rythm of the heart starts from SA node---atrial tissues -----AV node ----ventricle bundle ----right and left bundle branches-----to while muscular to produce normal cardiac output

Antiarrhythmic Drugs

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Cardiac Arrhythmias

Definition. any disturbance in the electrical pathway

Etiology: Any disturbance in heart rhythm will affect the heart function

- **Hereditary** genetic causes of arrhymias or non-arrhythmias
- **Acquired**

Types: two types of abnormalities:

- **Abnormalities of Impulse Formation:**
  electrical system in the SA , AV nodes or in ventrical and artrium
  - **Rate disturbances.** could be high or slow lead to tachycardia or bradycardia
  - **Triggered automaticity.**
    abnormality in any part in the heart to produce actio potential
- **Abnormalities of Impulse Conduction:**
  heart blocks-----delay of transduction
  - **Blocks.**
  - **Reentry.** reciculation of cardiac action potential in the same place

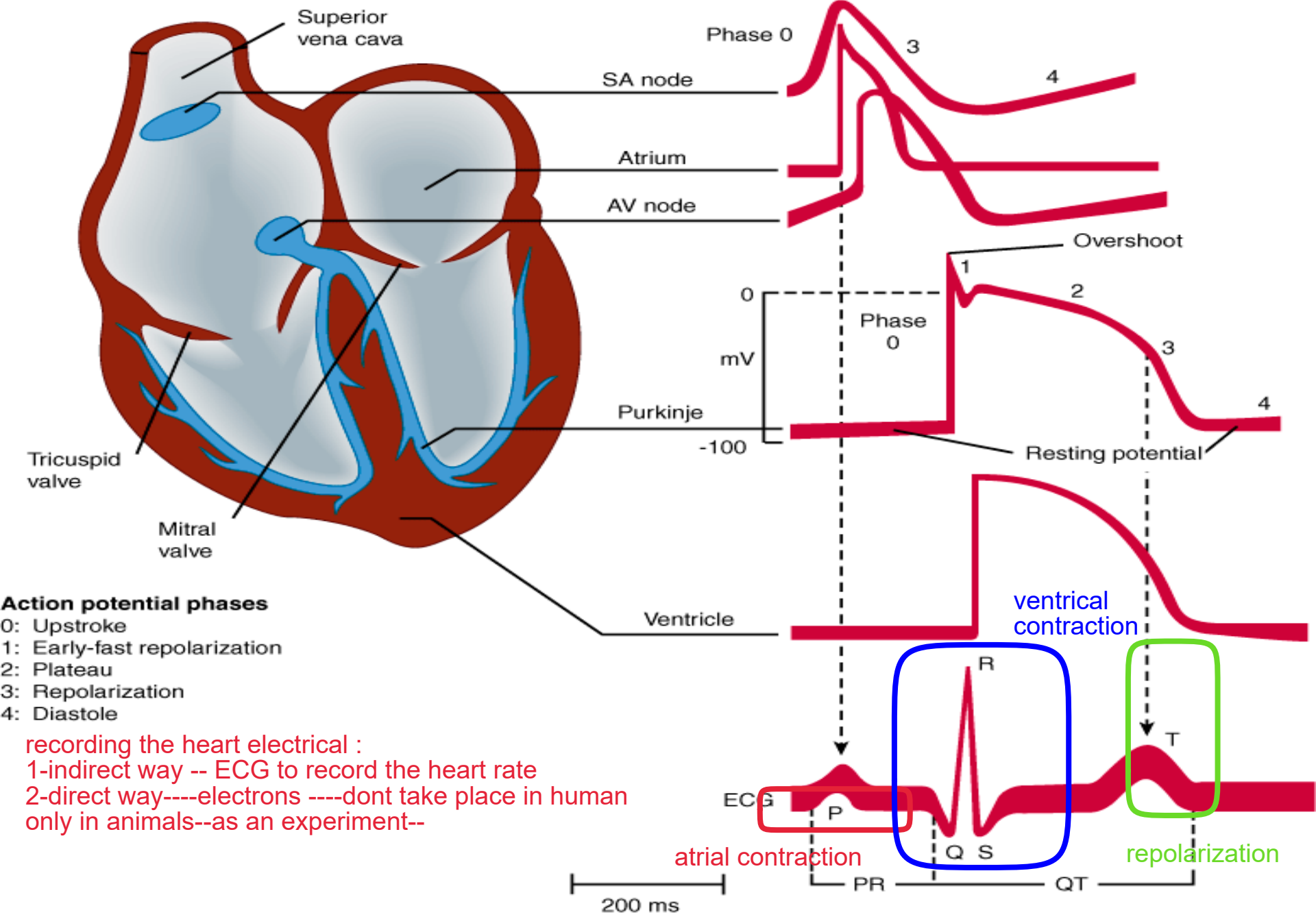
Cardiac Causes of Arrhythmias

- **Ischemic heart disease.** affect the muscle
  affect the neuropathway
- **Inflammation.** viral disease----causes ----endocarditis
- **Trauma e.g. heart surgery.** having heart failure or maybe death after surgery
- **Congestive heart failure.** causing dialation , hypertrophy of the heart then cause heart failure
- **Hypotension.** will affect baroreceptor---- to increase the heart rate--- then having tachycardia

Non Cardiac causes Arrhythmias

- Electrolyte imbalance.
- Acid-Base imbalance.
- Hypoxia.
- Drugs:
  - Digitalis most important cause-----> used in heart failure
  - Anesthetics
  - Tricyclic antidepressant drug
  - Diuretics
  - Bronchodilators: sympathomimetic. useful in asthma will stimulate the heart rate
- Reflexes.

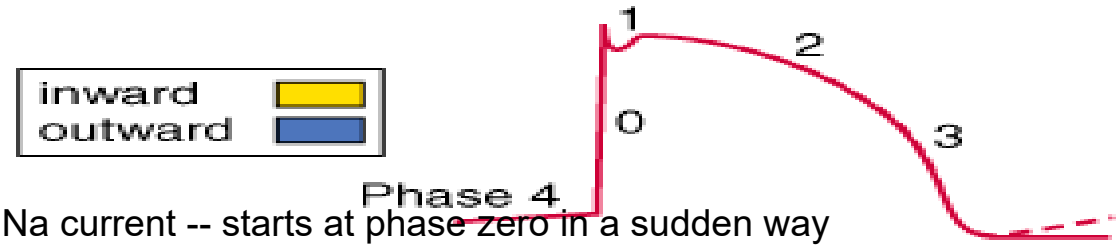
such as GI reflexes , vasovegal reflexes--------> can cause bradycardia



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

recording the heart electrical :
1-indirect way -- ECG to record the heart rate
2-direct way----electrons ----dont take place in human
only in animals--as an experiment--

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



genes controll of the channels

Na current -- starts at phase zero in a sudden way

		Gene/protein
Na^+ current		*SCN5A*/Nav 1.5
Ca^{2+} current	L-type	*CACNA1*/Cav 1.2
	T-type	*CACNA1G, 1*/Cav 3.1, 3.2

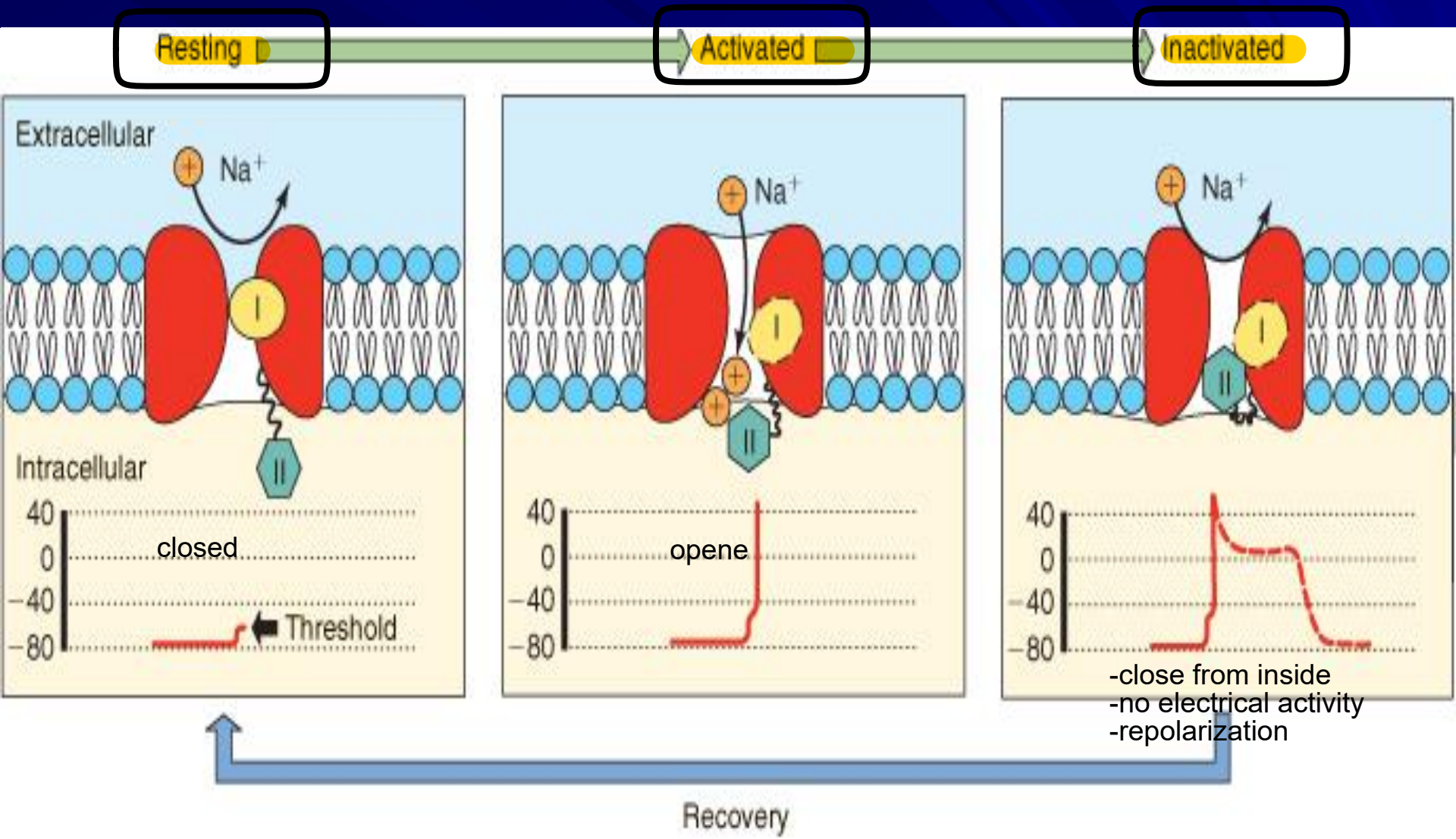
ca current --- appears in phase 1,2,3

transient outward current	I_{TO1}	*KCND3*/Kv 4.3
	I_{TO2}	*KCNA4*/Kv 1.4
delayed rectifiers (I_K)	I_{Ks}	*KCNA1*/KvLQT 1
	I_{Kr}	*KCNH2*/hERG
	I_{Kur}	*KCNA5*/Kv 1.5
	I_{KP}	??
	I_{Cl}	*CFTR*/CFTR
inward rectifier, I_{K1}		*KCNJ1*/Kir 2.1
pacemaker current, I_f		*HCN2, 4*/HCN2, 4
Na^+-Ca^{2+} exchange		*SLC8A1*/NCX 1
Na^+, K^+-ATPase		*NKAIN1-4*/Na, K-pump

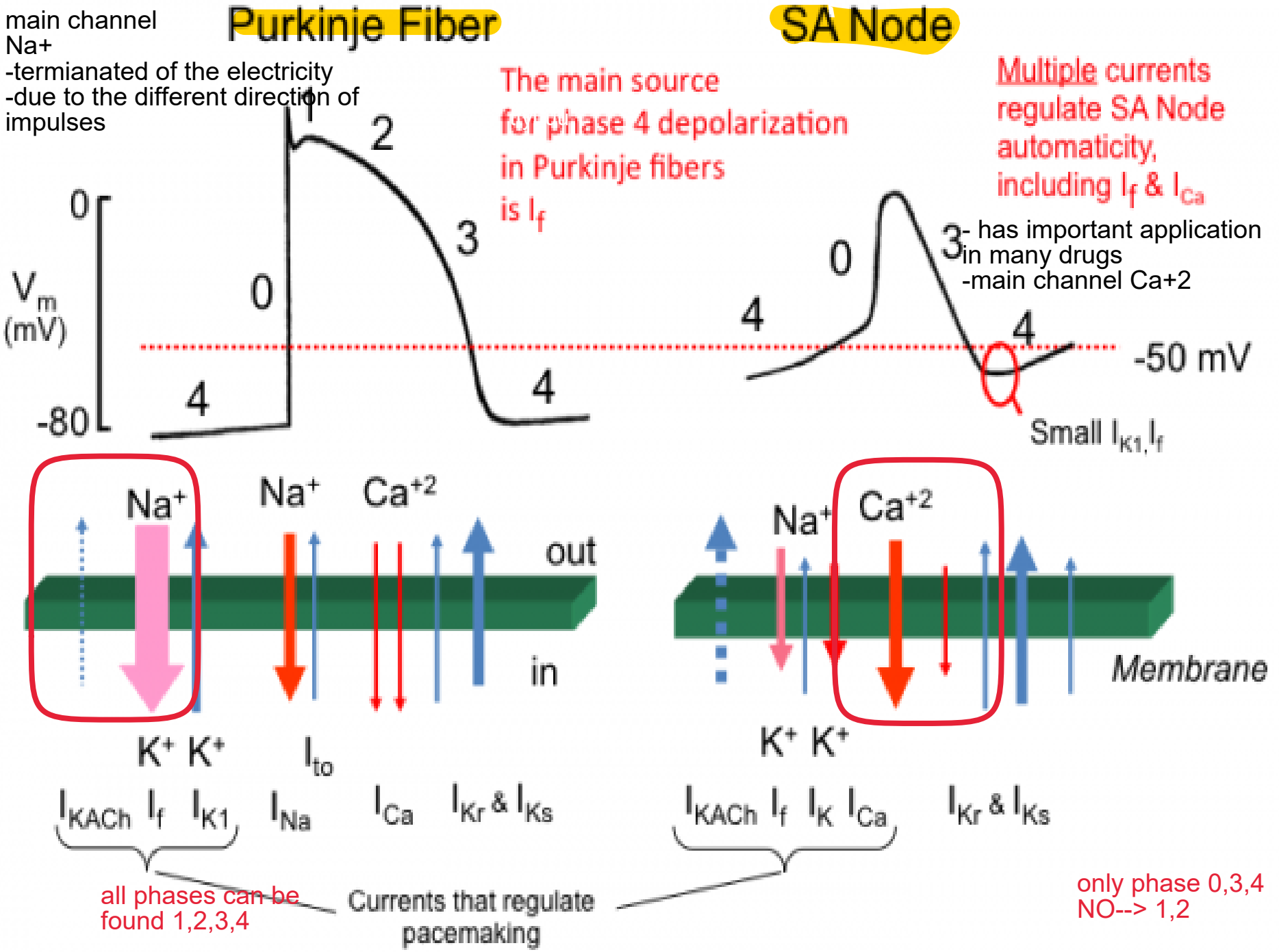
they consumed energy -- found all over the body

sodium goes out , potassium enters

Cardiac Na+ channels

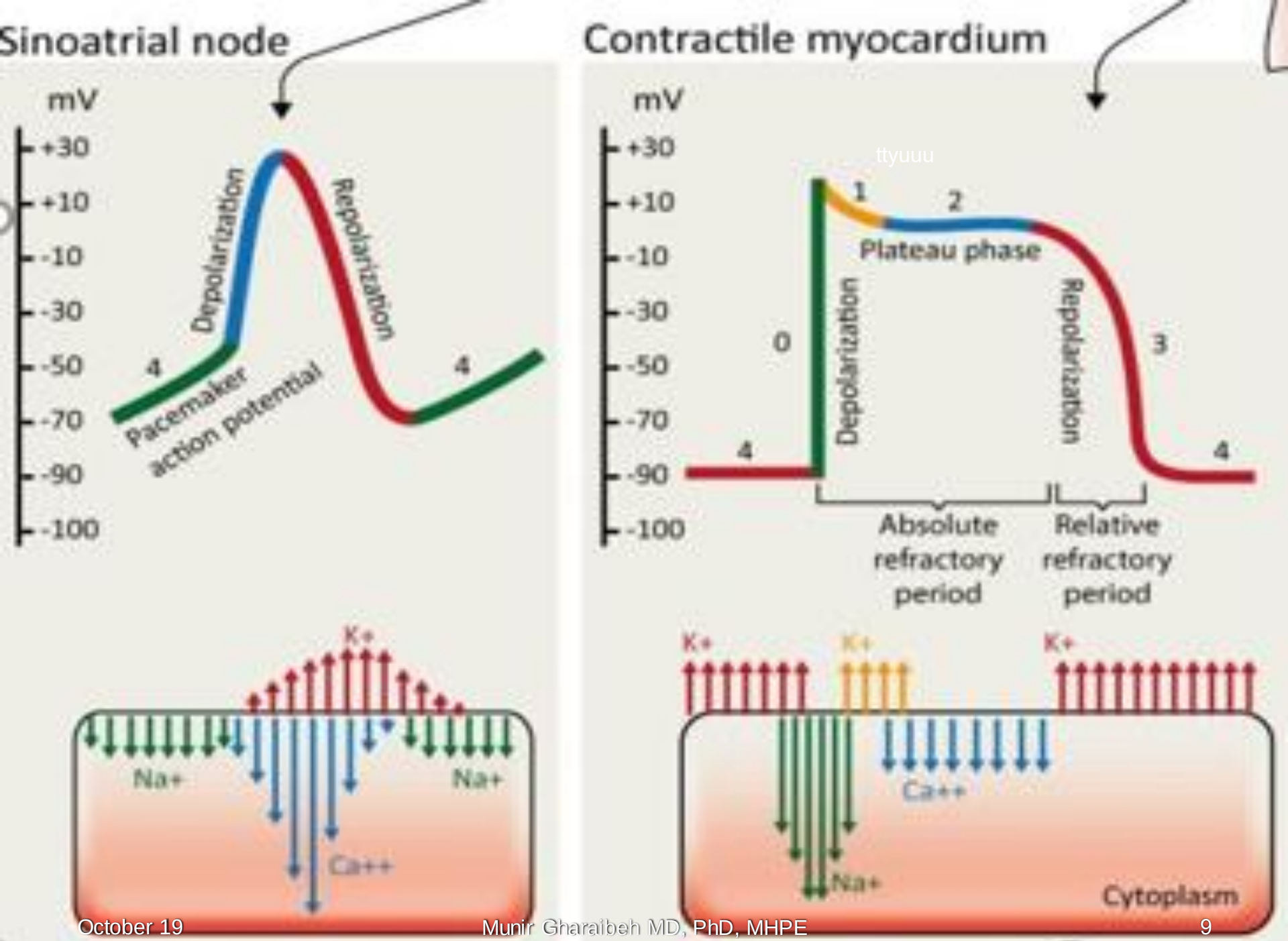


main channel
Na+
-termianated of the electricity
-due to the different direction of impulses



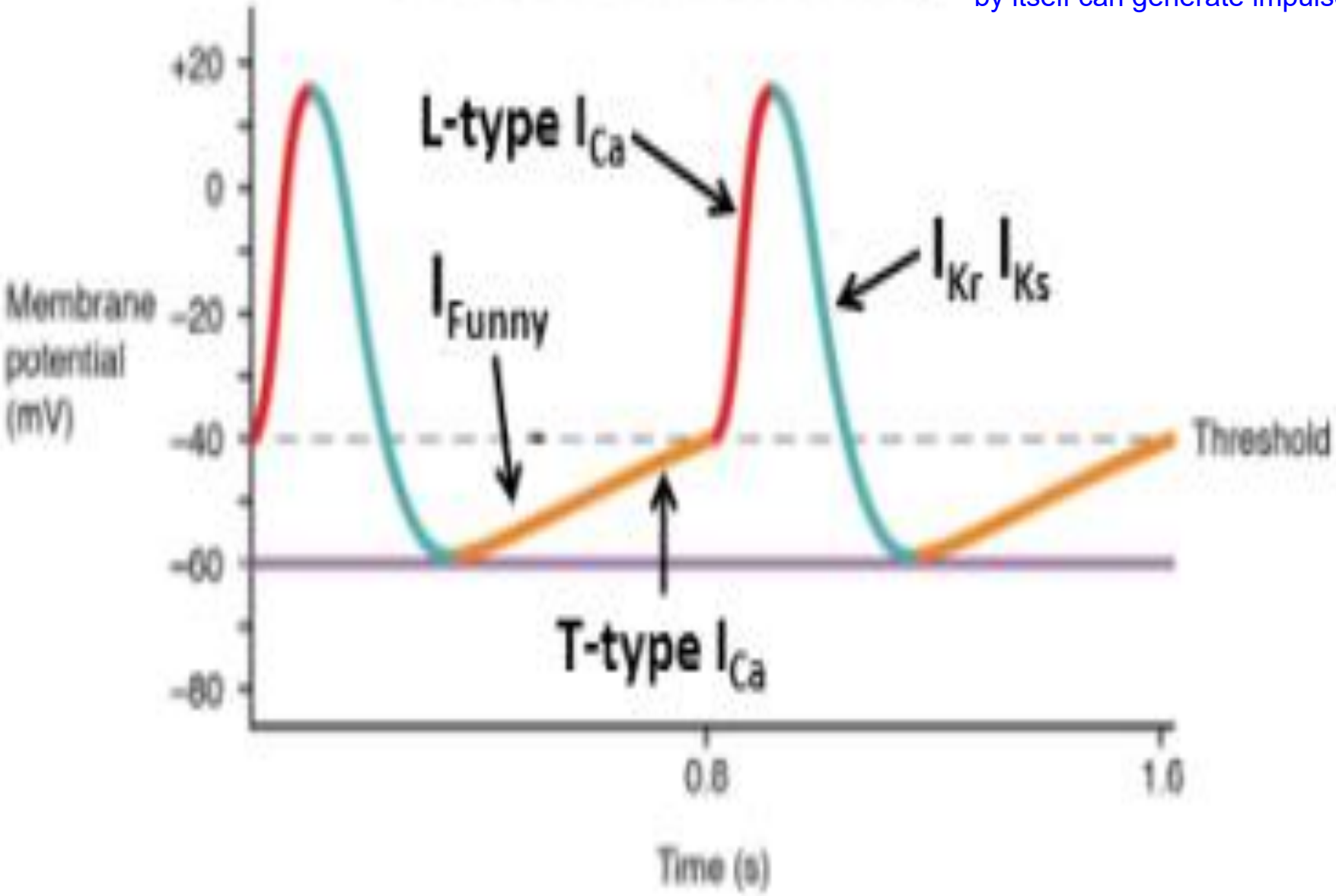
all phases can be found 1,2,3,4

only phase 0,3,4
NO--> 1,2


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
3
4
4
Depolarization
Repolarization
Absolute
refractory
period
Relative
refractory
period
K+
Na+
Na+
Ca++
K+
K+
K+
Ca++
Na+
Cytoplasm

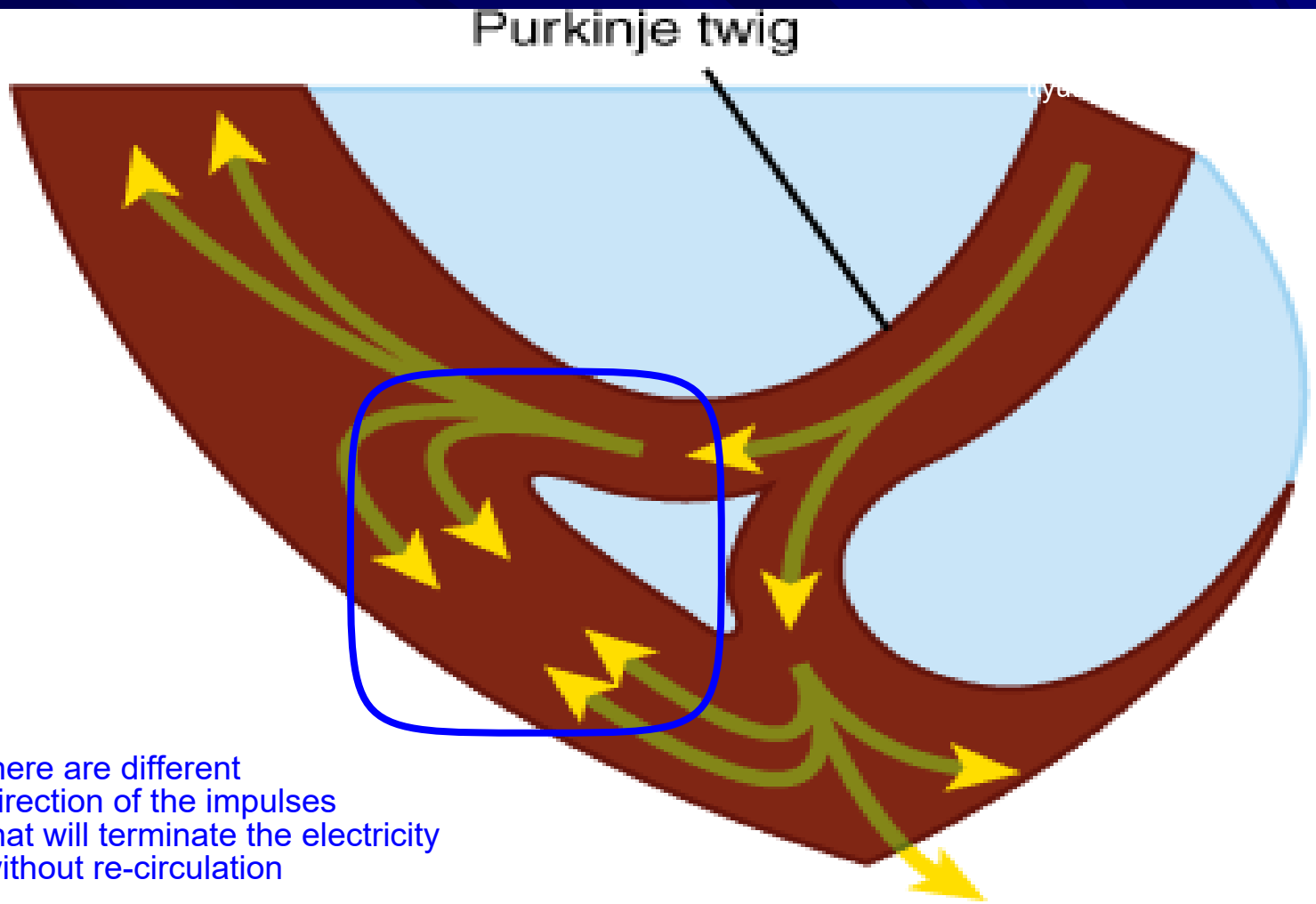
SA node automaticity

ability to produce (generate) impulses without any help---> by itself can generate impulses



Normal Circuitry

ttyuuu

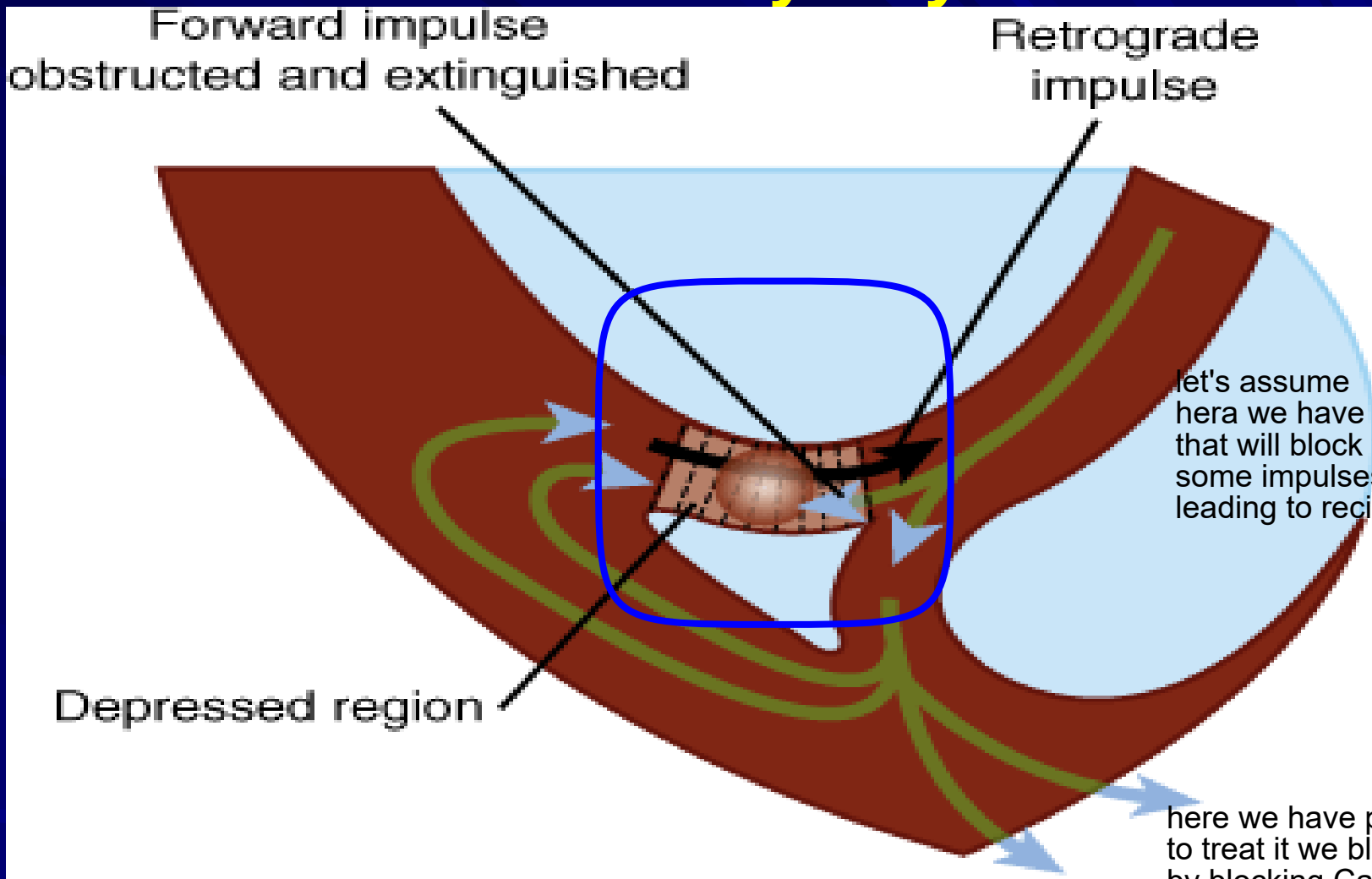


there are different
direction of the impulses
that will terminate the electricity
without re-circulation

A. Normal conduction

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

Re-entry Rhythm

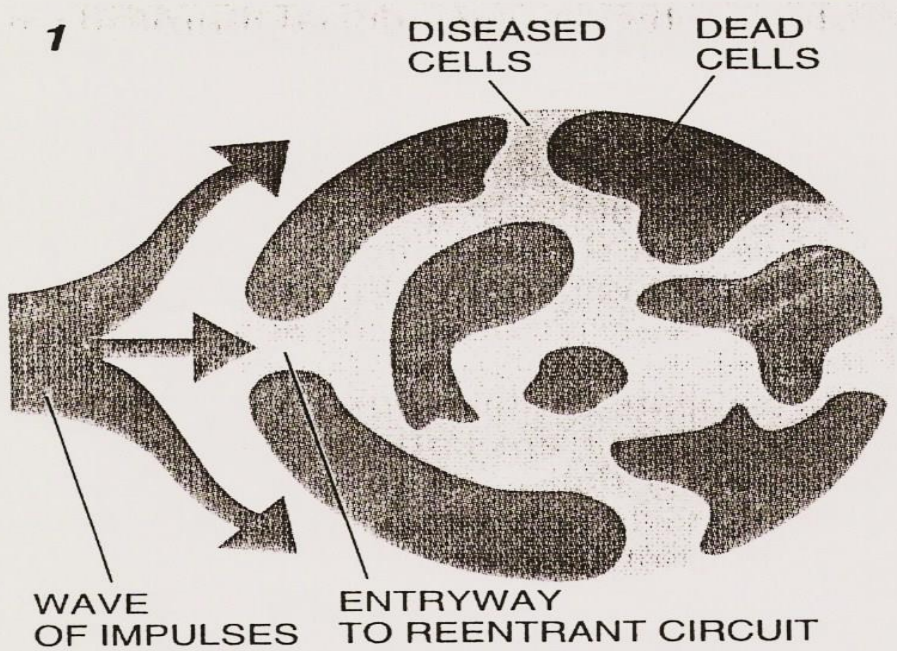


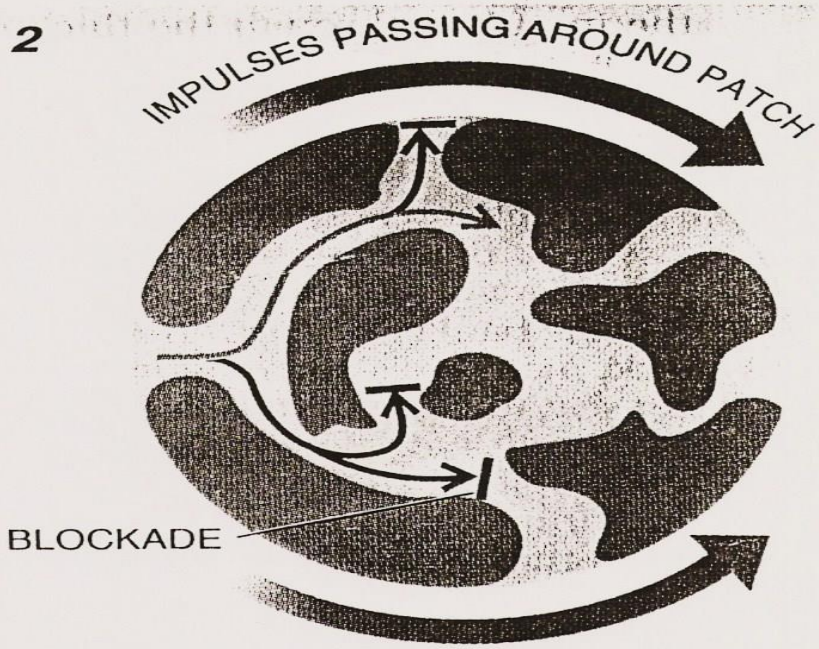
let's assume
hera we have ischemia
that will block the pathway of
some impulses
leading to recirculation

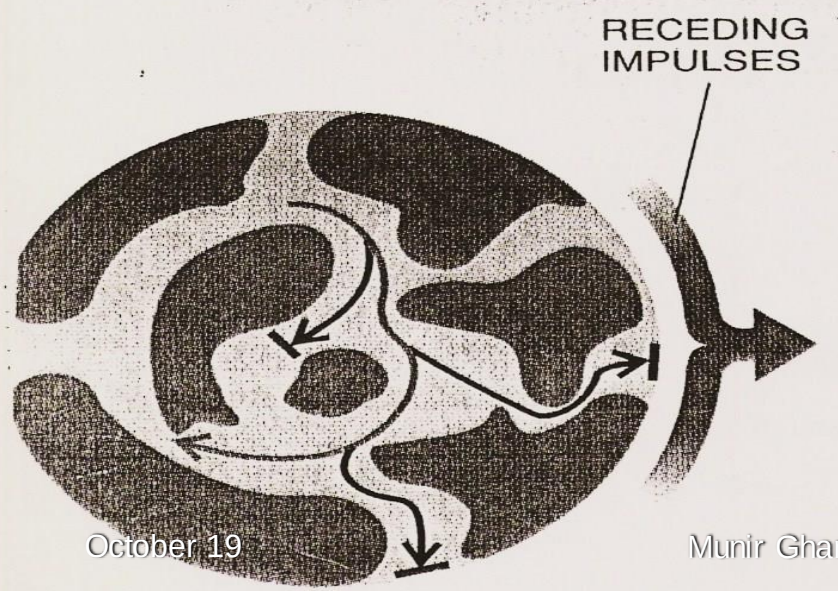
here we have partial blockage
to treat it we block whole area
by blocking Ca+2 channel

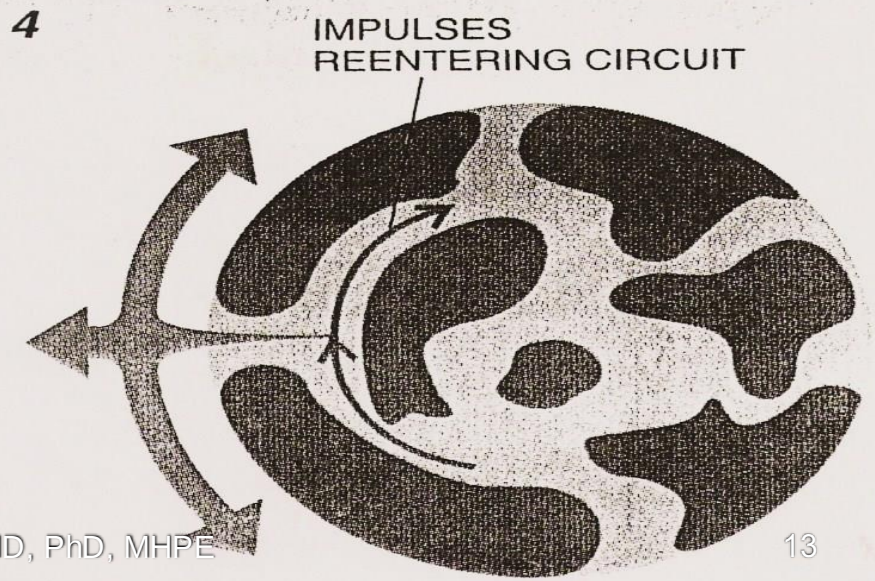
B. Unidirectional block

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.

has different types

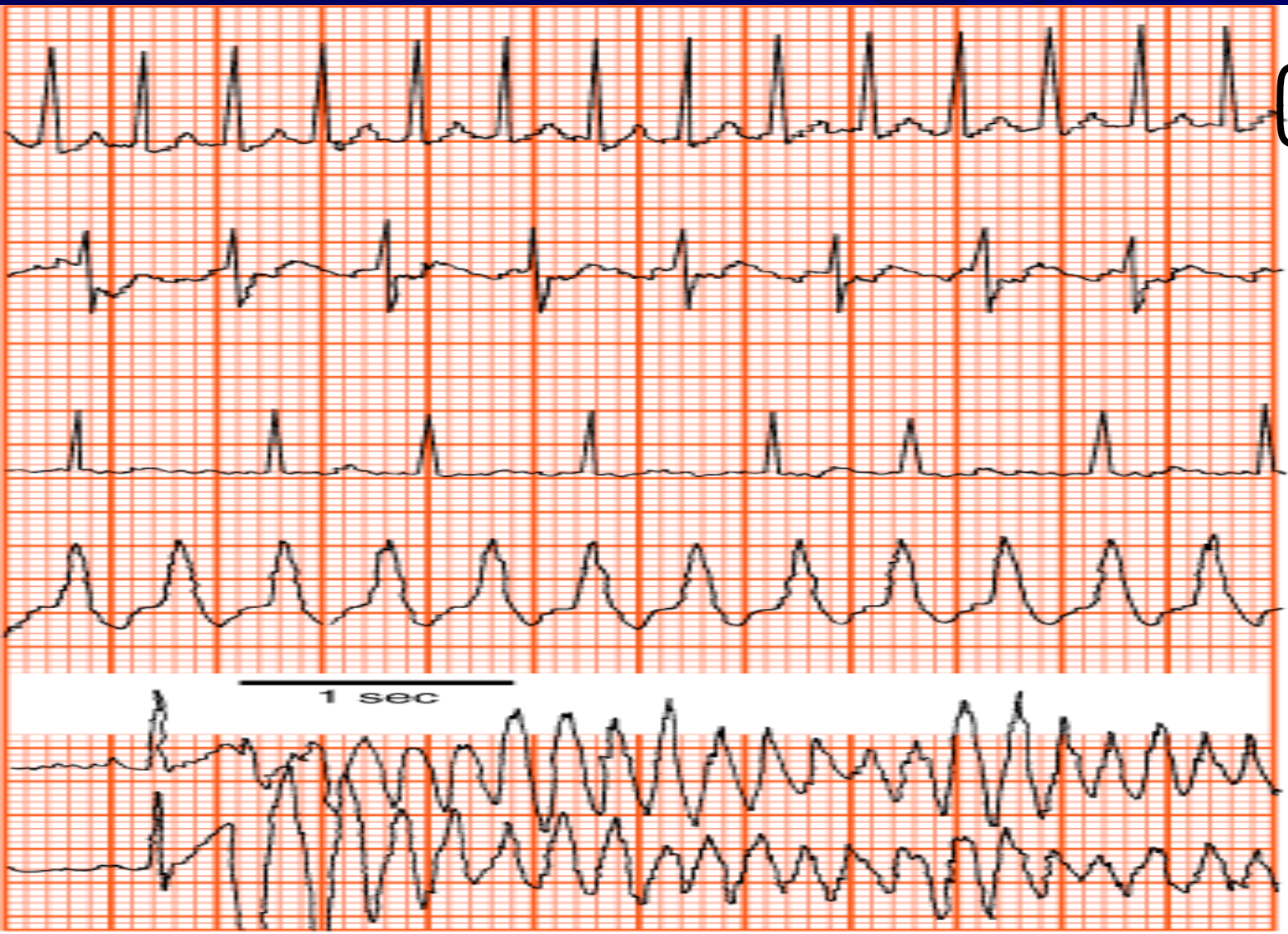
Type	Chromosome Involved	Defective Gene	Ion Channel or Proteins Affected	Result
LQT-1 long QT	11	*KCNQ1*	I_{Ks}	LF
LQT-2	7	*KCNH2 (HERG)*	I_{Kr}	LF
LQT-3	3	*SCN5A*	I_{Na}	GF
LQT-4	4	Ankyrin-B[1]		LF
LQT-5	21	*KCNE1 (minK)*	I_{Ks}	LF
LQT-6	21	*KCNE2 (MiRP1)*	I_{Kr}	LF
LQT-7[2]	17	*KCNJ2*	I_{Klr}	LF
LQT-8[3]	12	*CACNA1c*	I_{Ca}	GF
SQT-1 short QT	7	*KCNH2*	I_{Kr}	GF
SQT-2	11	*KCNQ1*	I_{Ks}	GF
SQT-3	17	*KCNJ2*	I_{Klr}	GF
CPVT-1[4] Caticholaminergic polymorphic venticular tachycardia	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

lose function

gain function

ECG of some Arrhythmias

can diagnose different types of arrhthmias , and sometimes iit can't



supraventicular tachycardia
- having high heart rate

they must be treated

Torsade de Pointes
Polymorphic Ventricular Tachycardia

long QT transient attack

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.**

action potential duration

Mechanisms:

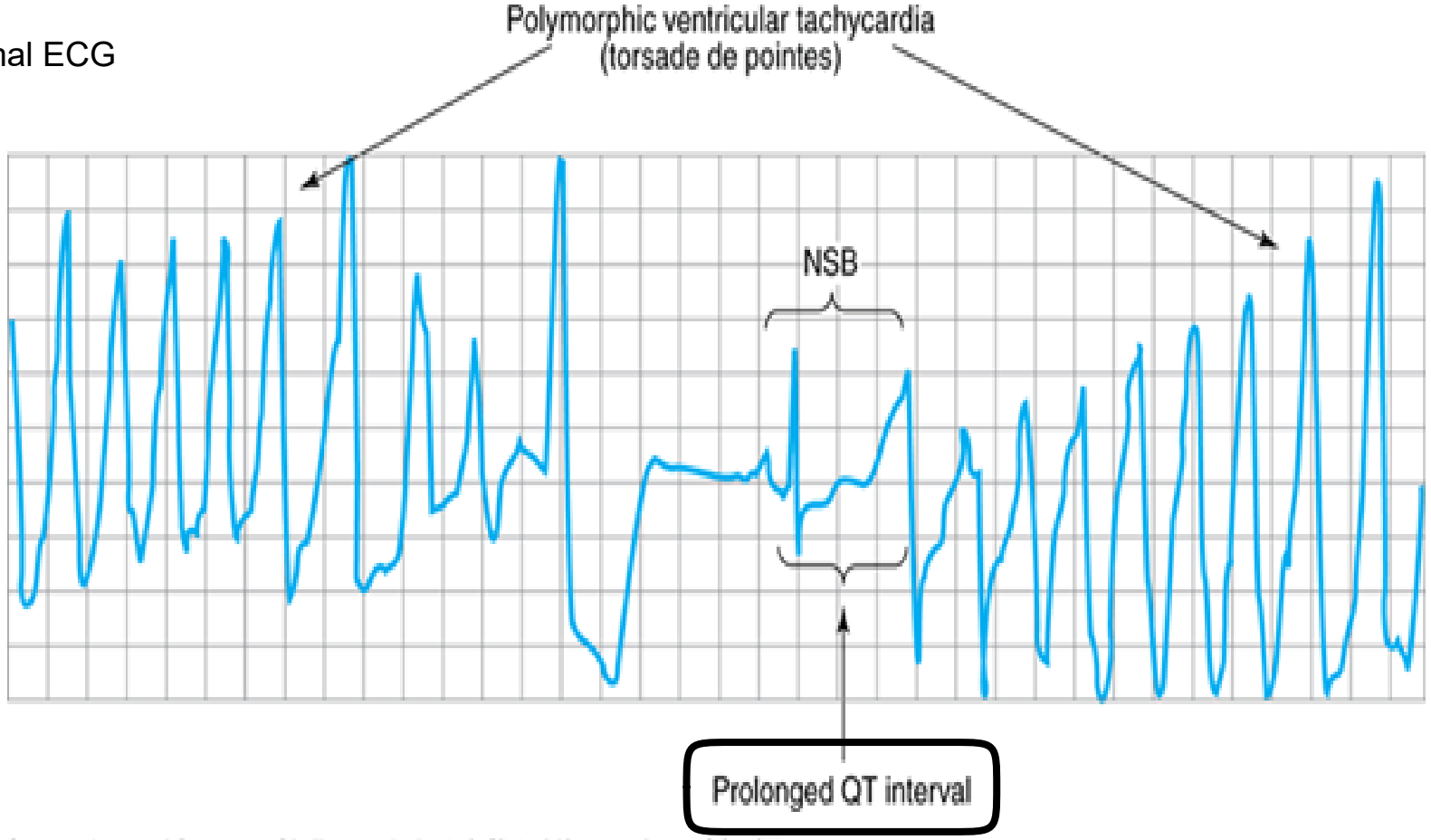
gain function

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

lose function

Figure 14-8

abnormal ECG



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:

having high level of K+
with normal renal function then K+ will get out through urine
* BUT
having renal failure the there will be accumulation of K+

- Bradycardia.
- Hypokalemia. Can cause various types of arrythmias
- Triggered upstrokes.
- Drugs which ↑ APD.

Treatment:

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

www.sads.org= sudden arrhythmia death syndrome foundation

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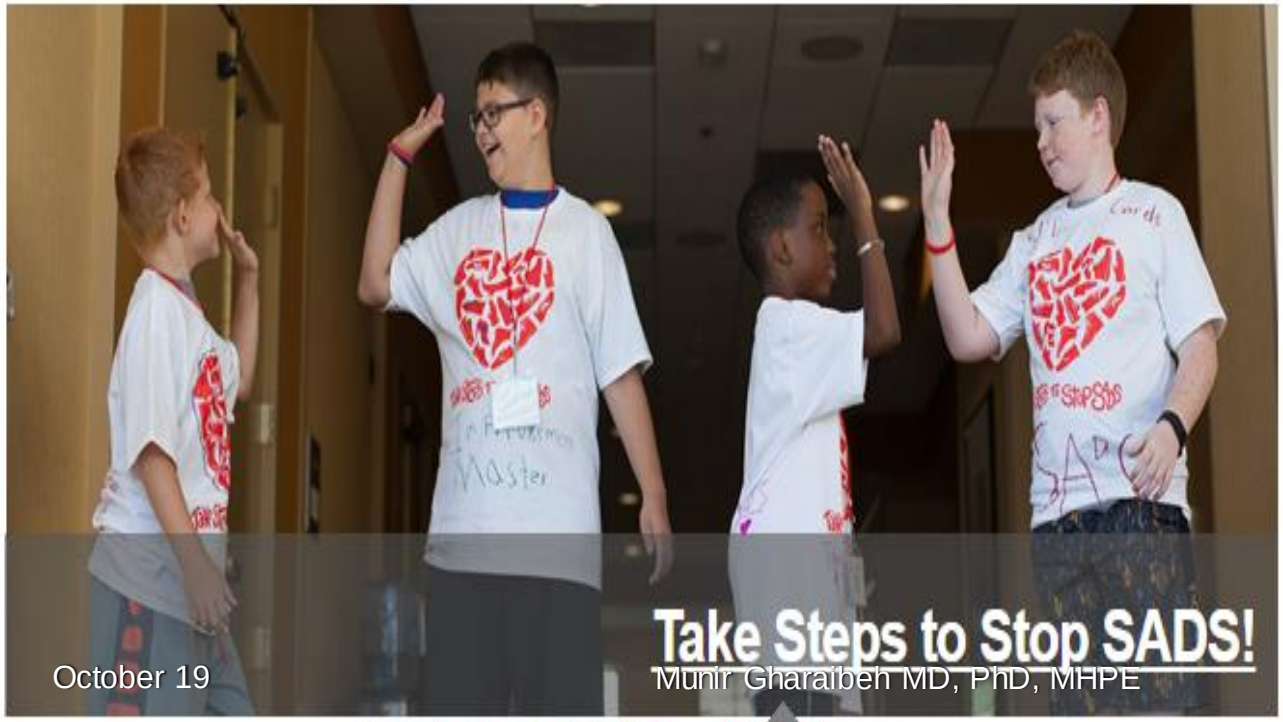

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Other Congenital Arrhythmias

- **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.

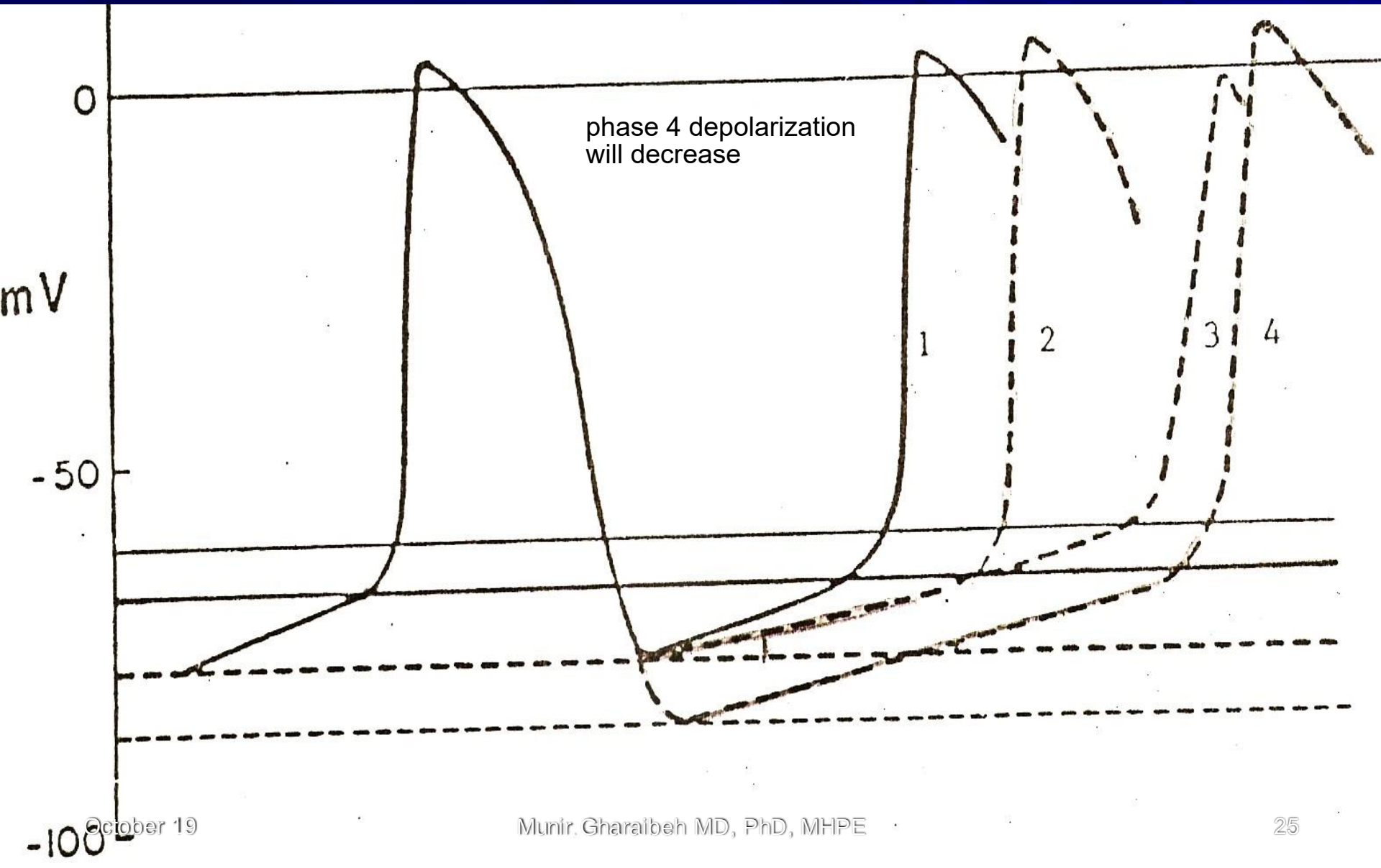
Nonpharmacologic Therapy

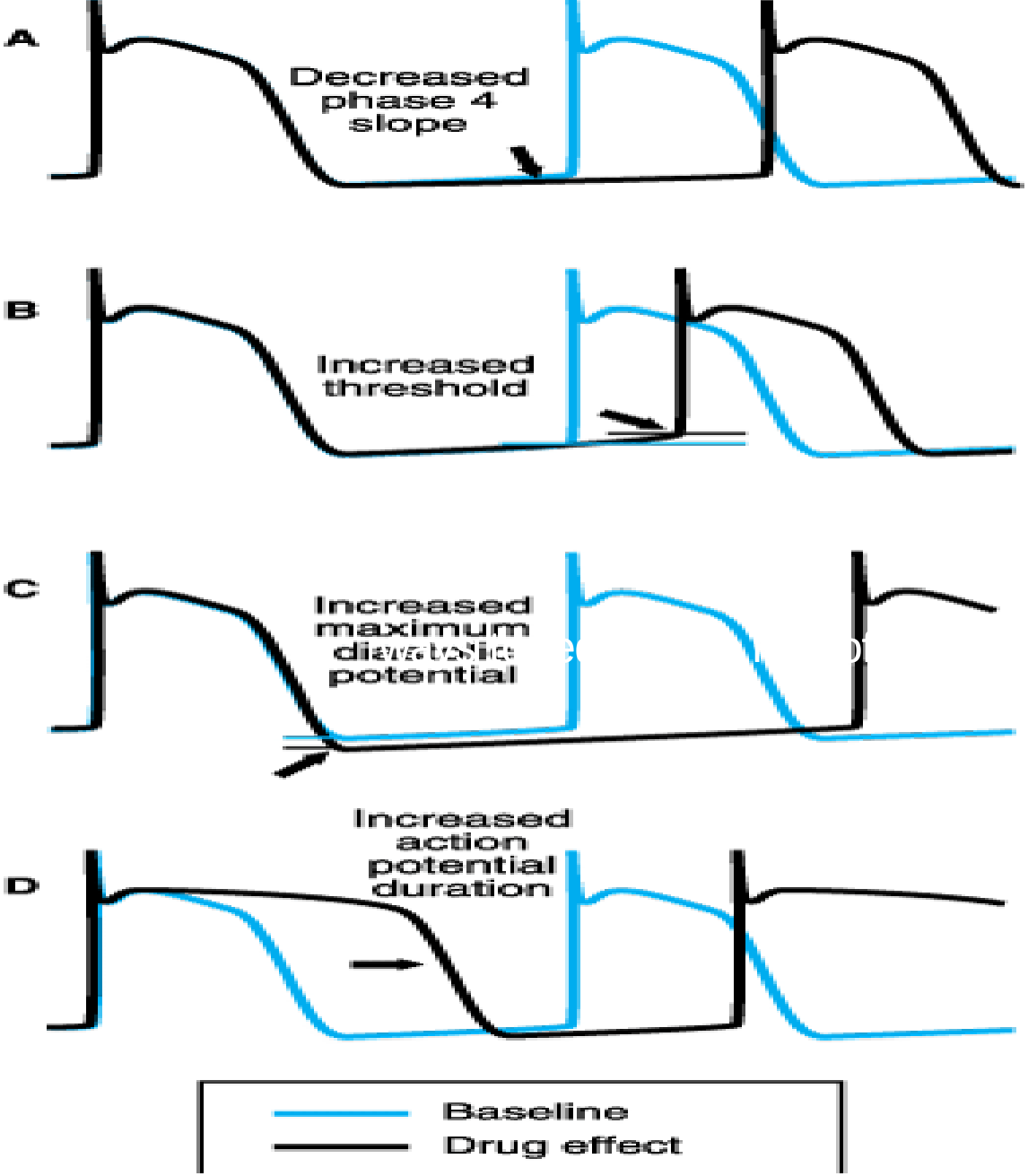
- **Surgery.**
- **Radiofrequency Catheter Ablation(إستئصال).**
- **Cryoablation.** extreme cold to destroy tissue
- **Implantable Cardioverter- Defibrillator (ICD).**
- **Gene therapy!!!!.**

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

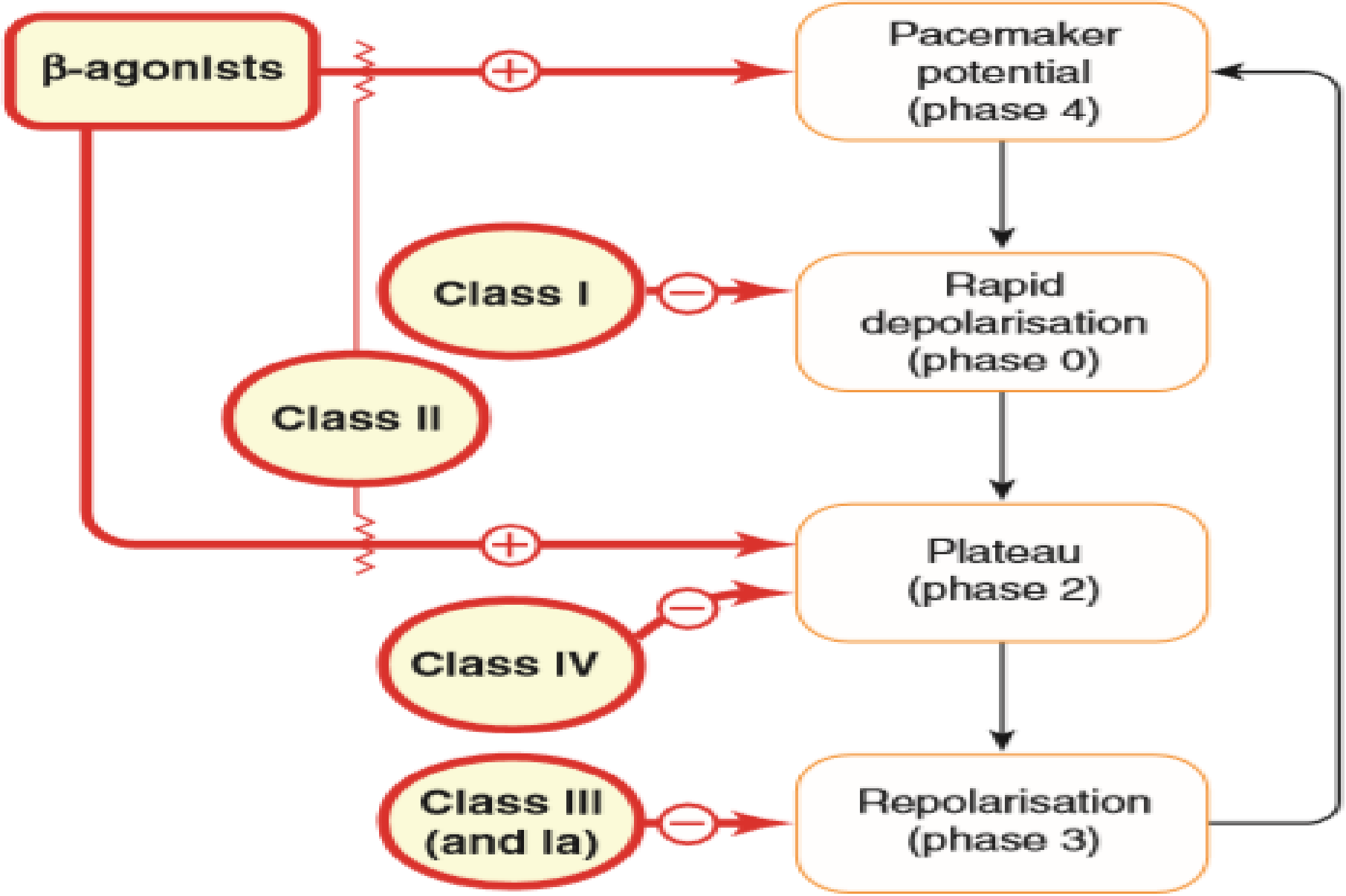
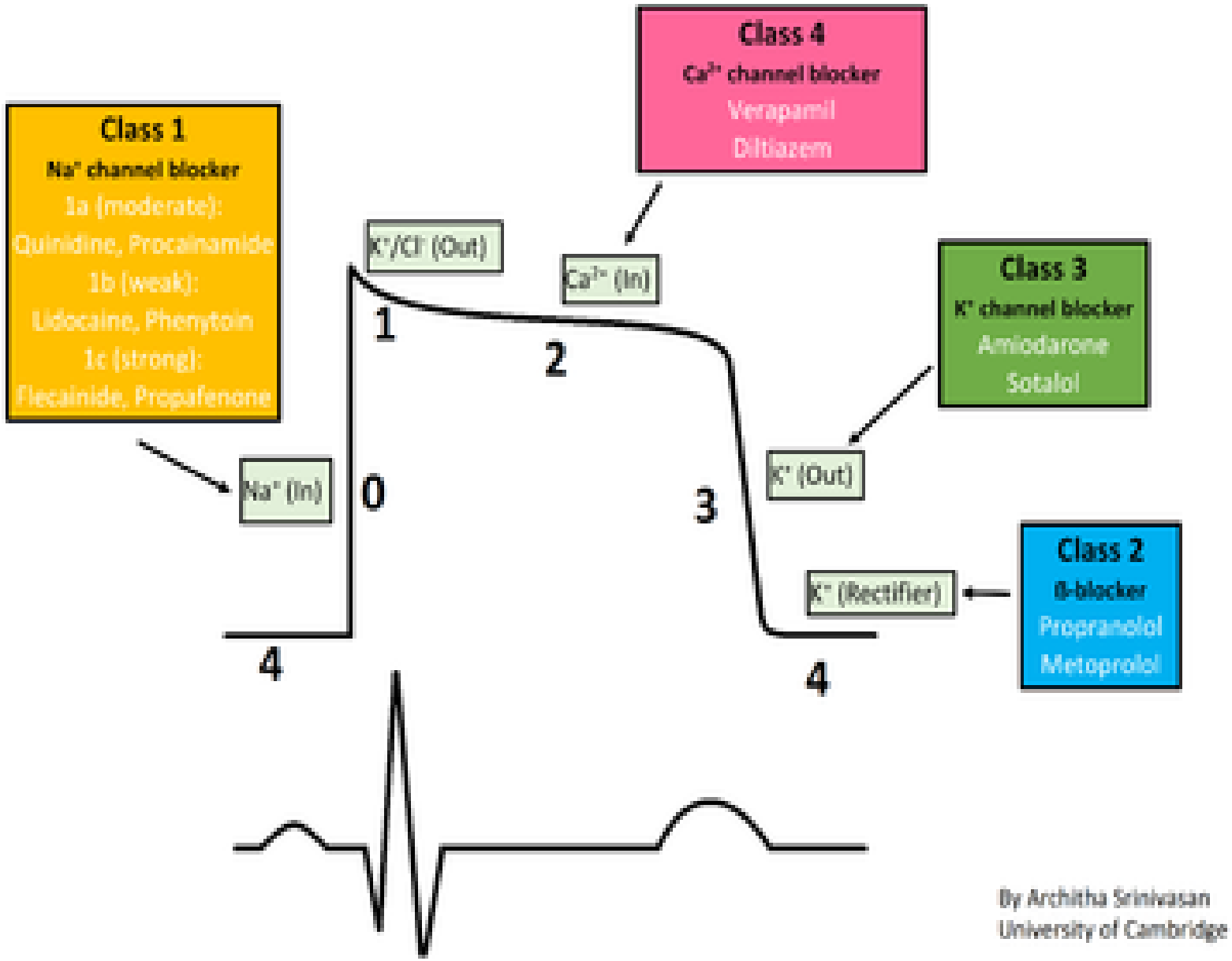


Fig. 21.9 Effects of antidysrhythmic drugs on the different phases (as defined in Fig. 21.1) of the cardiac action potential.

Drugs Affecting the Cardiac Action Potential



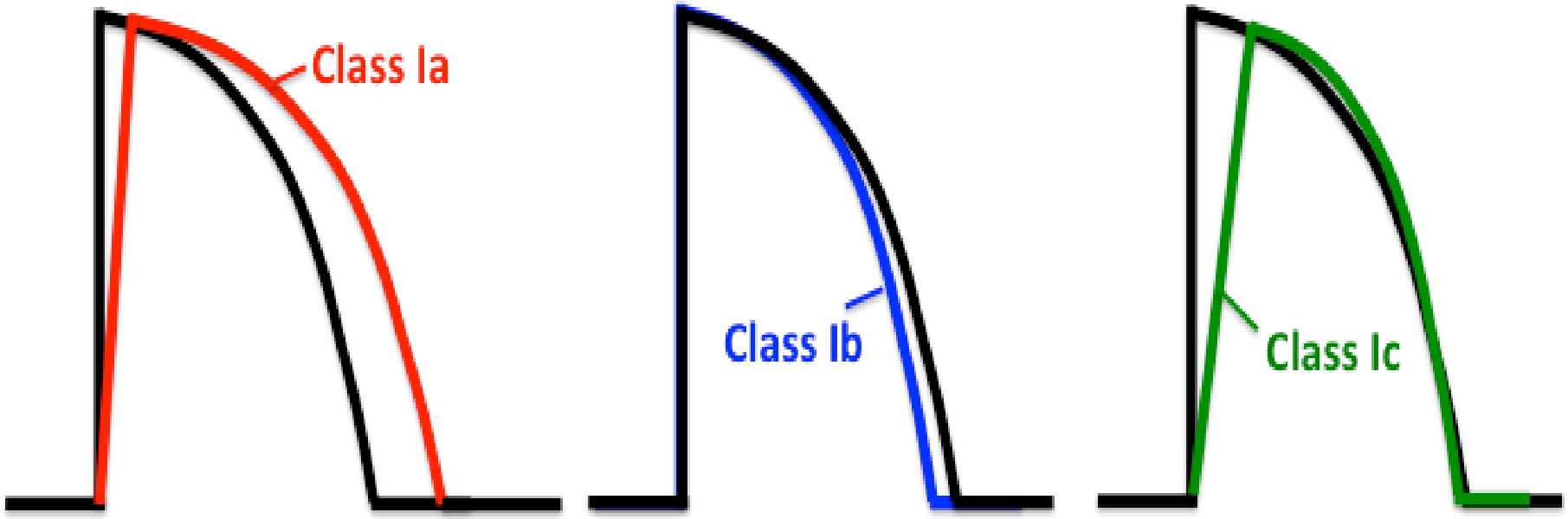
By Architha Srinivasan
University of Cambridge

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:



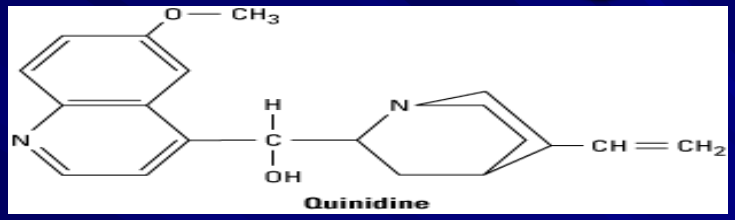
On the ECG:

that why antiarrhythmic drug could be proarrhythmic
because it lead to have long QT

↑QRS & ↑QT ↓QT ↑↑QRS

Class 1A Drugs

old drug



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

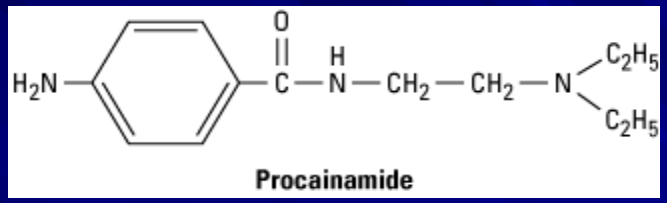
Side Effects: Toxic

- 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.** common side effect in antiarrhythmic drug but much more common in Quindine

Class 1A Drugs

new agent

Procainamide:



Procainamide

- Oral, but has short t½.

lupus erythematosus

- L.E. (30% of patients Tx over 6 moths)

converted to

- Acetylated → NAPA (Class III) action

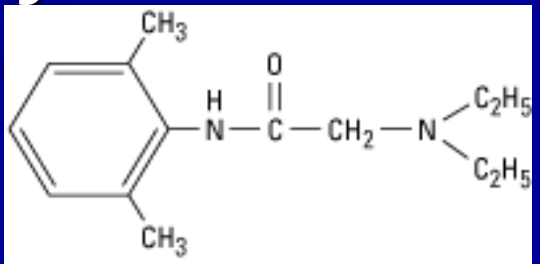
Disopyramide

- More anticholinergic effects but less diarrhea than quinidine

Class 1B Drugs

Lidocaine: for venticular arrhythmias

- 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: IV another name xylocaine

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.**

main side effsct at high doses — reduce by sedative

- **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.

has CNS effect can can cross BBB

Class II Drugs

Propranolol:

old drug - prototype-
can reduce the demand of O2 to the heart
can reduce the electrical activity of the heart

- 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:

2-3 times per day

- 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

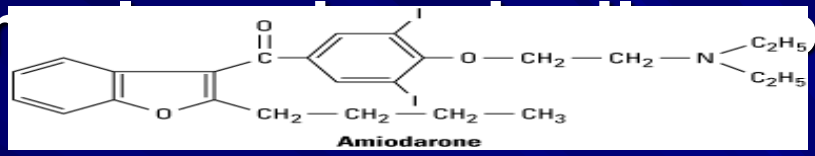
can be classified as class 1,2,3,4

Amiodarone:

prevent artrial and ventrical arrythmias

prevent the entery of K+

- Blocks K+ char… …olongs APD.



Amiodarone

- Class I actions.
- Blocks α and β Receptors.
- Ca++ blocking actions. class 4
- ***Effect is due to alteration of lipid membrane.***
- ***Reserved for life-threatening atrial and ventricular arrhythmias.*** treatment for chronic arrythmias
- Slows heart rate and AV conduction.
- Low incidence of TdP despite significant QT prolongation. can prevent the conversion of ventrical arrythmia into ventrical fibriliation
- Peripheral vasodilator (only with IV).

subjected to drug interaction

Class III Drugs

it inreases QT
NO Tdp

Amiodarone:

because it has long half life

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

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

no effect on the heart

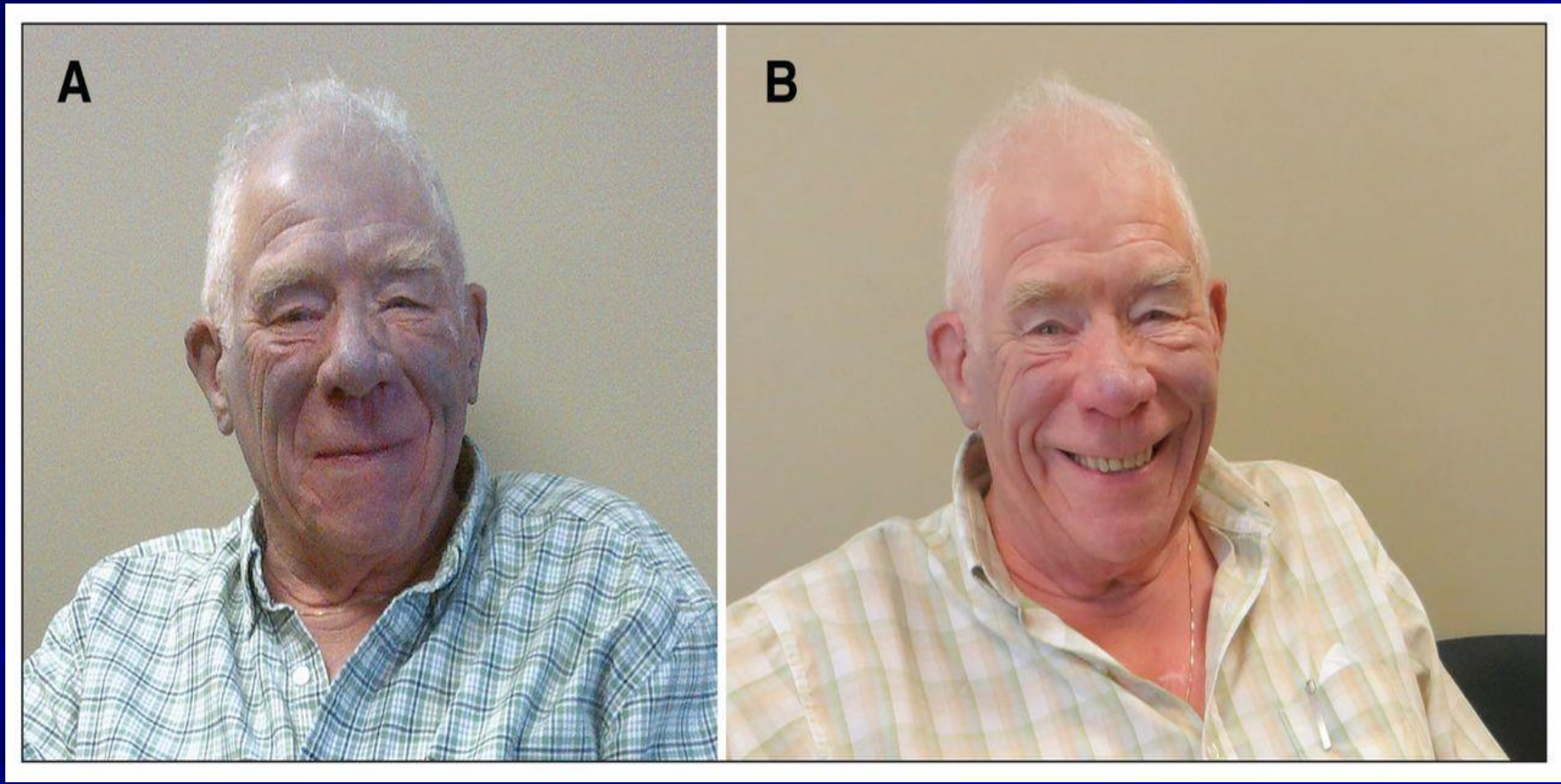
major side effects:

- Lung fibrosis (1%). this one can affect the heart
- CNS.
- Thyroid(hypo and hyper). in hypo- can be treated by given thyroxin
- GI and liver.
- Corneal deposits,
- Skin: photodermatitis and discoloration

blue man syndrom , to treat this state --> by reducing the dose

- ↑ 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.

side effects:

- 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.

Heart failure

can inhance TdP

- **Ibutilide.**
- **Dofetilide.**

calcium can cause vasodilation

Class IV Drugs (Ca++ Channel Blockers)

calcium is important in our bodies: stimulate some of hormones to be ralease neurotransmitters,and the movement of chromosomes during division

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.*** benign form
- **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.** very important in treatment of HF

Table 21.1 Antidysrhythmic drugs unclassified in the Vaughan Williams system

Drug	Use
Atropine anticholinergic drug	Sinus bradycardia
Adrenaline (epinephrine)	Cardiac arrest intracardial injection
Isoprenaline beta agonist	Heart block
Digoxin	Rapid atrial fibrillation and heart faliure
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. on SA node
- Vagotonic Effects. stimulate vagus nerve indirectly
- ↑ AV refractoriness.

Unclassified Drugs

can prevent the absorbtion of calcium in the GI

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.