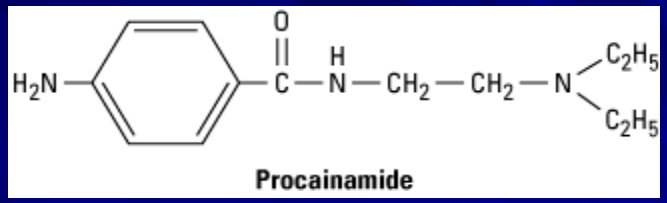
- Use nowadays restricted to patients with normal hearts(no failure, no ischemia), but have atrial or ventricular arrhythmias.

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 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

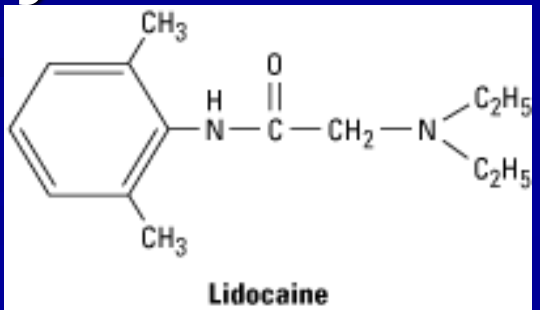
Disopyramide

- 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 in 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, 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.
- For Digitalis- induced arrhythmias.
- For arrhythmias after congenital heart surgery.
- Also for, 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 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 Drugs

Esmolol:

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

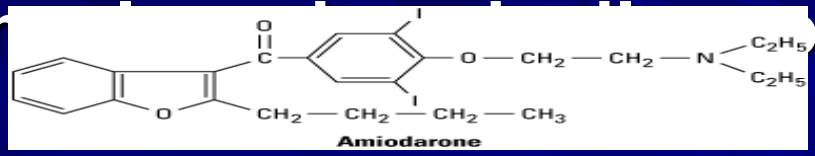
Acebutolol:

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

Class III Drugs

Amiodarone:

- Blocks K+ char… …longs APD.



Amiodarone

- 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

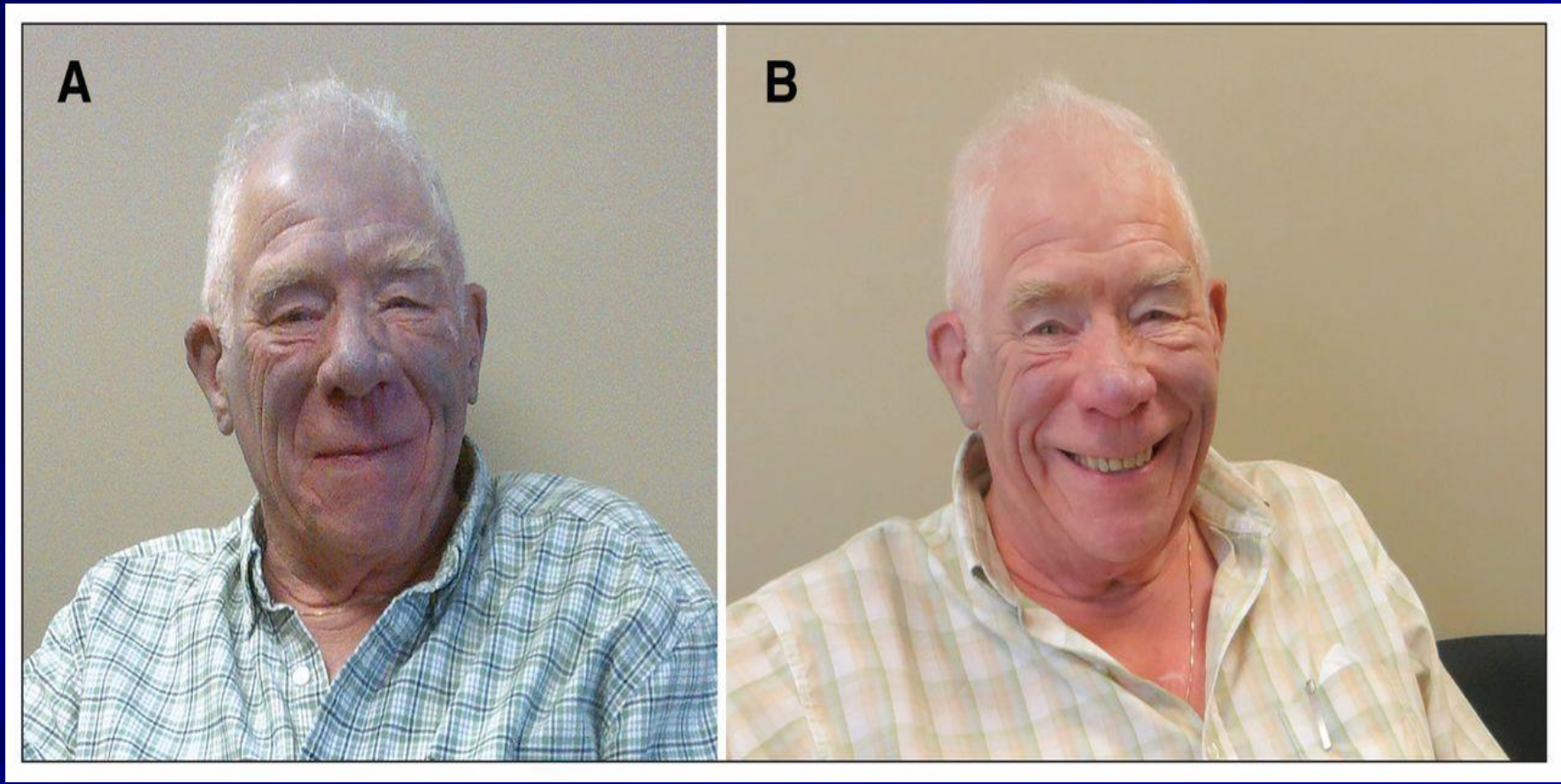
Amiodarone:

- Given IV (Loading dose 10gm) and orally.
- 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.

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.**
- **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.**
- **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

Unclassified Drugs

Digoxin:

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

Unclassified 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.

Unclassified Drugs

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.

Unclassified Drugs

Adenosine:

- 90-95% effective in supraventricular 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.