Pharmacology - CVS

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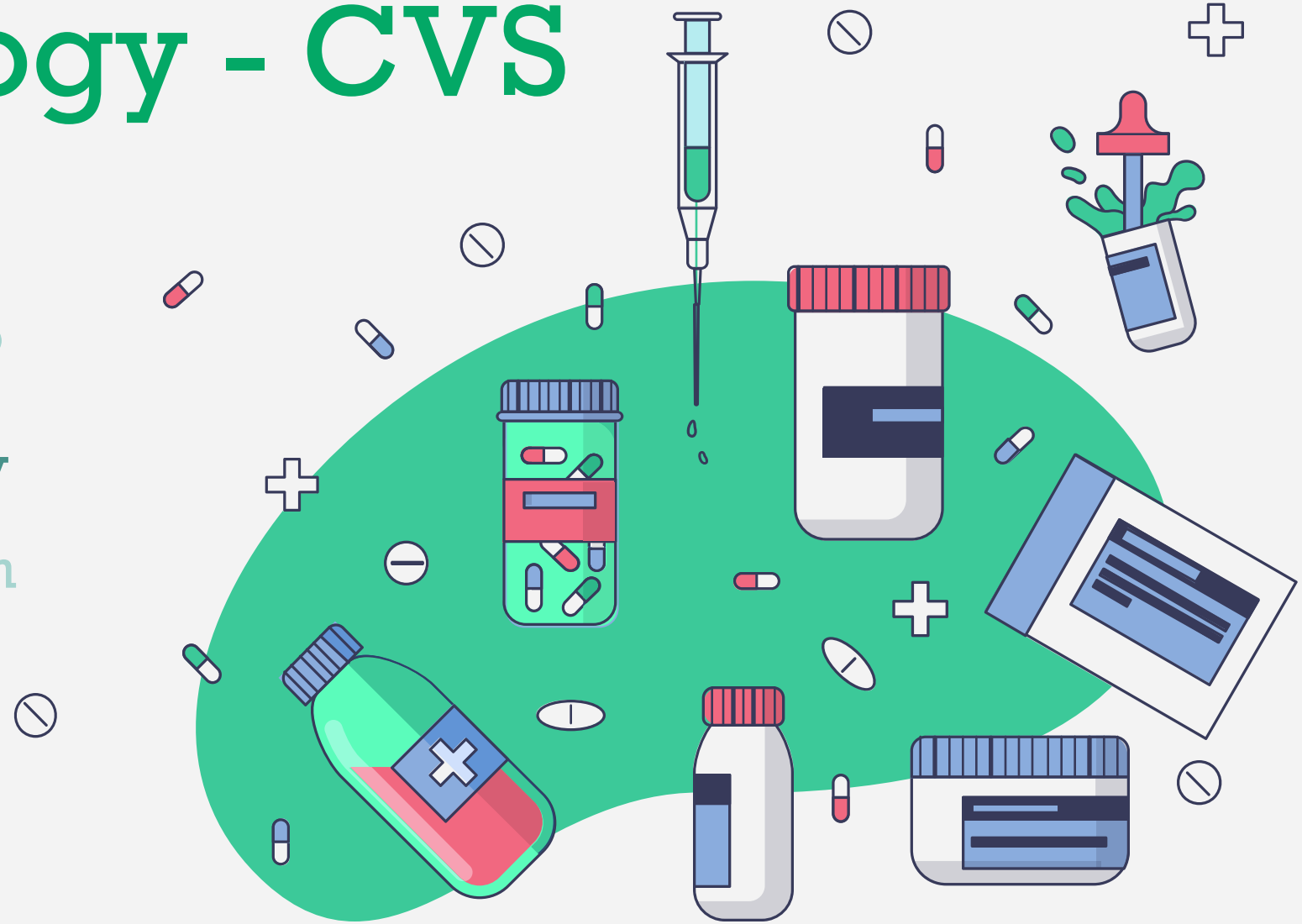

النادي الطلابي
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Antiarrhythmic Drugs

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Cardiac Arrhythmias

Definition:

They are abnormalities of the cardiac rhythm or the electrical activity. As you know, our heart works as a pump which involves both electrical and muscular activities. The nervous control of the heart depends on the nervous tissue present in the heart which is illustrated by the SA node, AV node, bundle of his, 2 bundle branches and purkinje fibers. These will transmit or propagate electrical activity to the muscular component of the heart to produce normal functioning of the heart. Abnormalities in the cardiac electrical activity are called cardiac arrhythmias which are treated by anti-arrhythmic drugs.

Etiology:

Hereditary

Acquired

Types:

Abnormalities of Impulse Formation:

- ✓ **Rate disturbances.**
- ✓ **Triggered automaticity.**

Abnormalities of Impulse Conduction:

- ✓ **Blocks.** Blockade of the passage of the electrical activity through the normal conduction pathway.
- ✓ **Reentry**. Reverberating (repeated) activity along the conduction system.

Cardiac Causes of Arrhythmias

- **Ischemic heart disease.**
- **Inflammation.**
- **Congestive heart failure**. (hypertrophy of the heart)

These 👆 affect the muscle (myocytes) as well as the electrical conduction system.

- **Trauma e.g. heart surgery.** [this is the most probable form of trauma to the heart, the direct damage from bullet shot or a knife is much less common]
- **Hypotension**. [elicits baroceptor reflex which stimulates the sympathetic system and inhibits the parasympathetic leading to various alterations in the heart and CVS]

Non Cardiac causes Arrhythmias

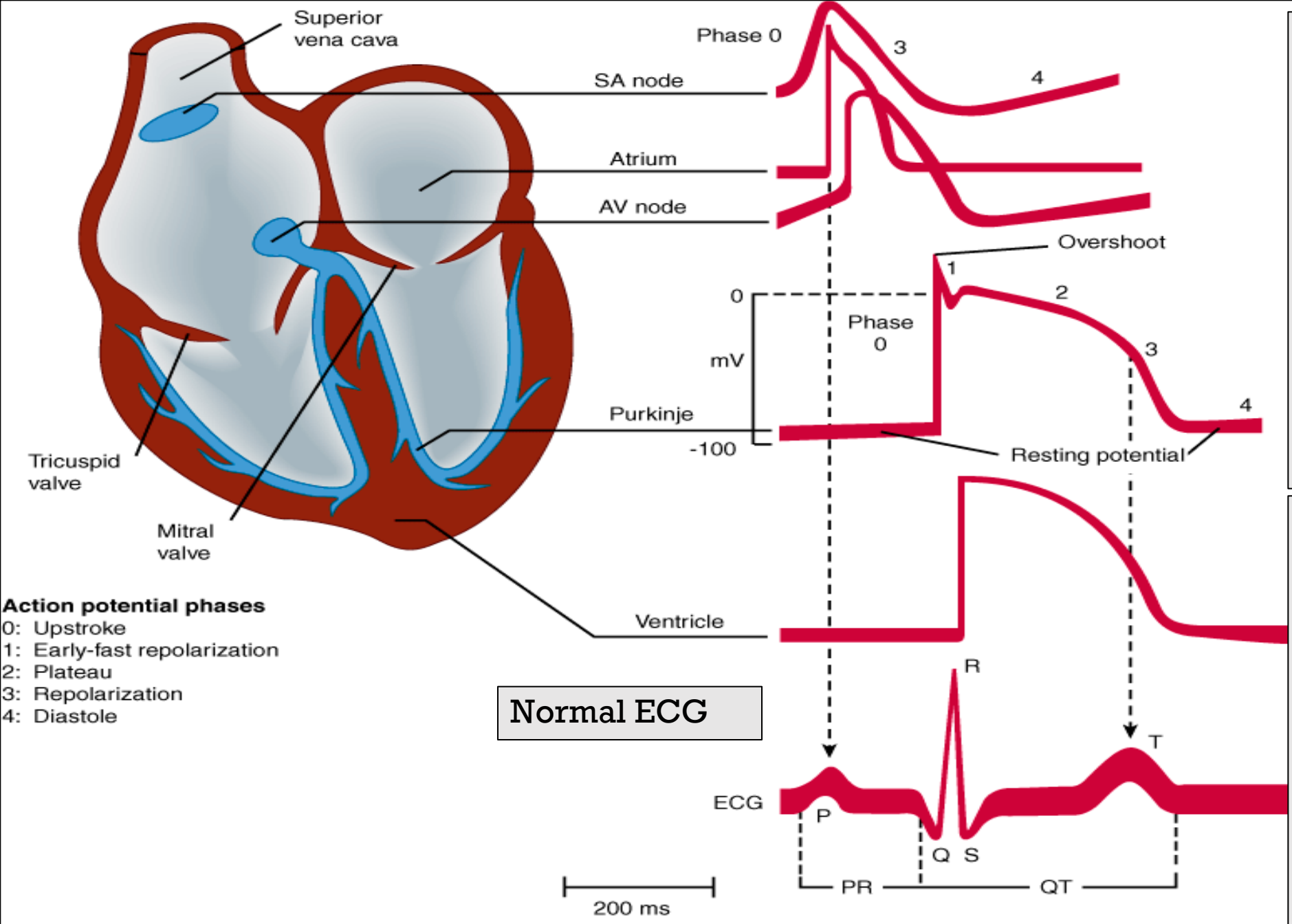
- **Electrolyte imbalance.** (mainly K+)
- **Acid-Base imbalance.**
- **Hypoxia.**
- **Drugs:**
  - **Digitalis**
  - **Anesthetics** (many people die after successful surgeries because of these drugs)
  - **Tricyclic** (used for depression)
  - **Diuretics** (cause electrolytes and acid- base imbalances)
  - **Bronchodilators: sympathomimetic.**
- **Reflexes.** (from GIT or upper part of the body)

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 abnormalities of cardiac rhythm, or arrhythmias.**



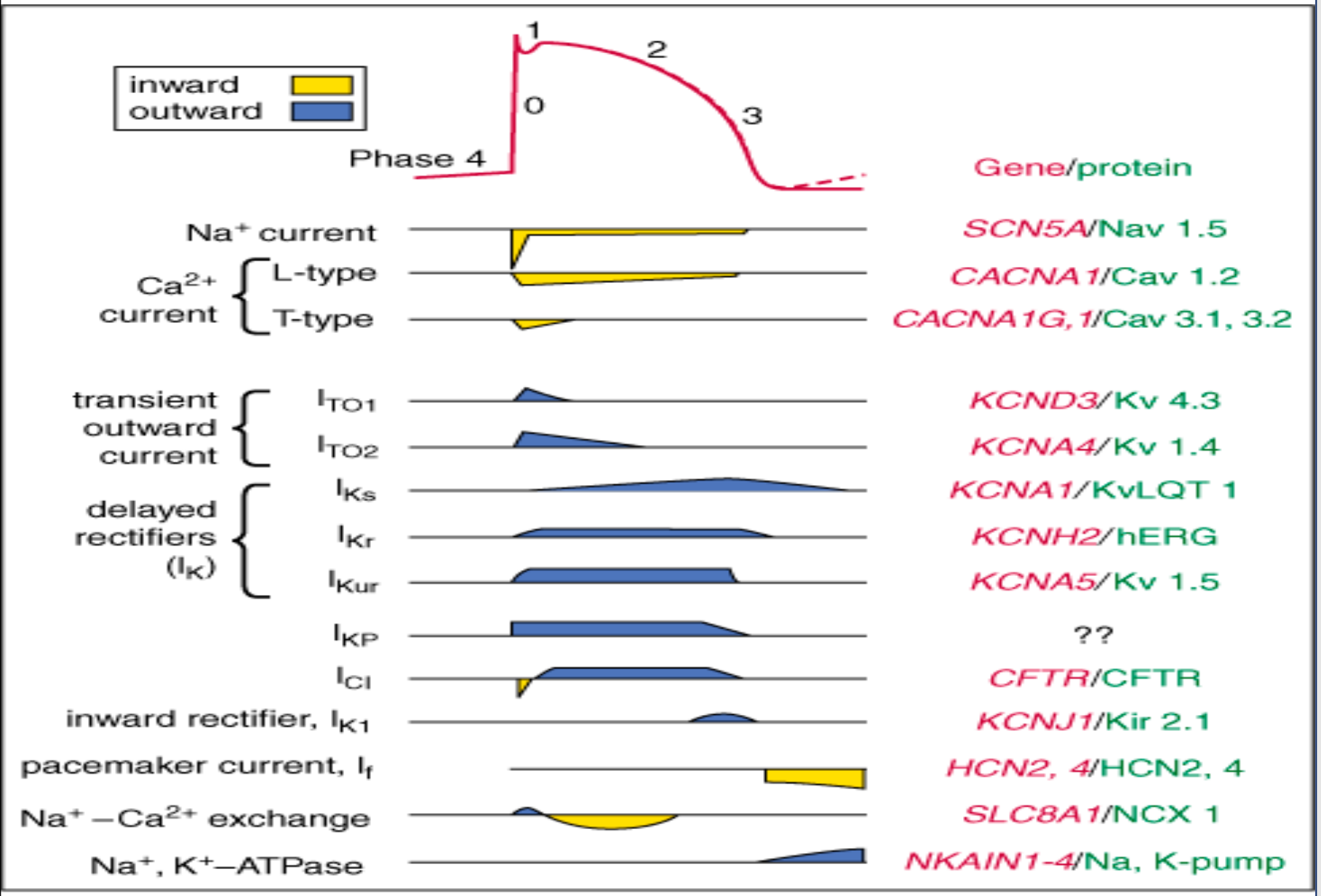
Action potential phases
0: Upstroke
1: Early-fast repolarization
2: Plateau
3: Repolarization
4: Diastole

Normal ECG

This is the diagram of the electrical system of the heart and the action potential generated. As we know, the electrical system of the heart starts from the SA node then the electrical activity is propagated through the atrial tissue into the AV node, bundle of his and burkinje fiber then into the ventricles which respond by contraction of the muscle

This action potential is recorded directly by placing electrodes in these cardiac sites but of course it's not done in humans but in experimental animals. In humans we put electrodes on the surface of the chest and record the voltage deflections (indirect) which is called ECG

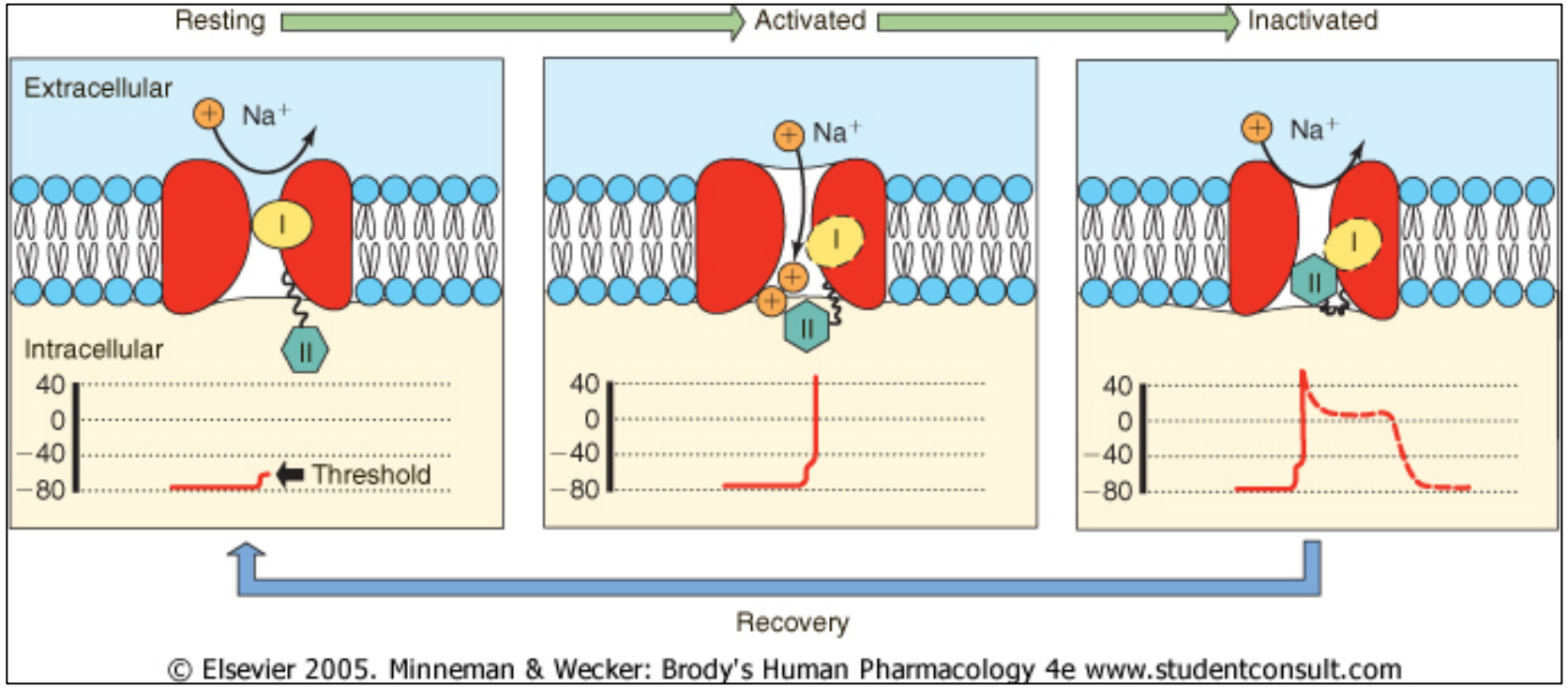
Main method for diagnosis of cardiac arrhythmias



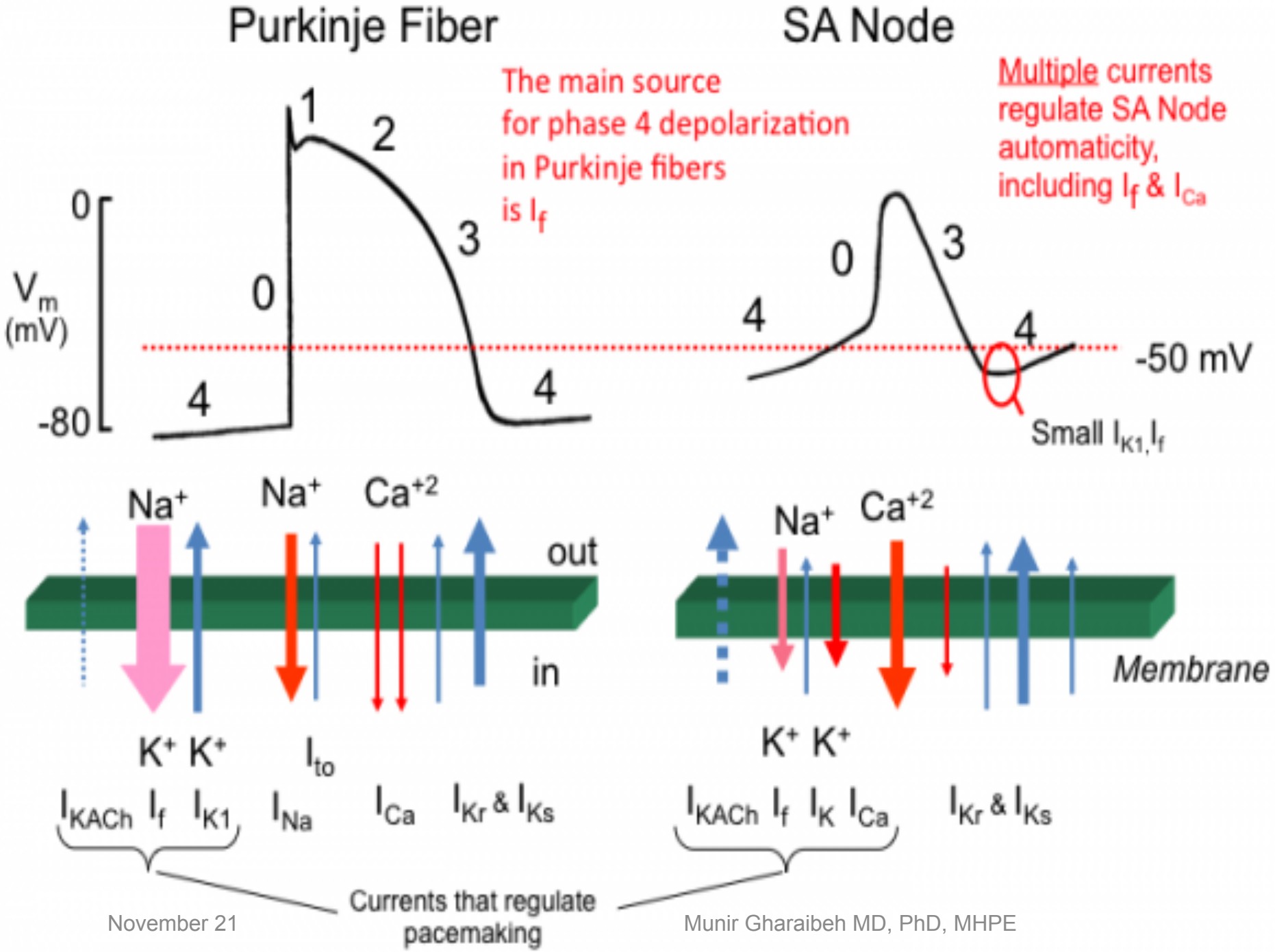
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

If we take one of these action potentials, you can see that it is composed of phases (4,0,1,2,3) , and the shape of the action potential depends on movement of ions-either inward or outward. These different ions will move through special channels specific for each ion and thus generate many currents. Channels are proteins in nature → protein synthesis Depends on enzymatic activity and genes →There is a significant relationship between the genetic background and susceptibility to cardiac arrhythmias. For example, regarding Na current, which is probably the major current in the heart, there is a gene which is called SCN5A which produces a protein called NAV 1.5.
You can see in the figure other currents as well as Na/K ATPase which makes the exchange between Na+ and Ca++ with the expenditure of energy

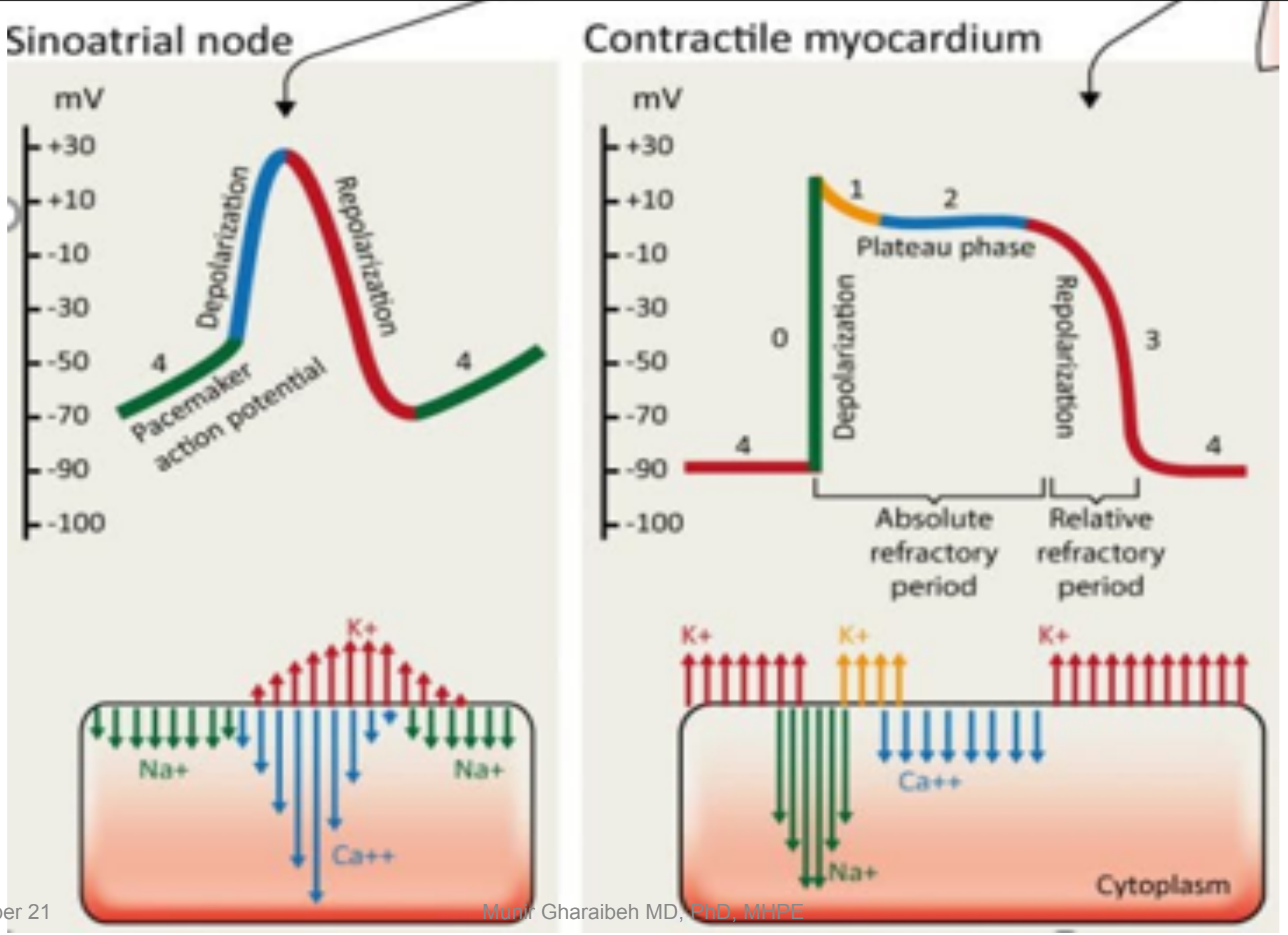
Cardiac Na+ channels

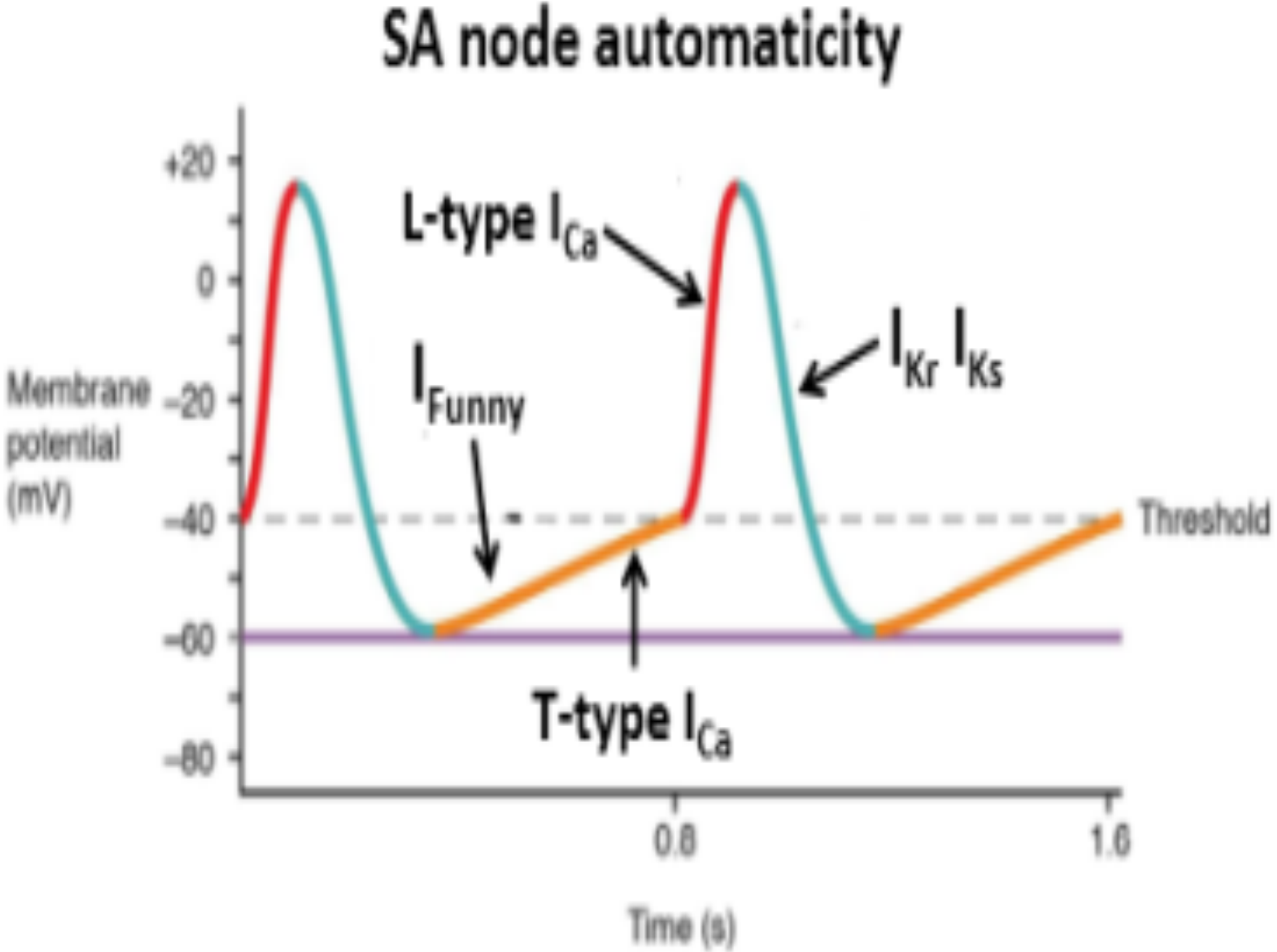


The most studied channel is the sodium channel, you know that it might be available in the resting state (Na can't go inside), activated state (Na is allowed to go inside) and inactivated state (relative inactivity due to conformational Change) phases. The entry of Na will cause different deflections in cardiac action potentials.



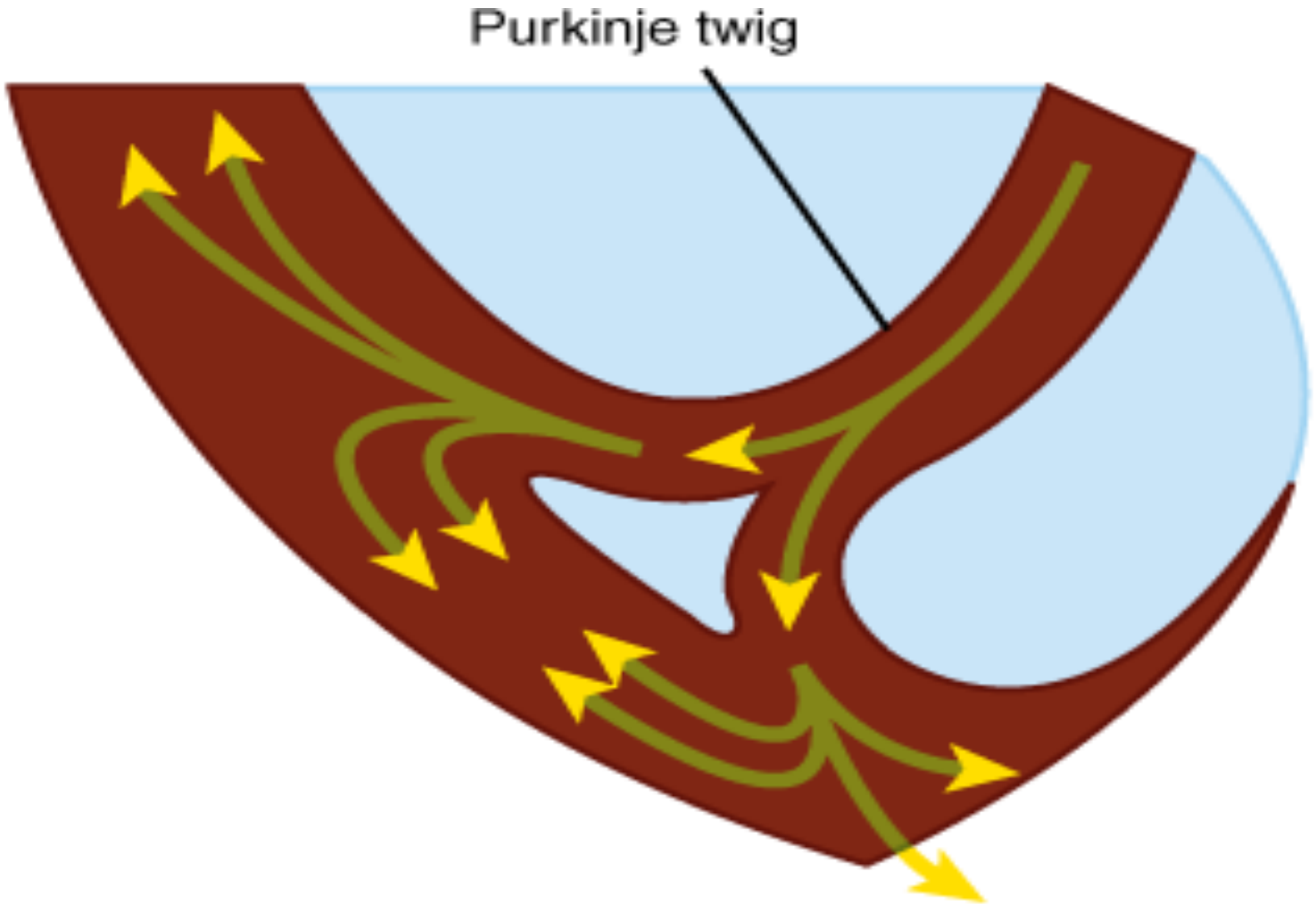
The following figure illustrates the difference in currents of AP between SA node and purkinje fibers (major depolarization in SA node is caused by entry of Ca+2 but In burkinje it's caused by entry of Na+)


Sinoatrial node
mV
+30
+10
-10
-30
-50
-70
-90
-100
Depolarization
Repolarization
4
Pacemaker
action potential
4
K+
Na+
Na+
Ca++
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+
K+
K+
Ca++
Na+
Cytoplasm



The SA node is the pacemaker of the heart because of its inherent activity to produce (or to reach the threshold) for excitation. And reaching the threshold will initiate (or will open the channels) for the AP and this will produce the depolarization which is followed by repolarization and then going down to the resting phase again .

Normal Circuitry



A. Normal conduction

Normally, the electrical activity goes through the heart very homogeneously and without any problems or delay.

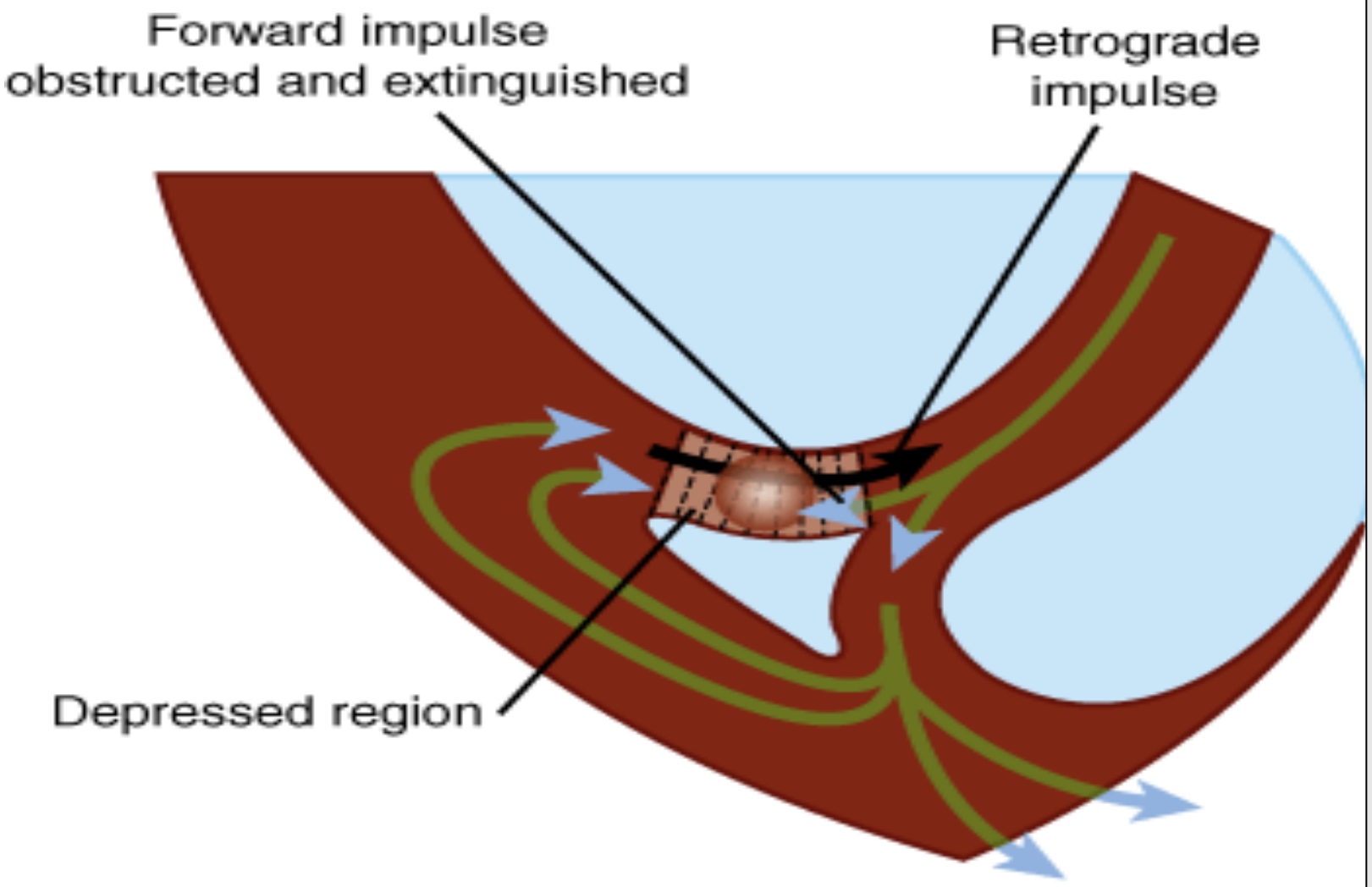
But how does the electrical activity finally terminate?

Electrical activity reaches the bifurcation of purkinje fibers which divides the current into two opposing directions. Having the same magnitude and intensity, these two vectors will eventually meet at a certain point and cancel each other out.

This normal passage depends on the effective refractory period

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

Re-entry Rhythm



B. Unidirectional block

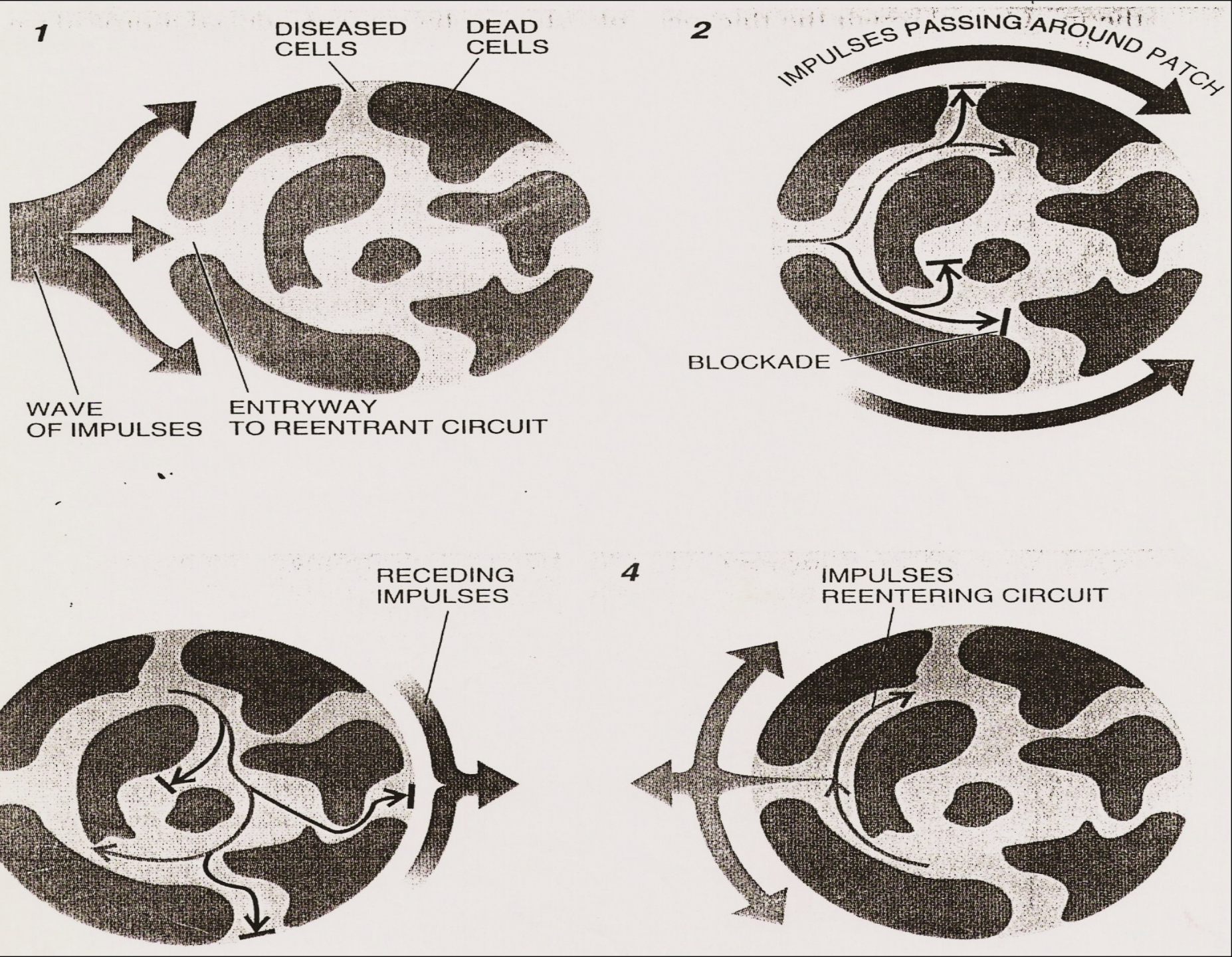
However, for example, in the presence of an ischemic change in one of the terminal passages of these minor currents, we can assume that this ischemic area contains dead tissues, diseased tissues, and normal tissues.

The impulse will not be able to cross the ischemic tissue (dead tissue) but will go with some difficulty through the diseased tissue and will go through the normal tissue in a normal fashion, speed and direction.

In dead tissue there will be some delay so other currents might arrive this ischemic area from backward flow. After the passage of the refractory period of the normal current, our current would reach the original point of bifurcation in a retrograde fashion and go back and forth to cause some sort of re-entry phenomena

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

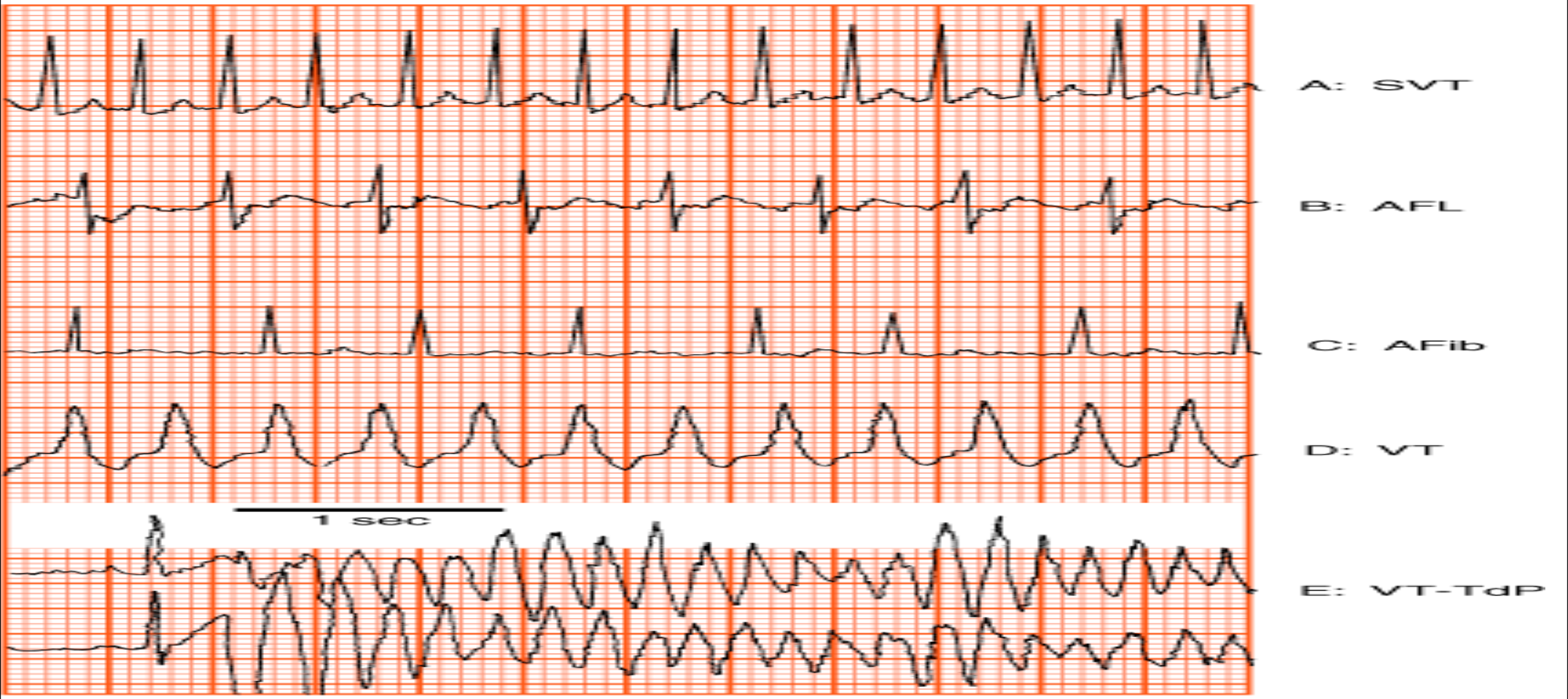
Currents moving in the diseased tissue would move in a circular path (almost), eventually going back to the starting point and can even re-enter the circuit causing reverberating cycles of cardiac arrhythmia.



Pre-requisites for Reentry (Circus Movement)

- **Anatomic or physiologic obstacle.**
- **Unidirectional block.** Notice that in the previous example the dead tissue stopped the forward conduction, but it allowed the backward current to move through it .
- **Conduction time around the circuit must be longer than the effective refractory period.** So, the abnormal activity should go through the area after the passage of the effective refractory period

ECG of some Arrhythmias



About the previous slide

A. Supraventricular Tachycardia (SVT): Multiple p waves occurring at a higher rate than normal originates in the atria. It is benign and can come for a short period of time and go spontaneously. Patients in this case are healthy and young but it may occur secondary to over-ingestion of stimulants e.g. coffee or tea, or due to stress and anxiety. (Very clear P waves)

B. Atrial Flutter: Same as A but at a much higher rate than SVT (apparent p waves) .

C. Atrial fibrillation: Atria work at an extremely high rate independent of SA node activity. Notice the tiny p waves which denote weak contraction.

D. Ventricular tachycardia: Arrhythmia occurs in the ventricles, this time independent of the activity of atria. Notice that unlike A, B, and C to some extent, there are no P waves this time. So, the ventricles take over the electrical activity and contract rapidly.

E. Polymorphic Ventricular Tachycardia-Torsade de Pointes: the rate and the strength of contraction is variable.we will talk about this one in more details.

Torsade de Pointes
Polymorphic Ventricular Tachycardia

LQT (long QT interval) **, syncope, and sudden death.** (affects young people)

Causes:

- **Familial long QT interval**
- **Drug - Induced (drugs which prolong APD** [action potential duration] **)**

these drugs are actually used to treat arrhythmias but at some point, they may cause them

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

Mechanisms:

- **Increased inward current (GF** [gain of function] **), or**
- **Decreased outward current (LF** [loss of function]**) 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

These are the relationships between the genetic background and some of the cardiac arrhythmias

LQT intervals can be recorded by simple ECG

We have many types of LQTs, either because drugs or familial tendency or mutations

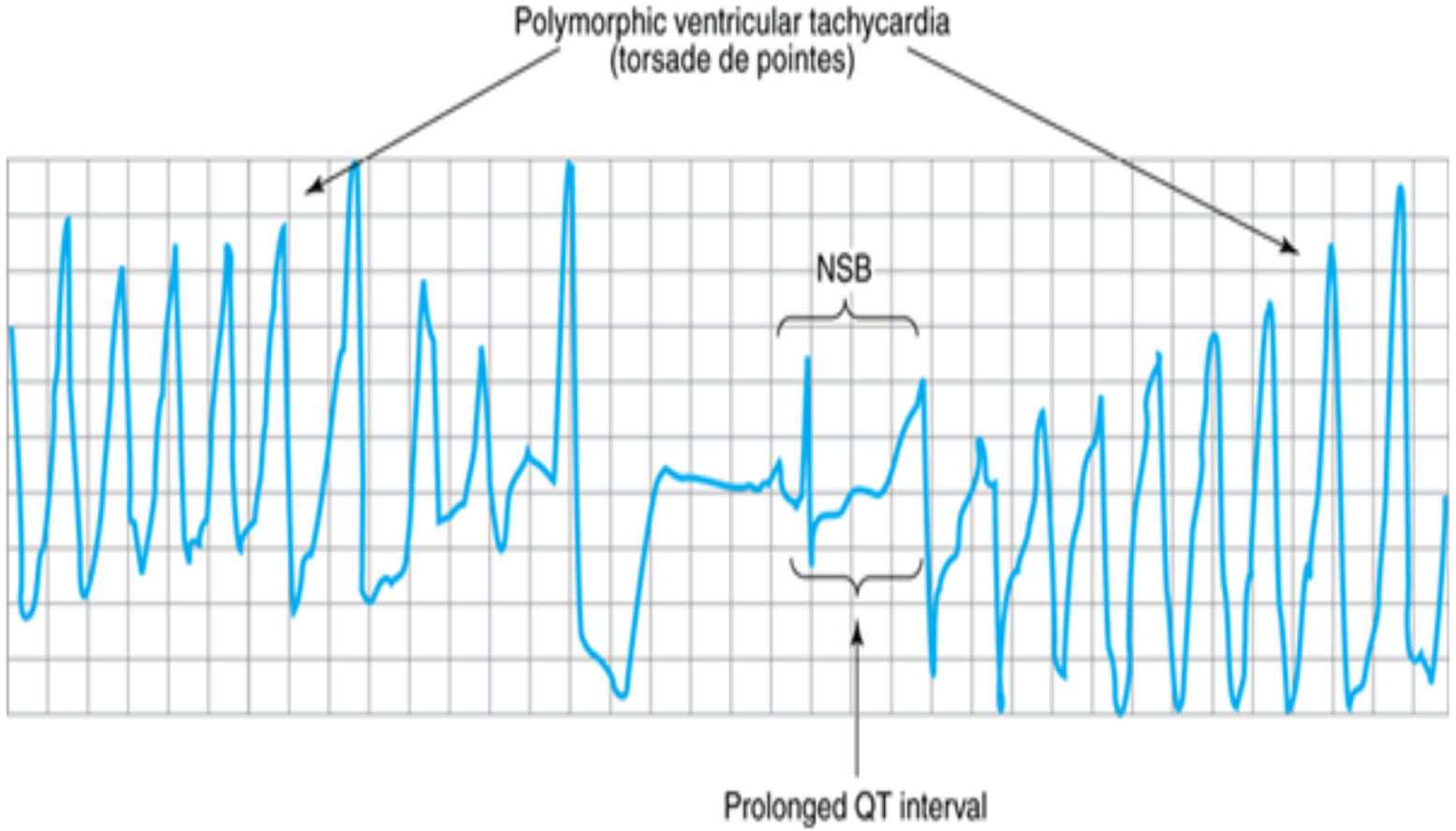
It was found that there is some chromosomal involvement

We have 8 types of LQTs , some have short QT (1,2,3) and we have other cardiac arrhythmias like CPVT , sick sinus syndrome ,Brugada syndrome , PCCD, and familial atrial fibrillation

We can see that 2 of these could be attributed to abnormalities in the same chromosome

Genetic abnormalities → protein changes → channel abnormalities → cardiac arrhythmias

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.)

- Here you can see an ECG for VT-TdP. It is pleomorphic (variable) in many things: strength, rate, and QT interval length. So, you can find normal sinus beats as well as abnormal ones (THE MAJORITY)

Torsade de Pointes

Risk Factors:

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

Treatment:

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

www.sads.org= **sudden arrhythmia death syndrome foundation**

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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.**
  - **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.** Can be effective in re-entry rhythms, abnormal pacemaker surgery itself can induce trauma and arrhythmia.

- **Radiofrequency Catheter Ablation(إستئصال).**

- **Cryoablation.** Using low temperatures in ablation.

- **Implantable Cardioverter- Defibrillator (ICD).** is used in cases of ventricular tachycardia to prevent repeated or recurrent tachycardia (notice that the external defibrillator can defibrillate cardiac arrhythmias, especially ventricular arrhythmias, from outside but if there is risk of recurrence, we use ICD).

- **Gene therapy!!!!.**

Anti-Arrhythmic Drugs: Introduction

- **Available anti-arrhythmic drugs suppress arrhythmias by blocking flow through specific ion channels or by altering autonomic function.** mainly by blocking the sympathetic division→ Blockade of many muscular and electrical activities → Ex: by using β-blocker that targets B1 receptors that are present in the heart
- The parasympathetic system has minor activity on the heart except for the heart rate (suppresses the SA node) so one of the atropine effects is increasing the heart rate).

- **Anti-arrhythmic drug therapy can have two goals: Termination of an ongoing arrhythmia** (acute arrhythmias like ventricular tachycardia) **or Prevention of an arrhythmia.**

- **Unfortunately, anti-arrhythmic drugs, not only help to control arrhythmias, but also can cause them, especially during long-term therapy.**

Principles of Mechanisms of Action of Antiarrhythmic Drugs

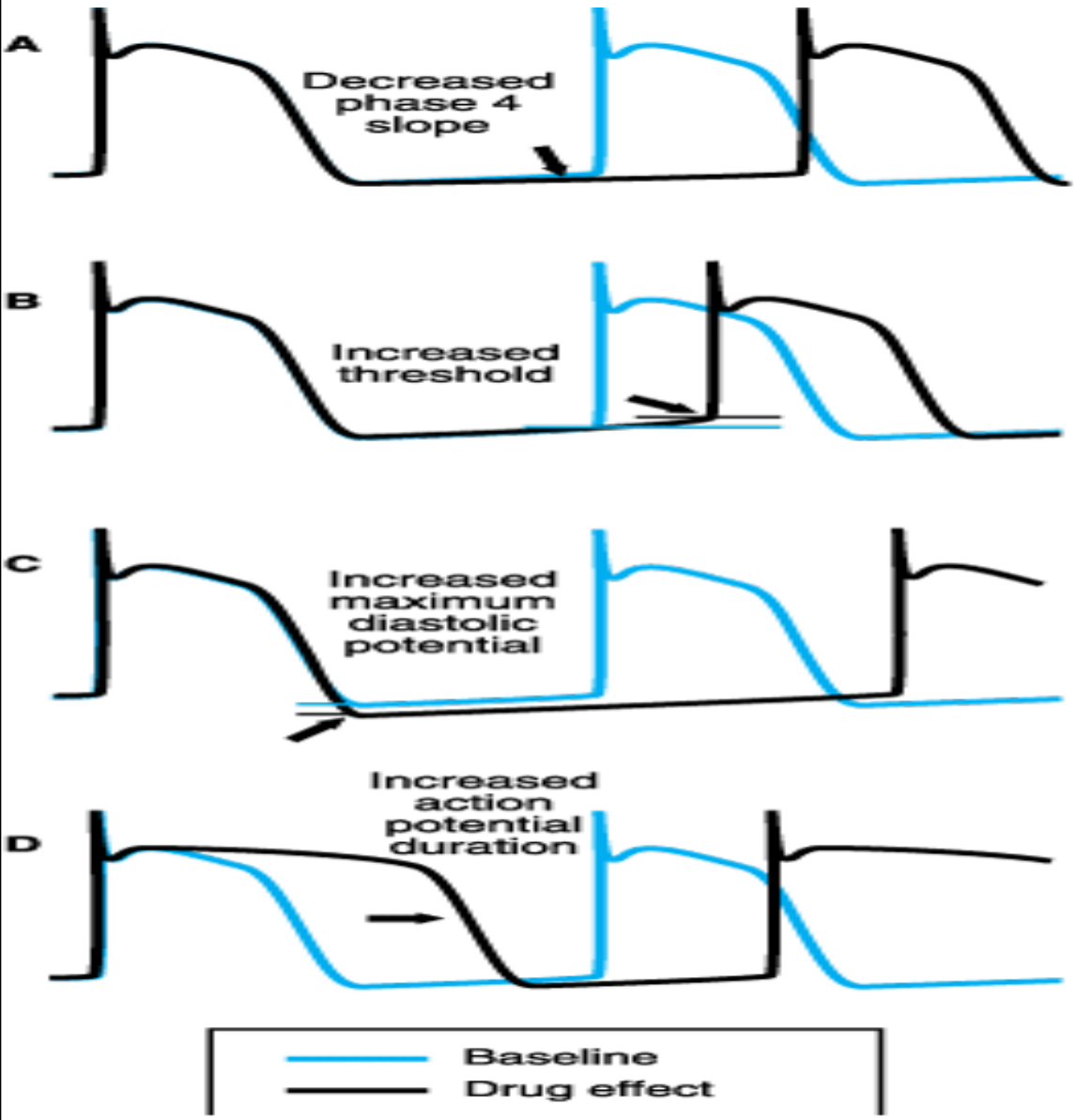
- **Readily bind to activated channels or inactivated channels, but bind poorly to rested channels. i.e.:** ***Use –Dependent or State-Dependent.***

- **Channels in normal cells will rapidly lose the drug from the receptors during the resting portion of the cycle**.(this is what we want)

- **This selectivity is lost with increasing doses, leading to drug-induced arrhythmias.** These drugs might be safe at low/therapeutic doses

- **Also, these drugs may become" *Proarrhythmic or Arrhythmogenic*" during fast heart rates, acidosis, hyperkalemia, or ischemia**. (If the heart rate becomes high, we expect that the rate of the binding of these drugs to cells will increase)

Possible Effects of Drugs on Action Potential



A. The drug caused a decreased phase 4 slope

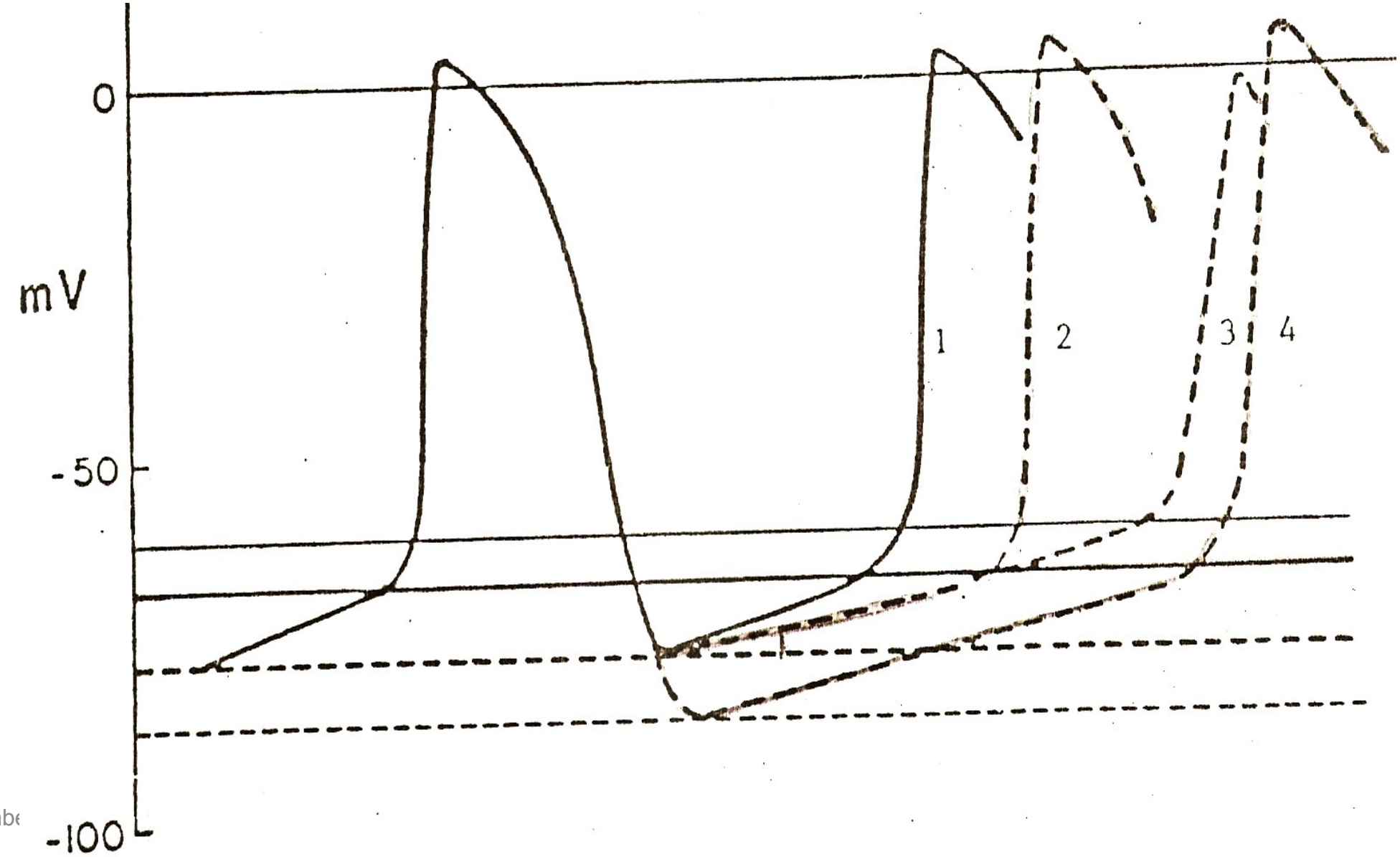
B. Here the drugs caused increased threshold and this will cause higher heart rate

C. The drug caused increased maximal diastolic potential

D. The drug increased APD

The normal baseline tracing is the blue line and the black one is the effect of the drug

Possible Effects of Drugs on Action Potential



About the previous slide

1.This is the standard AP (normal tracing)

2. Decreased phase 4 slope (reaching threshold becomes slower → delay in AP)

3. Higher threshold (less negative, reaching threshold takes more time due to the increased threshold) (decreased slope)

4. Lower resting potential (more negative) and increased threshold leads to a delay in initiation of AP. (Same slope as 1)

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

As you can see in the table , they are divided into 4 classes: I, II, III, and IV. Class I is further divided into 3 subclasses: a, b, and c

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.

Miscellaneous group

Drugs Affecting the Cardiac Action Potential

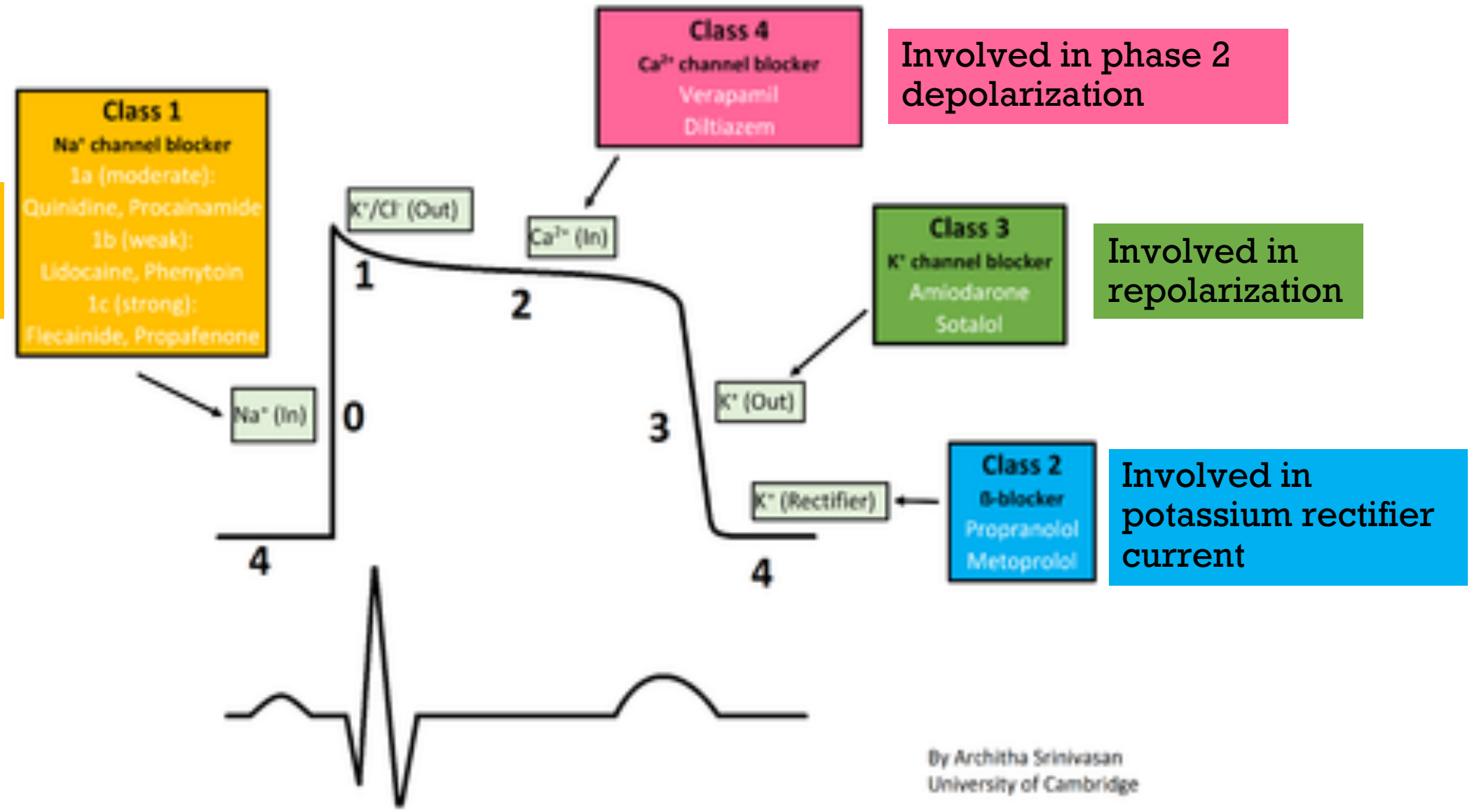


TABLE 14–3 Clinical pharmacologic properties of antiarrhythmic drugs.

Drug	Effect on SA Nodal Rate	Effect on AV Nodal Refractory Period	PR Interval	QRS Duration	QT Interval	Usefulness in Arrhythmias: Supra-ventricular	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

Or atrial