CVS
PHARMACOLOGY

Modified NO: 9+10

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المحاضرة طويلة شوي لأنها عبارة عن محاضرتين استعينوا بالله و ابدأوا

بسم الله نبدأ

✍️📃 The flow of information in this lecture:

1. Continuation of the last lecture (antihyperlipidemic drugs).
2. Discussing the cardiac arrythmias.
3. Discussing "AV nodal dependent" Atrial arrhythmia drugs (class II drugs).
4. Discussing Monomorphic Ventricular arrythmia drugs and WPW (class I drugs).
5. Discussing Polymorphic ventricular arrythmia drugs (class III drugs).

Color code
Slides
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Additional info
Important

First, we will Continue the antihyperlipidemic drugs lecture 💊

- **Continuation of the last lecture (antihyperlipidemic drugs):**

- **Fibrate (Fenofibrate ,bezafibrate and gemfibrozil):**
- Adverse effects of fibrate:
- Lithiasis : In hyperlipidemia, gallstone formation is influenced by increased cholesterol levels, leading to bile supersaturation. Fibrates, used to lower lipids, can exacerbate this by increasing cholesterol secretion into bile. Also, tension happen to the alpha hydroxylase, and this increase the viscosity of the surroundings place (the gallbladder), These changes increase bile viscosity and reduce gallbladder motility, creating conditions favorable for stone formation.
- Myositis (mild)

- **Combination therapy between fibrates and statin:**
  - Normally we Don't combine the fibrate with statin; because of the drug-drug interaction and the overlap of the side effects, but you might be forced to give them since no drugs can give the same effect as fibrate and statin
  - There is a difference between "fibrate" (what end in fibrate) and gemfibrozil in drug-drug interaction.
  - High LDL and high VLDL and high Triglyceride → the most found in Jordan
- So, we likely to decrease two things together, like LDL and VLDL
  - To decrease the LDL → we use statin
  - To decrease the VLDL and triglyceride → we use fibrates
- So, to decrease LDL and VLDL we need to use fibrates and statin together despite the drug-drug interaction, and the overlap of the side effects.

Here we have to differentiate between fenofibrate and gemfibrozil:

1. **Fenofibrate** → the interaction is mostly on the adverse effect (its side effect is myositis and statin side effect is myopathy)
   - ➢ If we prescribe fenofibrate and statin "at the same time" → 1. rhabdomyolysis (muscle breakdown, because of the overlap adverse effect of the two drugs on the muscles) and 2. dangerous for patient who have renal failure and rheumatic disease.
   - ✓ As a solution we give them → one in the morning (fenofibrate) and the other in the evening (statin)
   - ? If there is interaction between there side effects, why then we prescribe them together? We don't have other choice!

2. **Gemfibrozil** → the interaction here is more complicated.
   - ❖ 5 of 6 statin (atorvastatin, simvastatin, lovastatin, fluvastatin, rosuvastatin) → is **metabolized by cytochrome p450 (CYP3A4 or CYP2C9)**
   - ❖ The last of statin → **Pravastatin** is metabolized by sulfation.
   - ➢ Gemfibrozil have a very high drug-drug interaction, it inhibit cytochrome p450 and this lead to increased levels of warfarin (as you remember),and also increase the level of **cytochrome p450 metabolized statins** also.
   - × If the statin level increase it will inhibit Q10 → So, the combination of gemfibrozil with **cytochrome p450 metabolized statins** is dangerous, so we avoid combining them together.
   - ✓ → The combination of gemfibrozil with **pravastatin** have fewer drug-drug interaction and we can combine them.

Drug to be combined:	cytochrome p450 metabolized statins (atorvastatin, simvastatin, lovastatin, fluvastatin, rosuvastatin)	pravastatin
Fenofibrate & Bezafibrate	We avoid giving them **at the same time** ✗ one in the morning (fenofibrate or bezafibrate) and the other in the evening (statin) ✓	
Gemfibrozil	avoid combining them together ✗	we can combine them ✓

Now, we are going to discuss the cardiac arrythmias in general 🫀

Modernized Classification of Cardiac Antiarrhythmic Drugs

- Arrythmia in general is a big problem, and it's common in the population.
- Atrial fibrillation for example happen in 2.5% of people over 40-year-old.
- Atrial flatter is less common, nearly 0.25%.

- ❖ Atrial arrhythmia in general affect the AV node.
- ❖ If there is Circus rhythm (reentry) in the atria or around the AV we end up increasing the autor-hythmicity of the AV node, the conductivity of the AV node will increase toward the ventricles.

❖ Abnormal conditions lead to arrhythmia:

- ➢ The circus rhythm happen around the AV node, caused by scares or fibrosis causes reentry.
- ➢ Triggered arrythmia : Ectopic foci generate autorhythmicity that reach the AV node.
- ➢ The autorhythmicity in the AV node itself is increased.
- **All these will increase the conductivity of the AV node**

- All atrial arrythmias (atrial fibrillation, atrial flatter, SVT) caused by increased conductivity of the AV node EXCEPT WPW (wolff-Parkinson-white) syndrome; since the electrical signals bypass the AV node.

- **Pay attention!!** In WPW don't give drugs that work on AV node, why? Because its slowdown and block the AV node to pass in another faster accessory pathway lead to 1. Slowing the conductivity of the AV Node and Promoting Reentry (Circus Rhythm), or 2. Creating a New Pacemaker and Uncontrolled Rhythm which is dangerous.
- Blocking the AV node in WPW patients with AF eliminates the protective "filtering" role of the AV node, allowing dangerously rapid conduction through the accessory pathway. This can precipitate ventricular fibrillation and sudden cardiac death.

• It's contraindicated to give WPW patient these four drugs (we will talk about them in next slides):
• Digoxin, Beta-blocker, Calcium-channel blocker and Adenosine.
•Then how to solve WPW? We have to target the myocytes themselves and rebuild the normal rhythm (called cardioconversion)

- Cardioconversion can be:

1. Electrical : by shock delivery OR 2. Pharmacologic

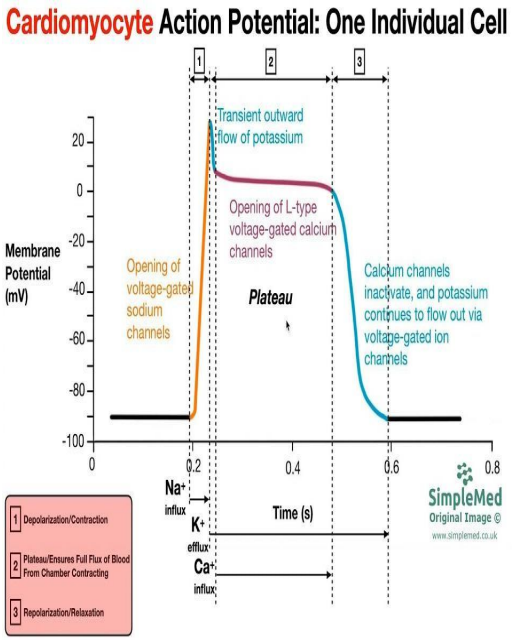
- WPW can be caused by:
  - ➢ The circus rhythm happen, caused by scares or fibrosis causes reentry.
  - ➢ Triggered arrythmia : Ectopic foci generate autorhythmicity that doesn't reach the AV node, making a new pacemaker.

❖ In WPW, we we can do two things:

1. Inhibit the sodium channel → less conductivity, since the sodium channel opening
   cause the start of action potential (look at pic).
2. Or we block the potassium channel → less efflux of potassium , lead to increased QT interval and action potential, so less frequency of firing (less contraction).

- Cardioconversion is very complex and precise process

➢ The drugs we use here is → class I drugs, mainly class Ic (more in the next slides).



Cardiac arythmias

- Disorders of rate, rhythm, electrical impulse generation or conduction in the heart
- Arrhythmias are due to problems with the electrical conduction system of the heart
- Can involve abnormal ion channel function and defective intracellular ion handling
- Conditions may range from mild to life-threatning
- Many anti-arrhythmic drugs can aggravate or generate arrhythmia, leading to search for alternatives
- All anti-arrhythmia drugs cause arrhythmia, all anti-cancer drugs cause cancer
- Then why use anti-arrhythmia drugs? It's an equation between risk and benefit, when benefit exceed risk, we have to use them.

Now, will discuss "AV nodal dependent" Atrial arrhythmia drugs (class II drugs) 💊🤯

EXCEPT WPW

- **caused by one of these three:**

➢ The circus rhythm happen around the AV node.

➢ Triggered arrythmia : Ectopic foci generate autorhythmicity that reach the AV node.

➢ The autorhythmicity in the AV node itself is increased.

❖ Now, in "**AV node" dependent atrial arrhythmias**, how can we stop the signals come from ectopic foci or circus rhythm around the AV node? We need to block the AV node!

- Drugs that block the AV node: 1. Digoxin, 2. Beta-blocker (block beta-1 adrenergic receptors (GPCRs) on the AV node), 3. Calcium-channel blocker and 4. Adenosine.

  - When we use these drugs, we block the conductivity increased by the ectopic foci or circus rhythm, preventing a higher conductivity to the ventricle that can increase the contraction of ventricle and lead to excess contraction.
  - Even if the ectopic foci or circus rhythm continue in the atria and relapse from period to another, as long as we block the AV node, we don't have a problem.

1. **First drugs used is:**

- **Beta-blockers and Calcium-channel blockers:** used as **prophylaxis**, why? Because it work on the conductivity of the calcium. As you remember, The AV node is calcium dependent, as you remember the funny channel open first then T-type calcium, then L-type calcium. Since the abnormal signals come from ectopic foci or circus rhythm around the AV node increases the conductivity of the AV node, Beta-blockers and Calcium-channel blockers will return the conductivity of the AV node to normal, by blocking the L-type calcium channels, leading to prolonged phase 0, leading to decreased conductivity in the AV node.

2. **Second choice:** in a more complicated like: If the conductivity is more than we can block using calcium channel blockers and beta blockers, we give here **digoxin or adenosine.**

- **Digoxin** increases the vagal tone increasing the release of acetylcholine, bind to M2 receptor (inhibitory GPCR), the alpha and beta subunits will inhibit the sodium leading to less sodium enter the cell, but the main activity is that the gamma subunit will open the potassium channels, releasing the potassium outside, leading to hyperpolarization due to decreased positive ions inside. (instead of -90, it might reach -110).

- But **Adenosine** act directly on cardiac receptors (adenosine A1 receptor) causing potassium efflux and hyperpolarization of the cell membrane. **Adenosine** cause complete hyperpolarization, causing no conductivity in the AV node for seconds, since the half-life for adenosine is seconds. (switch of the AV node 💤).

➢ ALTHOUGH complete repolarization will stop the conductivity of the AV node, it's only for a few seconds, giving the heart the ability to work again and the AV node switch on again, BUT sometimes the heart doesn't work again, which is a feared side effect of the bolus of the adenosine. 😱

➢ As result we limit the dose to about 6mg, giving it near the heart for less distance, if it doesn't work, we might give another dose of 6mg, we might also give a 3rd dose of 6mg or not depending on the severity of the situation, more than this we fear a complete block of AV node.

- **Adenosine** is given as a rapid IV bolus.

- In cases of acute supraventricular tachycardia (SVT), atrial flutter, or atrial fibrillation—especially if associated with hypotension or when the reentrant circuit involves the AV node—**adenosine** is the first-line treatment for AV nodal-dependent arrhythmias, we can also give digoxin in special cases.

- **The adenosine is better here than digoxin**, since digoxin cause arrhythmia because its effect is not limited to the AV node, it depolarize the myocyte (the opposite effect it have compared to the repolarization effect on AV node).

- Digoxin affect the potassium in AV node but in the myocyte, it affect the calcium.

❖ Now, why we don't solve the arrhythmia instead of prophylaxis and short time working drugs (such as adenosine)?

1. We might solve it by ablation of the ectopic foci by laser.
2. Until we solve it by laser, or we cannot solve it by laser, we use prophylaxis, but we don't treat it by drugs, why? Because all anti-arrhythmia drugs cause arrhythmia.
3. In cases of acute arrhythmias, we give adenosine or digoxin.

"AV node" Atrial arrhythmia drugs EXCEPT WPW	Patient have SVT, atrial flatter or atrial fibrillation	Patient have acute SVT, atrial flatter or atrial fibrillation (attack or hypotension)
Beta-blockers and Calcium-channel blockers	Prophylaxis against the recurrent of arrythmia after treatment	
digoxin		Hyperpolarization
adenosine		Complete hyperpolarization

anti-arrhythmic drugs

- The majority of currently available anti-arrhythmic drugs were specifically designed to target ion channels

- Anti-arrhythmic drug use has decreased over the past 15 years because of problems with side effects, particularly a paradoxical capacity to create more serious rhythm disorders than the ones being treated

- This phenomenon is called ‘proarrhythmia.

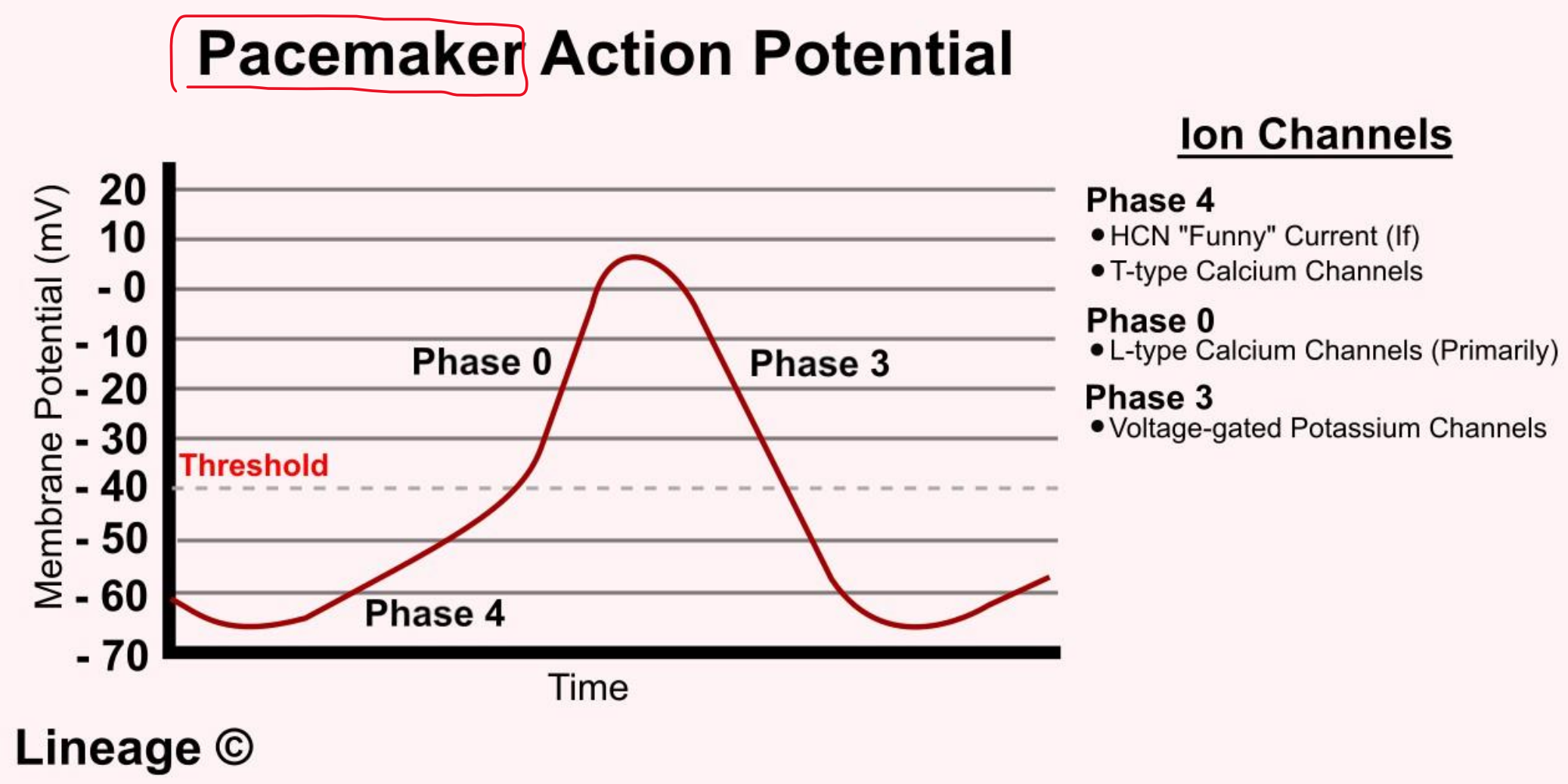
- Pro-arrhythmia is largely due to powerful effects of the drugs on ion channels, often in cardiac regions other than the arrhythmic zone being treated

Normal cardiac physiology

- The cellular basis of cardiac electrical activity is the cardiac action potential (AP), which is based on ion fluxes through specific membrane structures, particularly ion channels

- The ‘firing’ or depolarization of cardiac cells and closely associated cardiac electrical conduction depends on the movement of positive ions into the cell

- Here the refractory period is shorter than non-pacemaker cells, because of the funny channel.
- In the AV node and pacemaker in general, we have slow autorhythmicity unlike the myocyte which have a fast autorhythmicity



Atrial fibrillation

In AF, the normal regular electrical impulses generated by the sinoatrial node are overwhelmed by disorganized electrical waves, usually originating from the roots of the pulmonary veins.

These disorganized waves conduct intermittently through the atrioventricular node, leading to irregular activation of the ventricles that generate the heartbeat.

The regular impulses produced by the sinus node for a normal heartbeat are overwhelmed by rapid electrical discharges produced in the atria and adjacent parts of the pulmonary veins.

Sources of these disturbances are either automatic foci, often localized at one of the pulmonary veins, or a small number of localized sources in the form of either a re-entrant

Atrial fibrillation

- in which one impulse reenters and excites areas of the heart more than once • The path of reentry may be confined to small areas (within or near the AV node), or it may involve a large area of atrial or ventricular walls.

- Although the electrical impulses of AF occur at a high rate, most of them do not result in a heartbeat. A heartbeat results when an electrical impulse from the atria passes through the atrioventricular (AV) node to the ventricles and causes them to contract. During AF, if all of the impulses from the atria passed through the AV node, there would be severe ventricular tachycardia, resulting in a severe reduction of cardiac output.

Class II

All beta-blockers belong to Class II, except for sotalol, which falls into another class that we will discuss later. Beta-blockers are effective for atrial arrhythmias but should never be used for ventricular arrhythmias, as they have no relation.

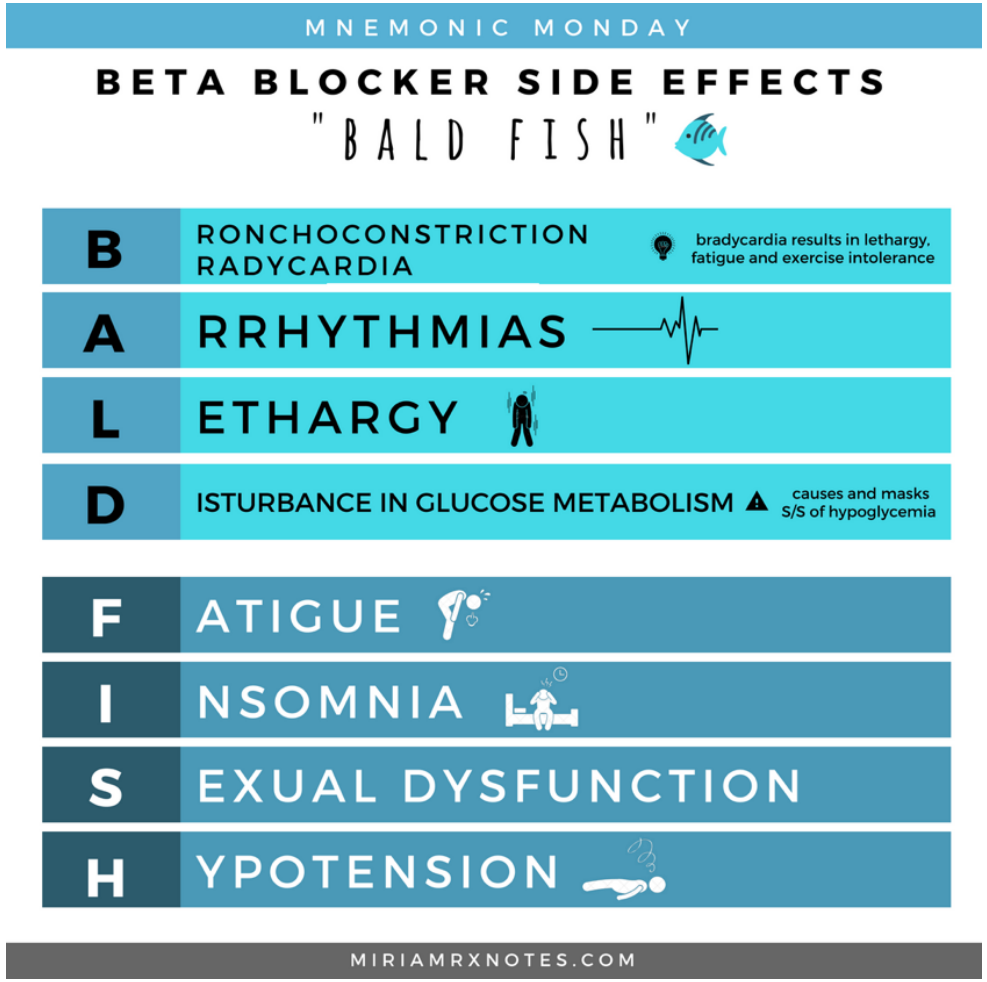
- Class II extends its coverage beyond an updated range of sympathetic β- adrenergic effects to further include **parasympathetic targets.**
- **Beta adrenergic receptors:**
  - β-adrenergic receptor activation causes successive Gs -protein and adenylate cyclase activation leading to increased cytosolic [cAMP]
  - The increased [cAMP]i activates protein kinase A, which phosphorylates a wide range of ion channels
  - cAMP also exerts a direct influence on hyperpolarization-activated cyclic nucleotide-gated channel activity and consequently on the pacemaking funny current [I f]
  - Finally, exchange proteins directly activated by cAMP have been reported to trigger RyR2-mediated **Ca2+ release.** So we work on AV node by this.

Class IIa

- Includes nonselective and selective β1 -adrenergic receptor **inhibitors** (beta blockers)
- Examples: Nonselective: **carvedilol and propranolol;**
  selective: **atenolol, metoprolol**
- Clinical indication: indicated in a wide range of tachyarrhythmias (sinus tachycardia, supraventricular and ventricular tachyarrythmias)
- Cause reduction in SAN automaticity; Reduction in AVN automaticity; Reduction in ectopic ventricular/atrial automaticity

Side effects of beta blockers

- Up regulation of beta- receptors with long term therapy, beta blocker withdrawal
- Sinus bradycardia, AV block
- Cold extremities
- Masks symptoms of hypoglycemia



Class IId

- Muscarinic M2 receptor activators
- Examples: **digoxin**
- Digoxin has *two principal mechanisms of action*, which are selectively employed depending on the indication:

1. **Positive ionotropic**: It increases the force of contraction of the heart by reversibly inhibiting the activity of the myocardial Na-K ATPase pump. Digoxin induces an increase in intracellular sodium that will drive an influx of calcium in the heart and cause an
increase in contractility. Cardiac output increases with a subsequent decrease in ventricular filling pressures.
2. **AV node inhibition**: Digoxin activates supraventricular M2 cholinergic receptors (parasympathetic nervous system activation), it slows electrical conduction in the atrioventricular node, therefore decreasing the heart rate.

- Clinical indications: Sinus tachycardia or supraventricular tachyarrhythmias

Digoxin adverse effects

- Visual changes (blurring, photophobia, disturbance
  - in vision color)

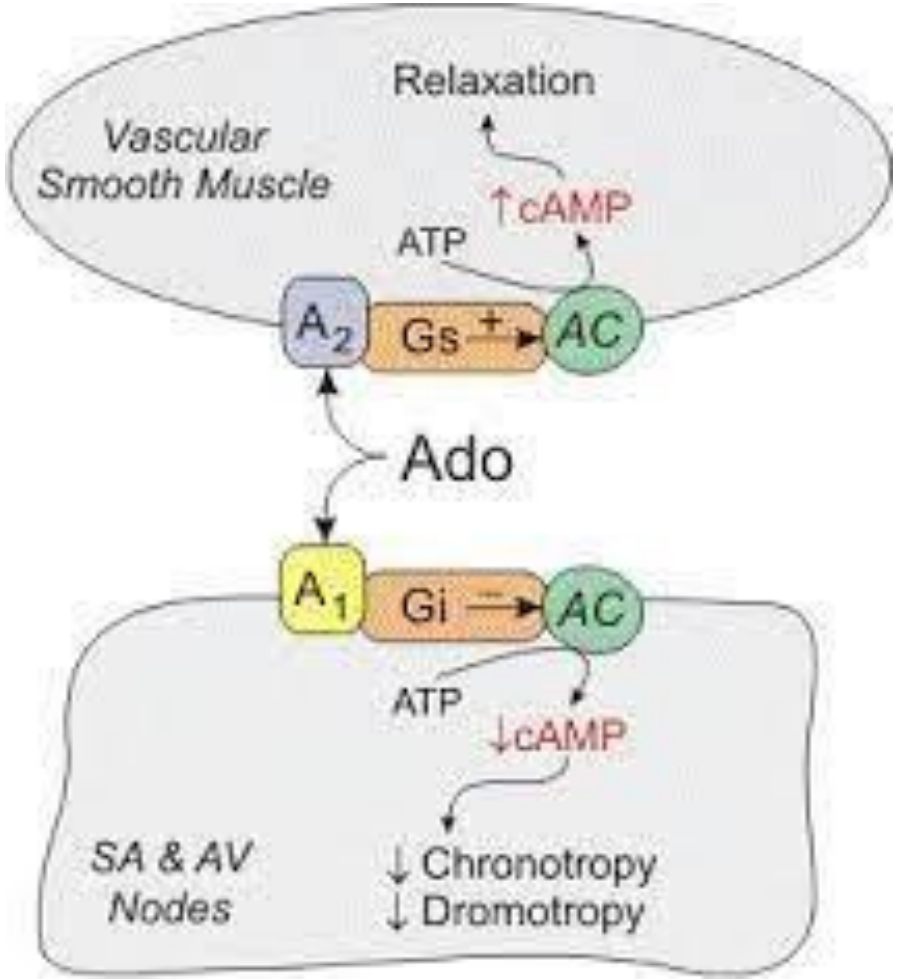
- GI toxicity: anorexia, nausea, vomiting

- Gynaecomastia, skin rashes

- Cardia adverse effects:
  - Bradycardia
  - AV block
  - Paroxysmal atrial tachycardia
  - Sino atrial arrest
  - Ventricular tachycardia

Class IIe

- Adenosine A1 receptor activators
- Examples: **Adenosine, ATP**
- MOA: Adenosine exerts a negative chronotropic effect by suppressing the automaticity of cardiac pacemakers, and a negative dromotropic effect through inhibition of AV-nodal conduction.
- Clinical indications: Acute termination of AVN tachycardia and cAMP mediated triggered VTs



- Digoxin acts on myocytes and the AV node:

- In myocytes, it inhibits potassium entry by binding to the sodium-potassium pump. This increases intracellular sodium, which in turn raises intracellular calcium levels, ultimately enhancing contractility.

- In the AV node, it acts on M2 receptors, leading to increased potassium efflux. This causes hyperpolarization, which decreases the heart rate.

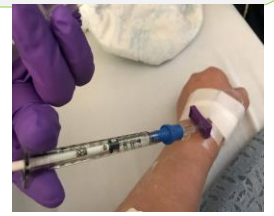
- Digoxin works on: Potassium --> AV-node Calcium --> Myocyte

- Adenosine works as an adenosine A1 receptor activator (similar to ATP but without the triphosphate group). This binding activates the receptor; however, activation in this context does not mean stimulation but rather inhibition—specifically, the inhibition of calcium influx and activation of specific potassium channels that will drive potassium outside.
- Go to additional sources to read more about adenosine if you want 😅

- M2 receptors and A1 receptors are both G-protein-coupled receptors (GPCRs).

Adenosine side effects

In acute phases, adenosine is administered as a bolus, leading to temporary inhibition of the AV node for specific moments rather than prolonged periods. As a result, adverse drug reactions to adenosine are rarely observed.
A bolus refers to a single, concentrated dose of a medication or substance that is administered rapidly, usually intravenously (IV). Please refer to the additional sources on the last slide to read more about this.



- Sinus bradycardia, sinus arrest or AV block Main side effect
- Atrial fibrillation
- Diarrhea.
- feeling of warmth.
- indigestion.
- loss of appetite.
- nausea or vomiting.
- redness of the face, neck, arms, and occasionally, upper chest.
- stomach pain, fullness, or discomfort.

So, to sum-up:

❖ Class II drugs:

1- Beta-blockers

2- Digoxin

3- Adenosine

And we learned how each one work. 😁

Now, will discuss Monomorphic Ventricular arrythmia & (Atrial) WPW drugs (class I drugs) 🔥

- In class II drugs, we address two problems: atrial flutter and atrial fibrillation, as well as any supraventricular tachycardia. However, sometimes the patient may still have issues in the atrium or ventricle. In such cases, we perform another process instead of targeting the AV node, which is **rhythm restoration**, helping the patient return to normal rhythm.

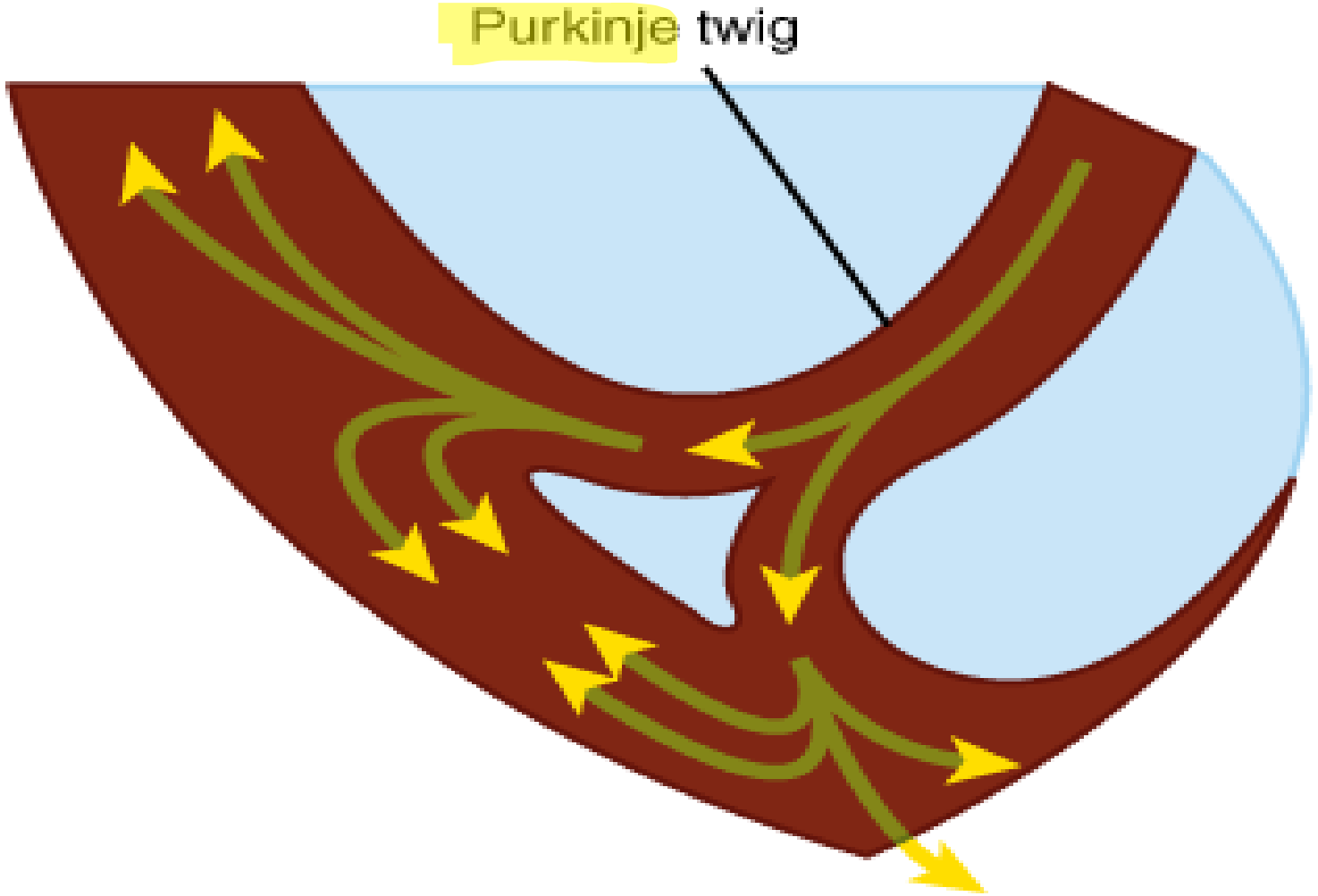
- The patient may lose rhythm due to an ectopic focus in the atrium, where it starts contracting on its own, or from a circular rhythm around the AV node or any location in the atrium. Additionally, fibrosis in the ventricles can lead to re-entrant or circular rhythms, causing the ventricle to contract independently, without input from the AV node, resulting in a loss of normal rhythm.

- It could be a monogenic rhythm (monomorphic arrhythmia), where the ventricular rate increases but not excessively. If multiple sites are triggered for automaticity or circular rhythm, it is called polymorphic arrhythmia (polymorphic intracardiac arrhythmia).

- What happens here is that in both monomorphic and polymorphic arrhythmias, you lose normal rhythm, but it's important to note that the rhythm loss occurs in the ventricles, not the atrium. Therefore, using drugs aimed at the atrium could cause problems. Instead, we will use different drugs, targeting sodium or potassium channels, because the problem in cardiomyocytes.

- The idea here is that I have a trigger, and I hold it back, How?! By drugs xD.

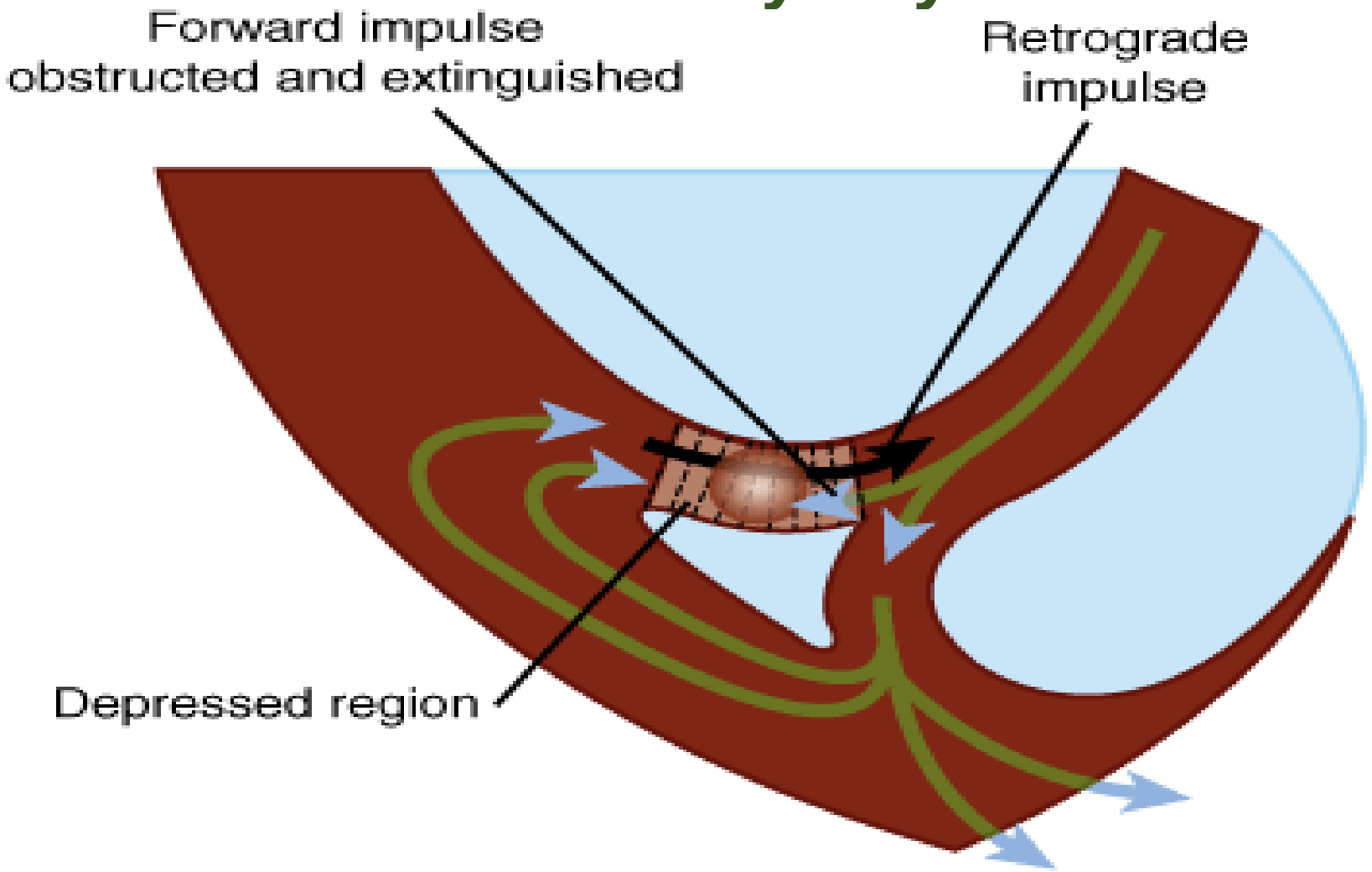
Normal Circuitry



A. Normal conduction

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

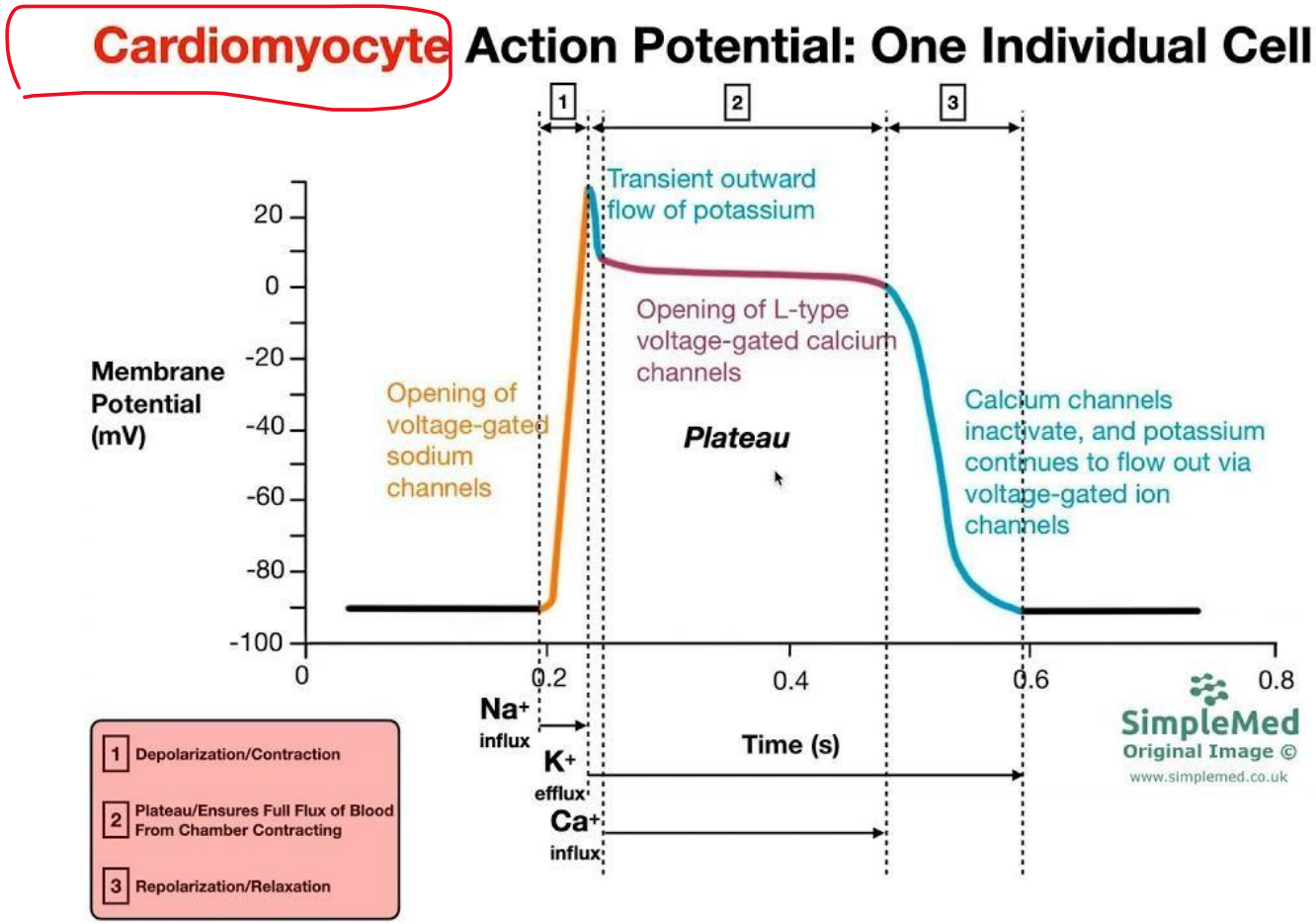
Re-entry Rhythm



B. Unidirectional block

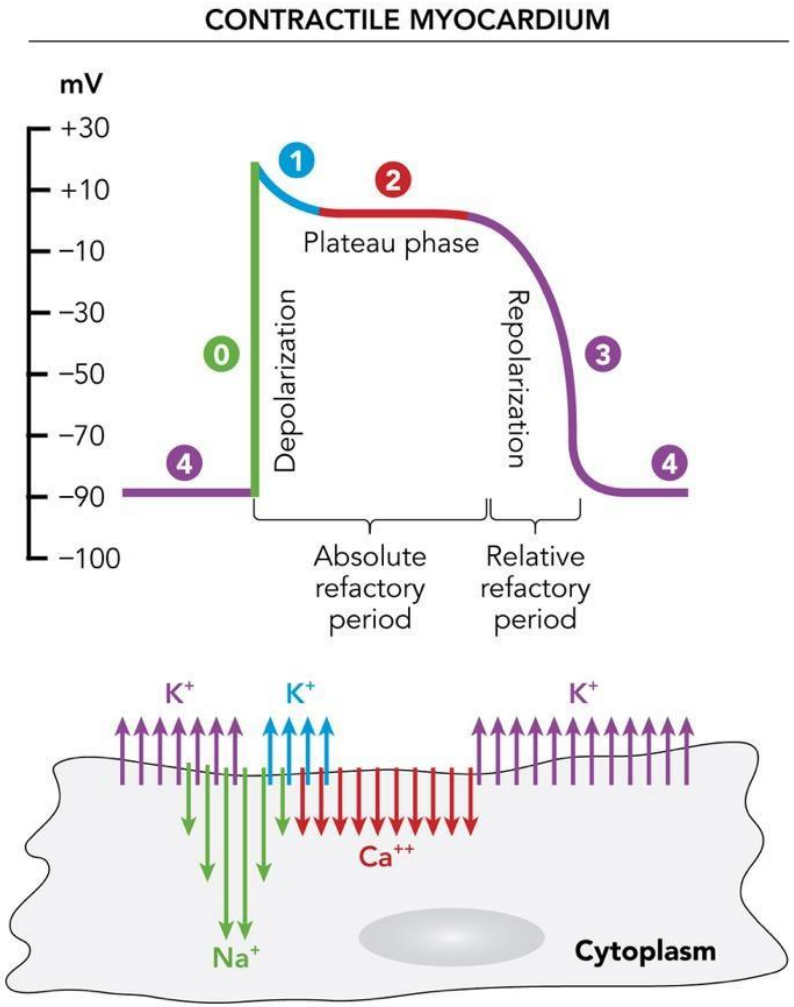
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: http://www.accessmedicine.com

- Once a cardiac cell is fired by being depolarized from its normally negative resting intracellular potential to a positive value (causing a phase of the AP called ‘phase 0’), it goes through a series of regulated repolarizing steps (AP phases 1 and 3), separated by a relatively flat phase of the AP (phase 2), to get back to its resting potential.



Cardiac cells are generally **unexcitable** once they have fired, and the time taken from initial depolarization to repolarization (called AP duration (APD)) imposes a limit (called the refractory period (RP)) on how soon a cell can be re-excited.

- APD is controlled by the rate of repolarization, which depends on the balance between **inward** movement of Na+ and Ca2+ that tends to keep the cell depolarized and **outward** movement of K+ through a series of highly specialized channels with typical time-dependent opening and closing properties.



- The main two sites we will work on are sodium influx (phase 0) or potassium efflux (phase 3), both of which we aim to decrease.

Class I drugs

- Class I subcategories list cardiac **Na+ channel (Nav 1.5) blockers**
- The different Class I actions influence their clinical indications for arrhythmias affecting different regions of the heart
- **Class Id:** includes drug acting on recently reported **late Na currents**

We will first discuss them in general (Class IC, IA, and IB), and then go into detail about each one.

Be patient, guys. I know getting to this slide has cost you a lot! xD 😭

- Looking at the diagram (blue, red, and green) in the next slide, we see a decrease in the slope of sodium influx. Which one is the strongest at achieving this? Class IC is the most potent in reducing sodium influx.

- All classes share the same basic mechanism, but they differ in their binding kinetics to the sodium channel. These classes are categorized based on their binding affinity and duration: Class IC is the strongest, followed by Class IA, and then Class IB (memorize them as CAB). Class IB has a unique feature—it decreases the action potential duration (APD) due to its preference for binding to sodium channels in their inactive state.

- What is the importance of this? Many arrhythmias occur due to QT interval elongation. If the cause of ventricular arrhythmia is QT interval elongation, I would be cautious about acting on potassium channels. Why? Because any interference with potassium channels can further prolong the effective refractory period, exacerbating the problem.

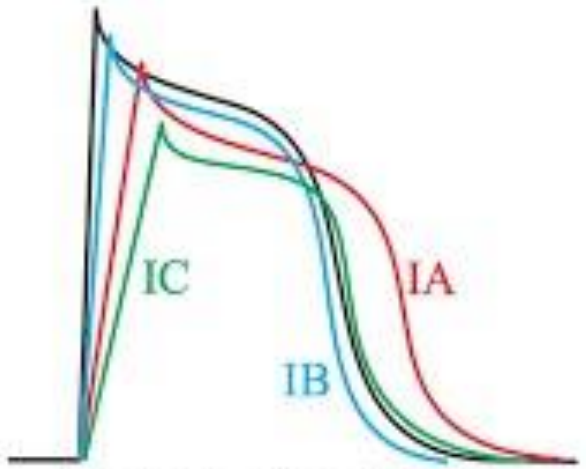
- Class IC and IB are particularly useful for patients with arrhythmias caused by QT interval elongation.

- If a doctor asks why you would use Class IC or IB ?, the answer is: to treat arrhythmias that manifest with QT interval elongation, which can potentially progress to torsades de pointes.

- Why don't we avoid sodium channel blockers altogether? Because we aim to reduce ventricular arrhythmias associated with QT interval elongation. However, Class IA drugs prolong the QT interval, limiting their use in such cases. Instead, we focus on Class IC and IB.

Class Ia

- bind to the open state of Nav1.5 with moderate dissociation time constants (τ) of ≈1 to 10 seconds (moderate block)
- reduce AP conduction velocity
- increase ERP and APD
- Includes: **quinidine, procainamide, disopyramide**
- Clinical application: supraventricular tachyarrythmias (atrial fibrillation) and **ventricular tachycaria** **Main Use**



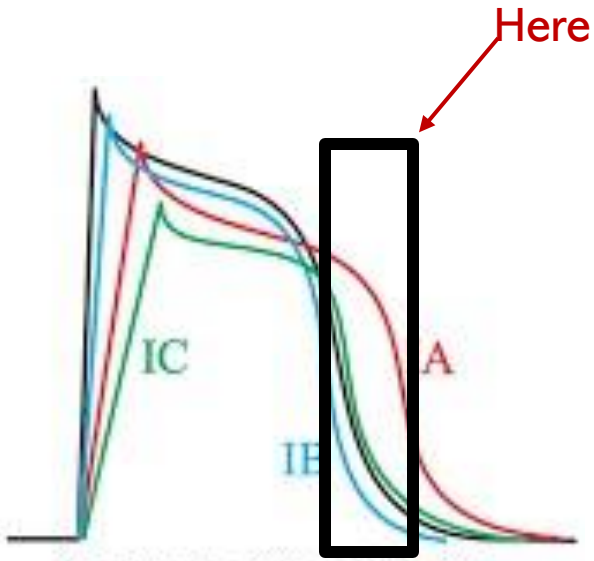
Ventricular Action Potential

Class IA: *e.g., quinidine*
- Moderate Na^+-channel blockade
- ↑ ERP

Class IB: *e.g., lodocaine*
- Weak Na^+-channel blockade
- ↓ ERP

Class IC: *e.g., flecainide*
- Strong Na^+-channel blockade
- → ERP

- Here, we decrease sodium influx and potassium efflux, leading to prolongation of the action potential duration (APD) and the effective refractory period (ERP).
- So, I have two mechanisms of action: 1) inhibition of induction, and 2) prolongation of the QT interval.
- In effect, I decrease the number of beats and prolong their duration.
- Always remember that arrhythmias occur during the effective refractory period (ERP), so you're generally protected. However, if you elongate the ERP, you might create a situation where ectopic beats can occur (as shown in the red diagram). Therefore, elongation of the action potential duration (APD) can actually produce proarrhythmic activity.
- Generally speaking about Class Ia, it is an effective drug; however, it is very proarrhythmic.



Ventricular Action Potential

Class IA: *e.g., quinidine*
- Moderate Na^+-channel blockade
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- Weak Na^+-channel blockade
- ↓ ERP

Class IC: *e.g., flecainide*
- Strong Na^+-channel blockade
- → ERP

Side effects

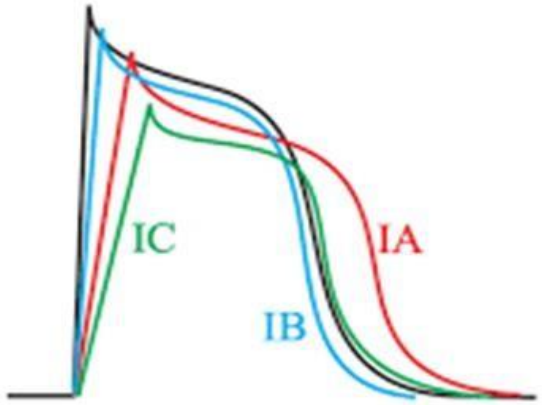
- **Quinidine:**
  - **Torsades de pointes** with QT interval prolongation
  - GIT side effects: diarrhea, nausea, vomiting
  - **Cinchonism:** a **syndrome** of headache, dizziness and tinnitus
  - **May increase the plasma concentration of digoxin leading to digitalis toxicity**
- **Procainamide:**
  - **Torsades de pointes** with prolonged QT interval
  - **Lupus-like syndrome(Like Hydralazine):** rash, small joint arthralgia, and arthritis
  - Pleuritis and pericarditis
  - Hypotension

A patient born with a long QT interval should not be given Class Ia drugs. If the arrhythmia is historically linked to QT interval elongation, or if the patient has taken medications such as quinolones (e.g., ciprofloxacin or delafloxacin), haloperidol (used for schizophrenia), or SSRIs (used for depression), **all of which can prolong the QT interval**, administering Class Ia drugs could immediately lead the patient into torsades de pointes.

- The main side effect: Torsades de pointes.

Class Ib

- drugs bind to the Nav1.5 **inactivated** state with relatively rapidly dissociation time constant τ of ≈0.1 to 1.0 second (weak block).
- shortens both APD and ERP in normal ventricular muscle and Purkinje cells
- Includes: **lidocaine**
- Clinical applications: **Ventricular tachyarrhythmias** (ventricular tachycardia, ventricular fibrillation)
- **Side effects**: CNS effects (slurred speech, drownsiness, dizziness, muscle twitching, seizures and hypotension)



- Lidocaine binds to sodium channels in their inactive state, and its binding differs from that of Class Ia and Ic. This unique binding leads to a decrease in action potential duration (APD), which can increase the heart rate slightly. But why would I do that to an arrhythmic patient? It's not a choice, my friend 😥😓 .
- What's beneficial about Lidocaine is that it has weak binding to sodium channels.

Let's talk about the side effects of Lidocaine:

- Lidocaine not only affects the heart but also has the ability to enter neurons and inhibit sodium channels. This can lead to various side effects, including CNS effects such as slurred speech, drowsiness, dizziness, muscle twitching, seizures, and Hypotension.

Lettle story about Lidocaine :

- Lidocaine is the anesthetic that dentists use, meaning it functions as a local anesthetic. It works by entering neurons and blocking sodium channels, reducing conductivity in the neurons, which prevents the patient from feeling pain.

- Here’s something cool to know: if there is inflammation, the area becomes acidic, causing Lidocaine to become charged and unable to enter the neuron. That’s why dentists tell you that if you have inflammation, they can’t proceed, as local anesthetics don’t work effectively in such cases. The inflammation must first be addressed for the anesthetic to take effect.

- Let's take this scenario:

- A patient with ectopic foci in the ventricle, not the atrium. The main issue in this ventricle is that it has been exposed to long periods of problems such as MI, congestive heart failure, or angina pectoris. In these three cases, hypoxia occurs, which is proarrhythmic. Why? Because hypoxic cells become more permeable, and this disrupts their electrical properties, creating a proarrhythmic situation.

- In such cases, we don't want to put additional pressure on the cells by closing sodium channels too strongly. Using Class Ic drugs in weak cells will exacerbate the situation, as closing the sodium channels too forcefully can lead to death, as shown in studies. This creates a proarrhythmic environment, effectively compressing the cells too much. Class Ia also increases the risk of death in these cases. However, they found that Class Ib is the best option for such conditions.

- The idea behind Class Ib is that it decreases conductivity but increases the heart rate. If you think about it, this actually helps return the heart to normal rhythm. By decreasing the likelihood of the first firing, I may shorten the action potential (AP), but I also slow down phase 0. The end result is a restoration of the normal rhythm that was lost, achieved by blocking the sodium channels.

- So, they found that for patients with MI, coronary artery disease, or congestive heart failure with low ejection fraction (which often involves remodeling and hypertrophy ودواليه✨), Lidocaine is the drug of choice in many cases when dealing with ventricular arrhythmias.

- The atrium, in general, is not significantly affected by conditions like MI, congestive heart failure, or angina pectoris. However, in a patient with WPW syndrome, Class Ic is a good choice because atrial cells are not as compromised as ventricular cells. If you want to stop atrial fibrillation, atrial flutter, or supraventricular tachycardia, you can use Class Ic without major concerns. On the other hand, Class Ia is problematic as it can lead to torsades de pointes, even in atrial myocytes.

- So, in patients with ventricular arrhythmias and a history of MI, congestive heart failure, or angina pectoris, we use Class Ib. If there is no such history, we opt for Class Ic.

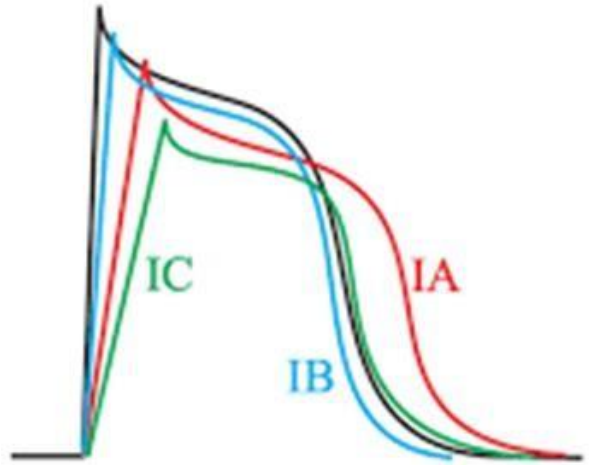
لا يُدْرِكُ الْغَايَةَ الْقُصْوَى سِوَى رَجُلٍ ثَبْتِ الْعَزِيمَةِ مَاضٍ حَيْثُ يَنْخَرِطُ

موديفايد طويل حبتين بس سهل ان شاء الله، توكلوا على الله وبتمشي 🌿😁

Class Ic

- Also bind to the inactivated Nav1.5, from which they dissociate more slowly, over τ >10 seconds (marked block)
- Reduce AP conduction velocity
- Maintain normal ERP and APD
- Include: **propafenone**, **flecainide** Remember this drug, the doctor said it is important ‼️
- Clinical applications:
  - Supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation).
  - Main use: Ventricular tachyarrhythmias resistant to other treatment

Explaniation in the next slide 😁



Ventricular Action Potential

Class IA: *e.g., quinidine*
- Moderate Na^+-channel blockade
- ↑ ERP

Class IB: *e.g., lodocaine*
- Weak Na^+-channel blockade
- ↓ ERP

Class IC: *e.g., flecainide*
- Strong Na^+-channel blockade
- → ERP

- Class Ic is the most potent because it binds to sodium channels with high affinity and dissociates slowly. By blocking the sodium channels, it reduces the slope of sodium influx, preventing the normal situation but still allowing enough activity to trigger a response.

- There is no effect on the effective refractory period (ERP).

- Clinical applications: Supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation);

- Why the atrium? Sometimes, it's necessary to restore the atrium to normal rhythm, as the atrium also contains myocytes. If the goal is to reproduce normal rhythm through electrical conversion, we use this drug.

- **Electrical conversion**, also known as **electrical cardioversion**, is a procedure used to restore a normal heart rhythm in patients with certain types of arrhythmias, particularly atrial fibrillation (AF) or atrial flutter. It involves using a **controlled electrical shock** delivered to the heart through paddles or electrodes placed on the chest to reset the heart's electrical system and restore normal rhythm.

Class Ic Side effects

these are the drugs that killed the patients in clinical trials that we talked about.

- **Flecainide:**
  - **Ventricular tachycardia in presence of ischemic heart disease or old MI**
  - **Vision problems**
  - Headache, dizziness
  - Has been shown to have **teratogenic effects**
- **Propafenone:**
  - **Ventricular tachycardia in presence of ischemic heart disease or old MI**
  - **Slowed sinus rate**
  - Dizziness, chest pain, **shortness of breath**
  - N/V, constipation/ diarrhea

Now, will discuss Polymorphic ventricular arrythmia drugs (class III drugs)
The last one 🥳

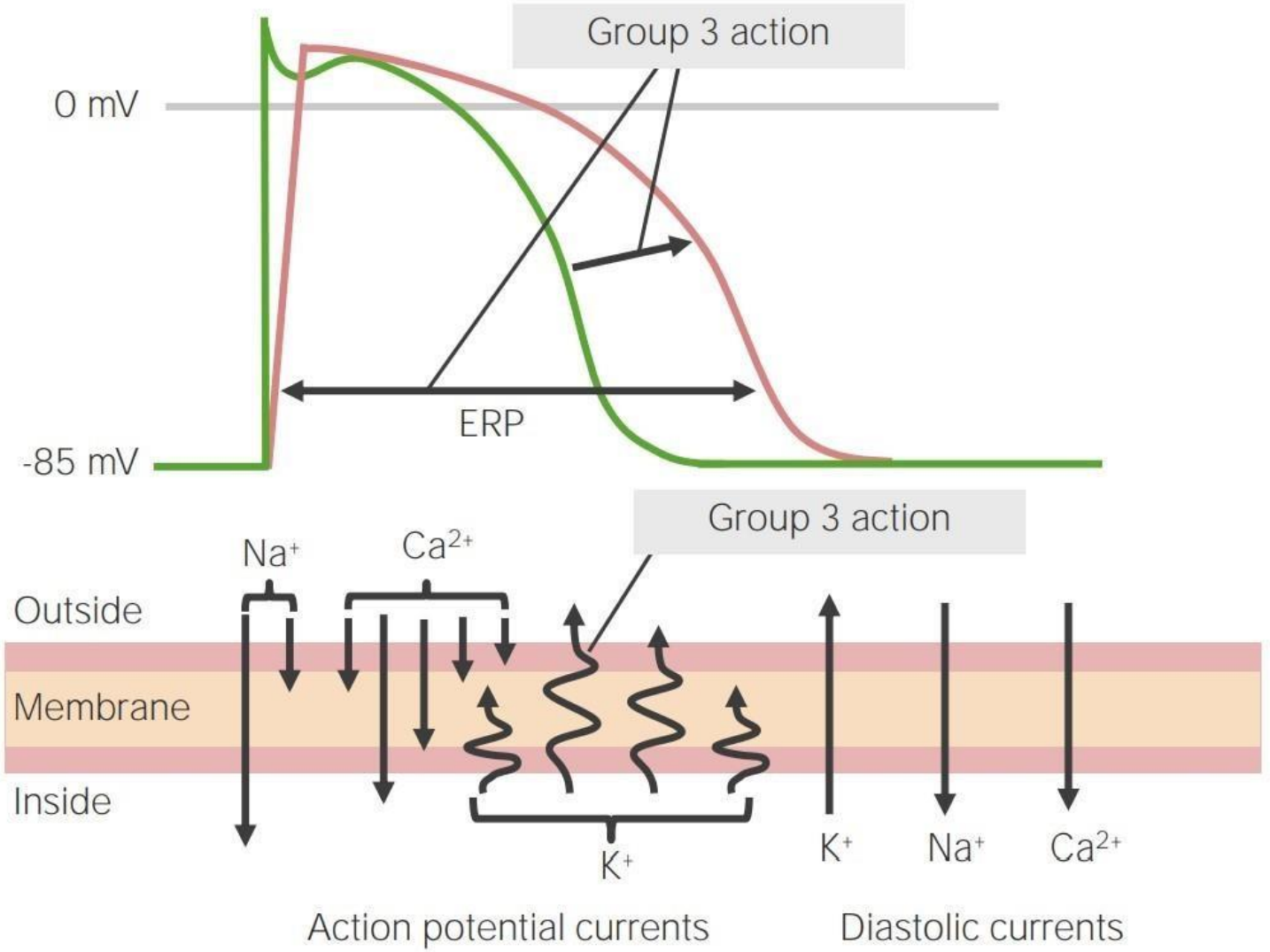
- If the previous drugs don't work, the situation transitions from monomorphic to polymorphic arrhythmia, such as torsades de pointes or polymorphic arrhythmia originating from different parts of the ventricle. In this case, there might be ectopic foci in both the right and left ventricles, with both beating simultaneously, and AV node conductivity adding to the complexity.

- At this point, the situation becomes quite difficult (الوضع صعب✨). Lidocaine might not be effective in such conditions, especially if the patient has a history of MI or the other factors we previously discussed.

- Here we come to the drugs amiodarone and sotalol. Sotalol has both beta-blocker activity and Class III antiarrhythmic properties.

Class III

- After phase 0 depolarization, complex components of transient inward current (I to) contribute to early rapid phase 1 AP repolarization.
- Class III agents includes wider ranges of voltage-dependent **K+ channel blockers**
- Examples: nonselective (**ambasilide, amiodarone**) and selective (**dofetilide, ibutilide, sotalol**) blockers
- They block multiple K+ channel targets resulting in prolonged atrial, Purkinje, and/or ventricular myocyte AP recovery, increased ERP, and reduced repolarization reserve


Group 3 action
0 mV
ERP
-85 mV
Group 3 action
Na+
Ca2+
Outside
Membrane
Inside
K+
K+
Na+
Ca2+
Action potential currents
Diastolic currents

Let's explain the previous diagram and what the drug does:

- Slope in phase 0: The drug reduces the slope of phase 0.
- Eliminates phase 1: Phase 1 is effectively deleted.
- Small changes in phase 2: There are slight alterations in the slope of phase 2.
- Blocking potassium channels: This increases the duration of phase 3.

- From this, you can see that this class exhibits a polymechanism of action.

- Some sodium channels are blocked, slightly affecting calcium channels (though not significantly).
- The most prominent effect is on potassium channels, leading to an increase in both the effective refractory period (ERP) and the action potential duration (APD).
- Conductivity decreases because the first firing relies on sodium, which is being reduced.
- The slope in phase 0 resembles that seen with Lidocaine.

- I am very strong with polymorphic application. So, if a patient has polymorphic ventricular arrhythmia originating from different sites, you need to target the treatment aggressively. However, be cautious of torsades de pointes, and ensure there is no congenital QT interval elongation or use of drugs that cause QT interval prolongation, or arrhythmias resulting from such factors.

- In a patient with MI, we can use this drug because we are addressing different types of arrhythmias.

- “I am amiodarone, I’m the best and the most famous and I’m unrivaled, but I have a small problem ” Dr. malek zuhlof said 😉

- The problem with Class III is that we cannot give them for long term treatment (as a prophylactic).

- It’s good to treat with amiodarone (IV), for 6 months, but longer than this can cause **many side effects:**
  1. **Torsades de pointes** [Since the Class III cause QT interval prolongation].
  2. **Heart block**
  3. **Bradycardia**

- **The side effects** caused by using class III **in the long term:**

1. Amiodarone main problem is that it contain iodine, which cause one of two:

1. toxicity, by apoptosis the cell of the thyroid die because its inability to utilize iodine causing → hypothyroidism.
2. the cell utilize iodine causing → hyperthyroidism.

So, it's depend on the thyroid, if it recognize the iodine of the amiodarone as a source of iodine then amiodarone will cause hyperthyroidism, but if the iodine of the amiodarone recognized as toxic material or the cell intake a high amount of the iodine leading to the cell apoptosis, then it will cause hypothyroidism.

2. Cardiac depression

- The main problem lie in its precipitation in certain places, because of its long half life (days), leading to →

3. lung fibrosis
4. Liver damage
5. Corneal microdeposits "bluish color on the eyes around the cornea"
6. Under the skin precipitation causing peripheral neuropathy.

- This drug has no similar drug with the two effects it have, so even though these side effects we still use it.

- The effect of **sotalol** (selective class III) is generally the same but the effect is weaker on the sodium channels.

- Its hold the ventricles from two aspects: the first is beta-1 blocking → decreasing the contractibility and conductivity and QT elongation, the second is blocking the potassium channels as other class III drugs (you will not see the tilt in the straight line of depolarization as amiodarone).

- The sympathetic overactivation can cause ventricular arrhythmia, if the patient have uncontrolled hyperthyroidism, or in situation when we give anesthesia (e.g., halothane) leading to sensitization of catecholamine toward the cardiac cells.

➢ If the ventricular arrhythmia is caused by sympathetic overactivation, then **sotalol** is a better choice than **amiodarone.**

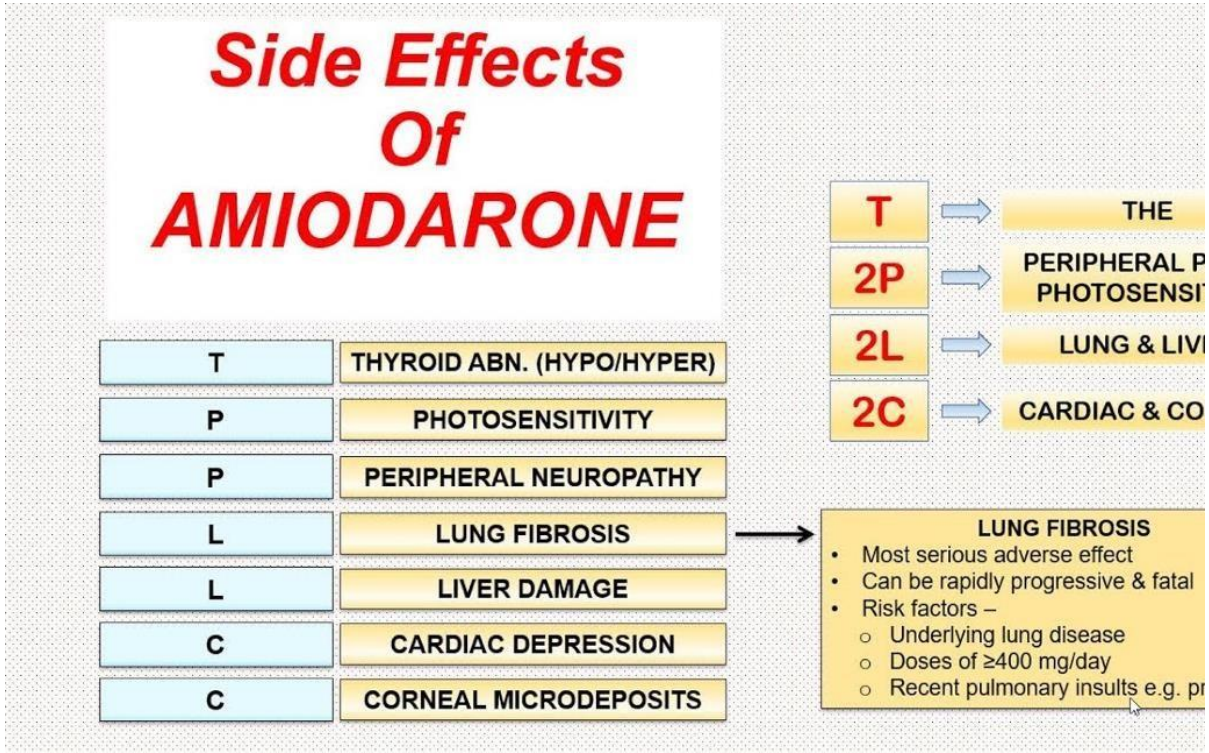
- **Amiodarone** and **sotalol** have the same side effects.

➢ **Dofetilide and ibutilide** can be used in SVT, A fib, flatter, they are weak so we don't give them in ventricular arrhythmias.

➢ **The Amiodarone** is the mostly used even in atrial arrythmia.

Class III side effects

- Torsades de pointes with QT prolongation Heart failure.
- Heart block
- Bradycardia



Class IV

The doctor didn't mention them

- The central importance of Ca2+ homeostasis to cardiac electrophysiological activity accounts for a wide range of potential applications directed at clinical arrhythmia
- Originally defined as **drugs blocking Ca2+ entry** through specific Ca2+ channels (CCB)
- It was extended to include drugs with a variety of actions that can be described as Ca2+ handling modulators

Class IVa

The doctor didn't mention them

- Surface membrane Ca2+ channel blockers
- Examples:
  - non-selective: **Bepridi**l
  - Selective: Phenylalkylamines (eg, **verapamil**), benzothiazepines (eg, **diltiazem**)
- MOA: Block of Ca2+ current (I Ca), resulting in inhibition of SAN pacing, inhibition of AVN conduction, prolonged ERP, increased AP recovery time, increased refractory period

Atrial arrhythmias

WPW →		**class Ic (flecainide)**		
"AV nodal dependent" Atrial arrhythmia	After treatment as → prophylaxis	**Beta-blockers and Calcium-channel blockers**	We might also use **Dofetilide and Ibutilide**	To stop atrial arrhythmia → **Class Ic**
	Patient have acute SVT, atrial flatter or atrial → fibrillation (attack or hypotension)	**Adenosine & Digoxin**		

Ventricular arrhythmias

Monomorphic Ventricular arrythmia	patients with arrhythmias caused by QT interval elongation	Class Ib (lidocaine) & class Ic (flecainide)	Class Ia ❌	
	Old MI, congestive heart failure, or angina pectoris	Class Ib (lidocaine) ✔	Class Ic & Class Ia ❌	
Polymorphic ventricular arrythmia drugs	Most polymorphic cases except 👇	**Amiodarone**		
	ventricular arrhythmia is caused by sympathetic overactivation	**sotalol**		

❖ These drugs usage has become much less recently because We might solve the arrythmias by ablation of the ectopic foci by laser

اللهُ عَظّمَ قَدْرَ جَاهِ مُحَمّدٍ وَأنَالَهُ فَضْلًا لديْهِ عَظِيمَا
فِي مُحْكَمِ التّنْزِيلِ قَالَ لِخَلْقِهِ "صَلُّوا عَلَيْهِ وَسَلّمُوا تَسْلِيمَا".

Additional sources
1- IV bolus vs IV infusion
2- Adenosine

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	28	Digoxin works on M2 receptors, which have inhibitory subunits. The gamma subunit interacts with potassium channels, blocking them and stopping potassium efflux.	We explained how digoxin works.
V2→V3	28	potassium efflux	calcium influx and activation of specific potassium channels that will drive potassium outside.

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!