Doctor.021
no. 9

CVS
PHARMACOLOGY

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Modernized Classification of Cardiac Antiarrhythmic Drugs

A small introduction for the lecture:

The topic of arrhythmias needs good understanding of the pathophysiological aspect before we dive into the pharmacological one , so lets get started with that (you probably wont be asked about this, its just for you to understand how things work):

Arrhythmia means simply, as the name states (A-rhythm) , loss or abnormalities in the rhythm, this comes in the form of abnormalities of impulse formation and conduction in the muscle of the heart.

it's a very complex family with a variety of different symptoms, disorders , and pathological mechanisms, but what we can say here is that it's a result of a problem or an abnormality in the myocytes themselves , or the conduction system of the heart(SA node, AV node, bundle of his, Purkinje fibers),and we can organize the arrythmias into their anatomical sites for better understanding of the problem. (for example we say ATRIAL fibrillation or VENTRICULAR.fib.) (don't worry we will get to them later in the lecture).

A small introduction for the lecture(cont'd):

- One thing that could lead to arrythmia is increased conductivity of SA node, or AV node, due to increased sympathetic stimulation(hyperthyroidism, increased levels of catecholamines) this could lead to tachycardia(heart beat could get to 110-120, not very severe)(physiology doctor says tachycardia isn't an arrhythmia , different sources say it is , but the doctor here said that it is)And in such cases we look for the underlying problem and solve it, its not very dangerous.

Everything in red is extra, everything in blue is from the doctor

- Other problems will be discussed throughout the lecture

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 → so here the abnormality is related to the myocytes
- Conditions may range from mild to life-threatning
- Many anti- arrhythmic drugs can aggravate or generate arrhythmia, leading to search for alternatives

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.

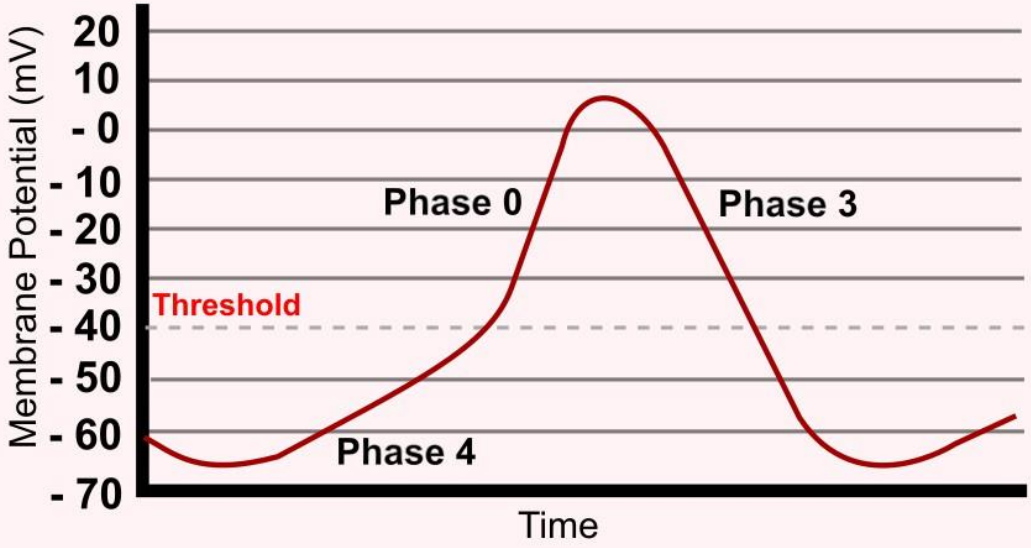
- Pro-arrhythmia is largely due to powerful effects of the drugs on ion channels, often in cardiac regions other than the arrhythmic zone being treated

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

Pacemaker Action Potential



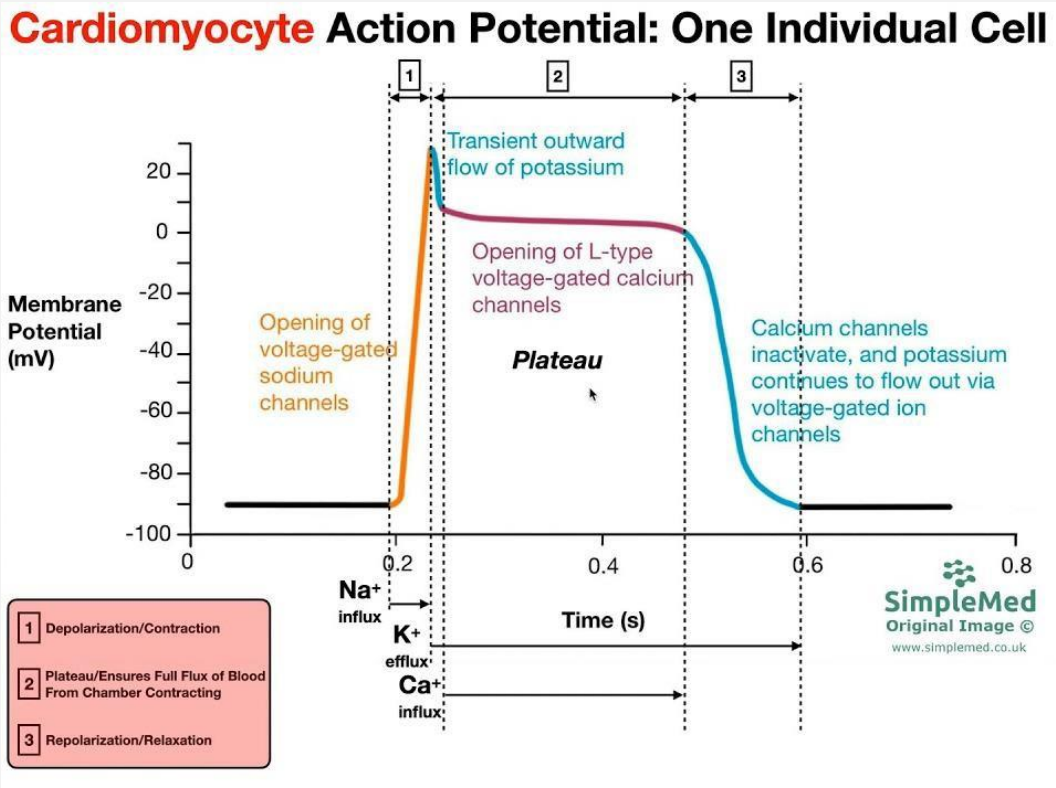
Ion Channels

Phase 4
- HCN "Funny" Current (If)
- T-type Calcium Channels

Phase 0
- L-type Calcium Channels (Primarily)

Phase 3
- Voltage-gated Potassium Channels

- 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.



Notes on the previous slide:

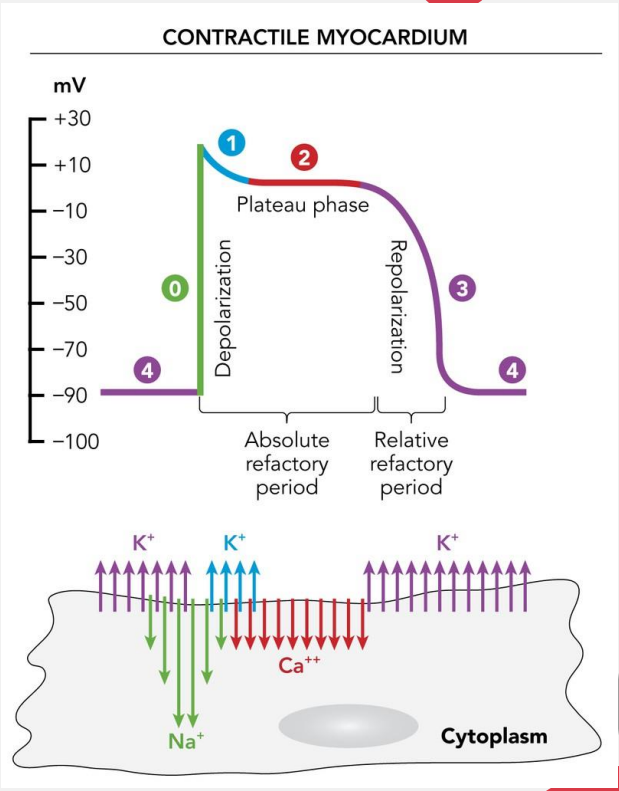
You probably know most if not all of what happens during the action potential of the cardiac myocyte, but just make sure to remember some things here:

- **The action potential duration is the duration between phase 0-3, and it gives a reflection of the QT interval (start of phase 0 till end of phase 3) in the ECG and vice versa.**

- **as you remember in physiology we know that the refractory period in the myocyte is almost throughout the whole action potential , and from (0.6s-0.8s) is what we call the resting phase.**

- Cardiac cells are generally **inexcitable** 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.



Atrial arrythmias:-

Before talking about atrial fibrillation, we need to talk about some problems resulting in atrial arrhythmias and abnormalities(they are of the main causes of atrial fibrillation):

- **One of the main causes atrial arrhythmic abnormalities is the formation of ectopic foci (can be one focus or multiple foci), which are foci that have automaticity of impulse (they can be pacemakers), the formation of such foci can occur in cases of atrial tissue ischemia , hypoxia, or fibrosis, and other forms of injury such as drug toxicity ,they produce their own action potential through the cells reaching the av node.**

- **Another main cause (and probably the most common) of atrial arrythmias is the formation of a re-entry impulse, a "circus" rhythm which can be caused by fibrosis, ischemia , or injury of areas around the av node, (it is also explained in the pictures in the next couple of slides. Explained as the following(the doctor didn't mention it , just if you want to understand what really happens in a circus rhythm):**

➢ **Normally , the impulse goes through the atrial myocytes until it reaches the av node and then has a delay there , and when depolarization of the atria ends, myocytes are still in the refractory period and won't be stimulated again, and by the time another impulse from the SA node comes this refractory period would have ended so another action potential occurs.(rhythm is maintained)**

Atrial arrythmias:- (cont'd)

Everything in red in those 2 slides is just extra explanation

- But in some cases , (such as what happens when we have ectopic foci , or a slow impulse conduction ,or a lengthened pathway of impulse) when the atrial impulse comes to an end, not all the myocytes are in the refractory period , so instead of ending all depolarization in the atrium and continuing through the av node , it finds more cells to depolarize , and so we have a re-entry of impulse , resulting in a circus rhythm . That all happened because either the impulse took too long to end(in the atria) , or the refractory period of some of those cells was shortened and ended fast.
- Ectopic foci contribute to the formation of circus impulses through:

1-slower conductivity, since they form within myocytes and their conductivity is markedly slower.

2-Ectopic foci continuously send impulses at a fast rate, this results in a shortened refractory period.

3-Excessive stimulation leads to decreased conductivity.

And those 2 main problems can cause atrial arrhythmias and av nodal arrythmias, and in cases of atrial , av nodal tachycardia , where the impulse reaches the ventricle, we call Supraventricular tachycardia, when this occurs we have decreased ejection time due to ventricles contracting at a high rate, so the cardiac output is decreased and this can be fatal.

Continuation of the previous notes:-

Those ectopic foci (around the AV node) do not only give impulses to the atria, they can also give impulses to the ventricles through accessory pathways other than the AV node, which can cause a syndrome called Wolff-Parkinson-White syndrome, in which the circus rhythm goes through the ventricle and back up again through the atria , it's as if the heart is beating on its own without utilizing the AV node to set the normal pace of conduction ,causing tachycardia, and as the doctor mentioned before when we studied digoxin , we don't give it in such cases because if we block the AV node , all the impulses will be from outside (not outside the heart but from the re-entry impulse itself that's going round the heart muscle through the accessory pathway , and that makes the impulses much faster since the av node delays it normally).

What's scarier is that those ectopic foci can occur in the ventricles themselves, causing what's called ventricular fibrillation, a fatal condition, where the ventricles wont have time to fill or pump properly because of the very rapid contractions

All of the previous abnormalities mentioned in relation to atrial arrhythmias can lead to atrial fibrillation

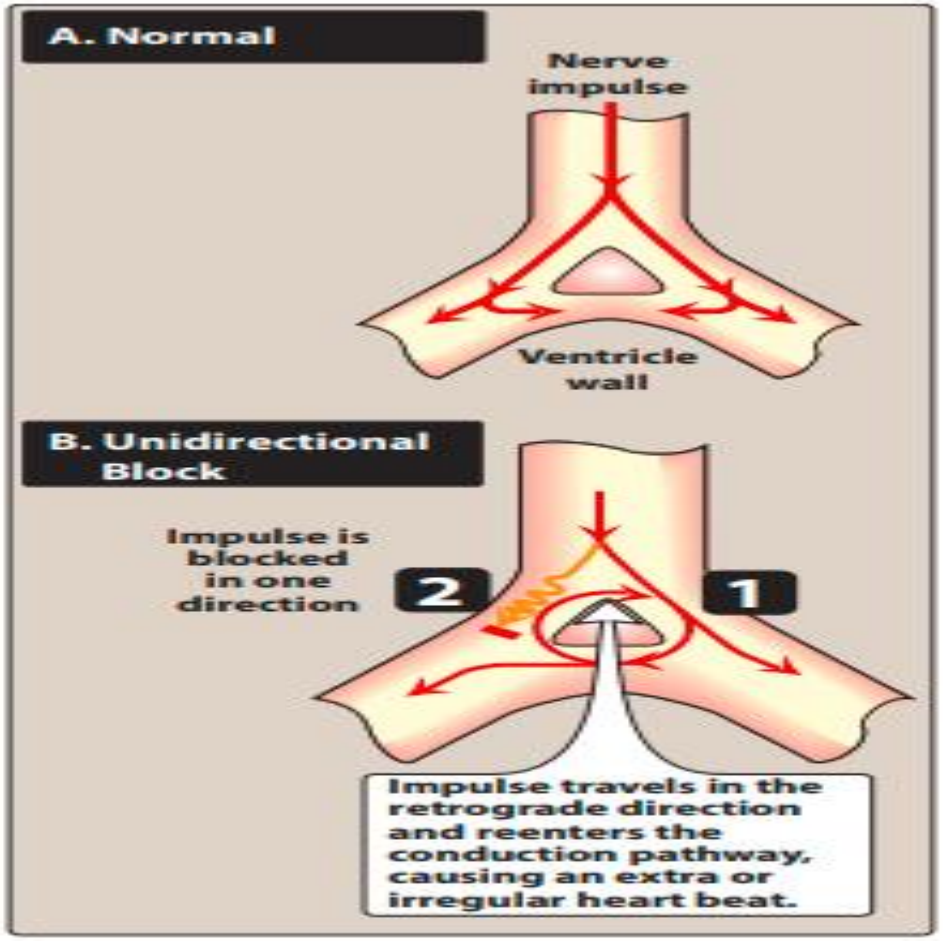


Figure 20.3
Schematic representation of reentry.

This picture represents a unidirectional block , which results from ischemia , tissue injury, hypoxia, drug toxicity….etc ,this block can cause a reentry circus rhythm , or / and the formation of ectopic foci, resulting in atrial arrhythmias.(it will be explained in a better way in the next pictueres)

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.**(due to ectopic foci around the pulmonary veins roots, or re entry circus rhythm)**

These disorganized waves conduct intermittently through the atrioventricular node, leading to irregular activation of the ventricles that generate the heartbeat.**(so we have 2 impulses , one originating from the SA node , and the other from the ectopic foci around the pulmonary veins, or from the circus rhythm that came from a block in that area.**)

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 a re-entrant impulse.

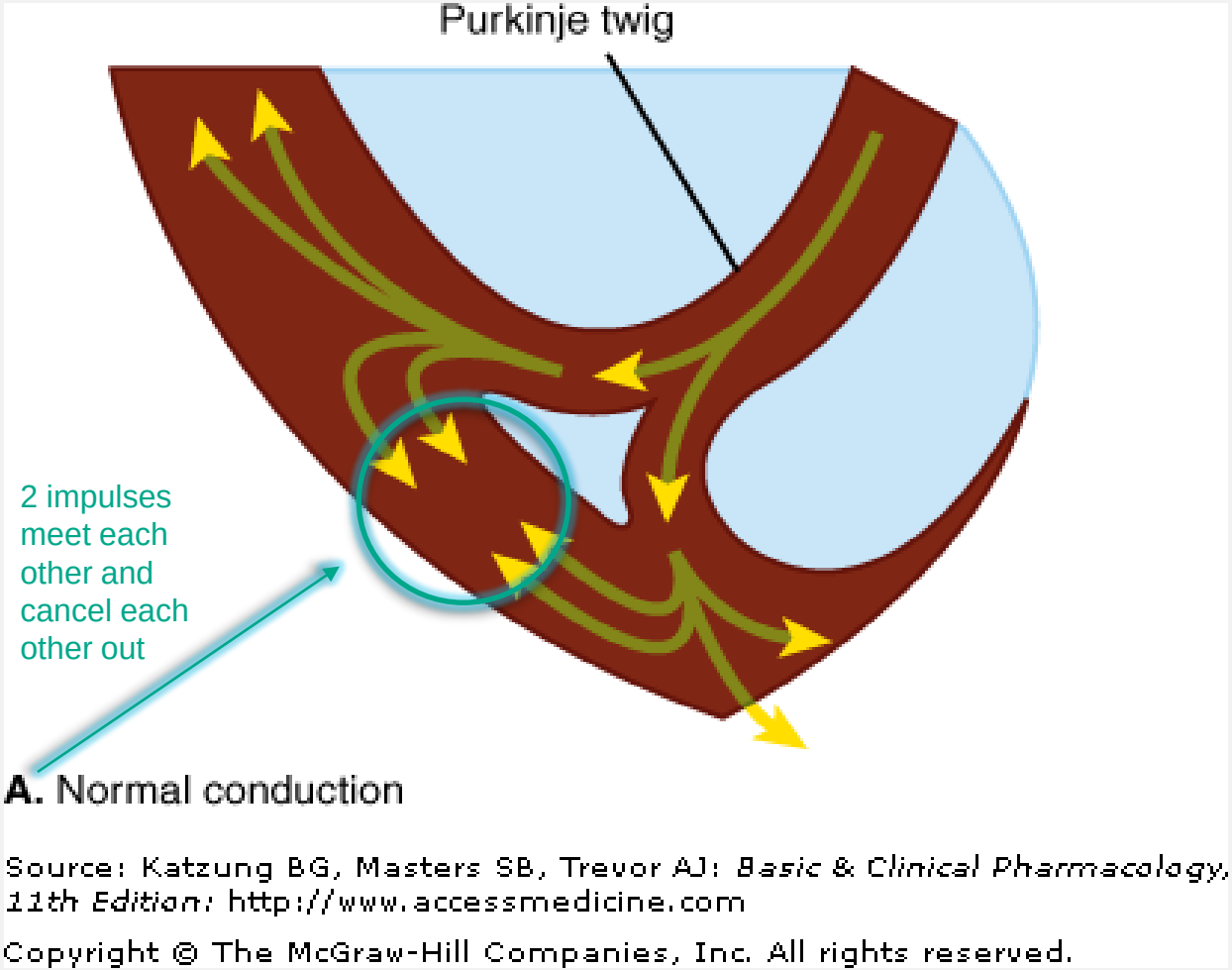
Atrial fibrillation

If you really want to understand the physiology mentioned in this file I suggest you read guyton, explains it very well

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.

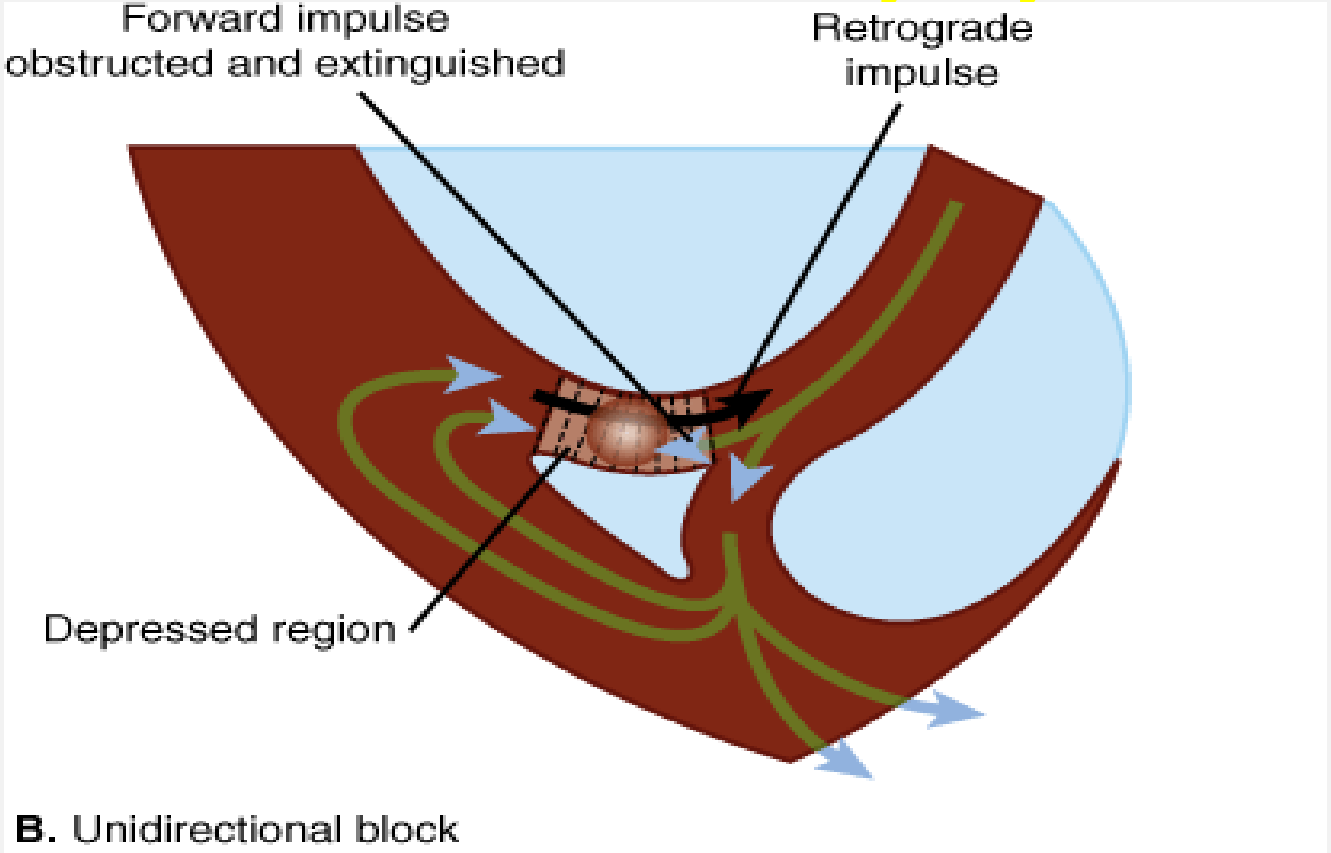
EXTRA: What happens in atrial fibrillation , is that this circus rhythm leads to a thing called “chain reaction”, in which each wave that came from the reentry will split into 2 smaller waves when it finds a patch of muscle cells that can’t be stimulated in front of it (cells that are still in the refractory period) and this will cause more splitting and more splitting the more I have cells in the refractory period , and those waves become smaller and smaller, so I have very random impulses stimulating different small patches of myocytes that are low in voltage and random in direction, and they keep on becoming smaller and increase in number, until I have reached a state where I have less cells in refractory period.



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

This is what should happen normally when I have 2 impulses meeting in one area, (for example here in the Purkinje fibers) when the 2 impulses meet in the middle, cancel each other out ,but if I have a block, resulting from any tissue injury , ischemia, hypoxia , toxicity,…..etc, I don't get this effect of cancellation , and the wave will re enter causing circus rhythm, OR if I have a stronger impulse coming from one area that's stronger than the other area ,in the end it will result in arrythmia

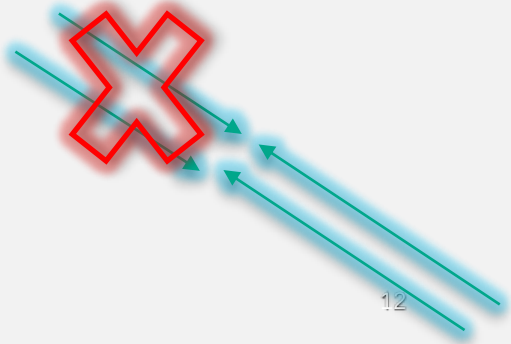
Re-entry Rhythm



B. Unidirectional block

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

Notice the direction of the arrows in both pictures, how they meet , and when this block occurs, I no longer have the opposite power for them to cancel out each other.



A small overview regarding the antiarrhythmic therapy:

- Our main focus in antiarrhythmic therapy is modifying the impulse generation and conduction, and preventing arrhythmias to occur, and reducing the symptoms (7 classes of anti arrhythmic drugs)
- But their side effects can be very serious and dangerous , such as QT prolongation (later)
- So we should always look whether the side effects outweigh the benefits of using such drugs, and this will differ from one drug to another and one case to another,since those drugs themselves can cause arrhythmia.

And now the real pharmacology starts , I know we talked a lot about pathology and physiology but as I said ,the doctor MOST PROBABLY wont ask questions about them , but he explained them as much as he can so he can explain the therapy of such problems.

Class II

- 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 channel.
  - 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.

Blocking those receptors will result in decreased cAMP , and thus in the end of this pathway we get decreased calcium release, so its like im blocking calcium channels, so the slope of the phase 0 will be decreased and conductivity will be decreased

Notes regarding the atrial anti arrhythmic therapy(class II and class IV):

In atrial fib.(mostly) ,supraventricular tachycardia, and atrial flutter (another form of atrial arrythmia where the impulse is a long continuous organized single wave going around the atria) the following is done:-

- If the ectopic foci or the circus rhythm is going through and around the AV node , we focus in our treatment on suppressing the AV node, using the following:-
- 1- non-dihydropyridine Ca+2 blockers(class IV) 2- B blockers (class II)

➢ And as u remember calcium channel blockers block the L type calcium channels that are responsible for the automaticity of the AV node, so we decrease it using those 2 drugs.

➢ This treatment is usually enough , but if its not enough we now turn to treating the myocytes themselves , but this is prophylactic most of the time because as we said the previous treatment is enough most of the time. **(Sodium and potassium channel modification)**

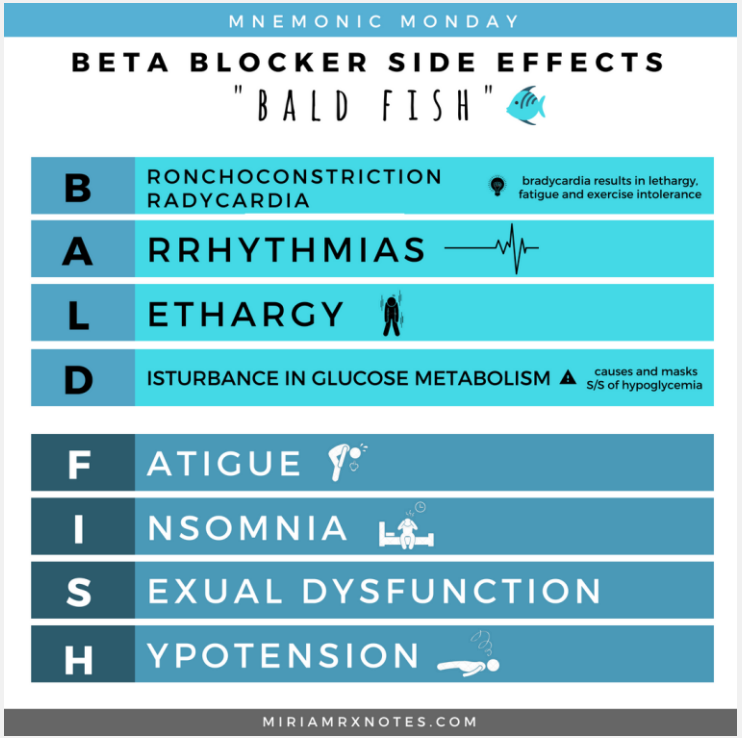
BUT in ventr. fib. We rely in our treatment on affecting the sodium current, because the ventricular depolarization is mainly due to fast firing of sodium, so we give Na+ channel blockers, and we cant give ca+2 channel blockers and b blockers in ventricular arrythmias because blocking the av node will result in increasing the impulses coming from the circus rhythm or the ectopic foci(multiple foci most of the time)

Class IIa

- Includes nonselective and selective β1 -adrenergic receptor **inhibitors** (beta blockers)
- Examples: Nonselective: **carvedilol and propranolol;** selective: **atenolol, metoprolol**
- Clinical indiction: indicated in a wide range of tachyarrhythmias (sinus tachycardia, supraventricular and ventricular tachyarrythmias) so basically atrial and av nodal arrhytmias
- Cause reduction in SA node automaticity; Reduction in AV node 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 IV

- 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

- 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

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**

When I want to treat and modify the action potential of the myocytes themselves , I use class I and class III anti arrhythmic drugs , but BE CAREFUL those drugs are also one of the most common causes for arrhythmia , they cause QT prolongation , which means I have a changed(prolonged) action potential duration and a changed refractory period , we call this "Pro arrhythmias" (what happens here is that when I prolong the QT interval I increase the probability of having a stimulus come to the cell whilst its in the relative refractory period)

Notes on the 3 subclasses of class 1

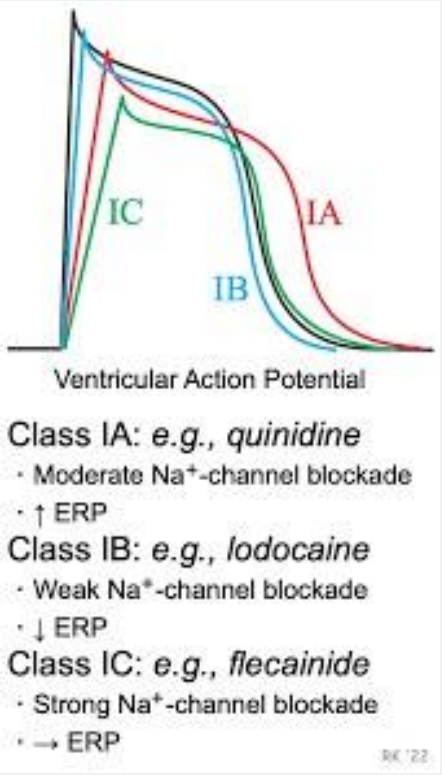
Class 1 anti arrhythmic drugs block Na+ channels ,they're subdivided into 3 subclasses:-

1-class 1a 2- class 1b 3- class 1c

Those drugs have been classified according to their effect on the duration of the action potential

And that depends on their affinity and their dissociation time constant (*time needed for the drug to dissociate from its receptor)* the more the slope will be decreased and the bigger the change of the Phase 0 (firing phase)

- **Class 1c having the highest dissociation time constant meaning it has the highest affinity , will produce the biggest effect and will make the lowest slope**
- **Class 1a has an intermediate affinity and effect**
- **Class 1b has the lowest affinity and lowest effect and change on the firing phase (highest slope).**



Class Ia

careful of qt prolongation

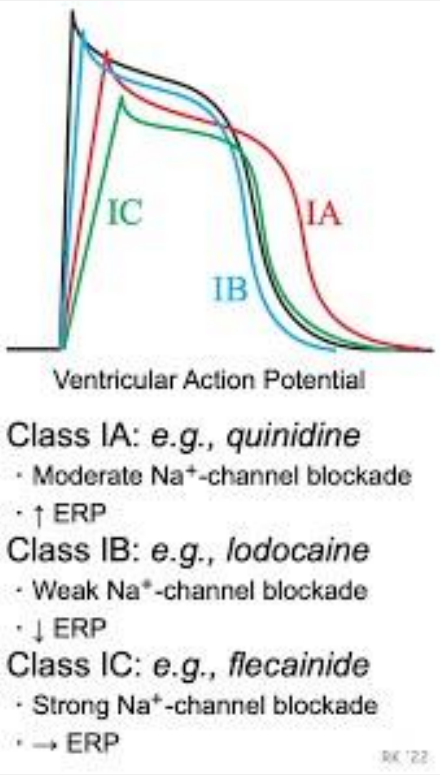
- bind to the open state of Nav1.5 with moderate dissociation time constants (τ) of ≈1 to 10 seconds (moderate block)
- reduce AP conduction velocity **(decreased myocyte node firing)**
- increase ERP**(effective refractory period)** and APD**(action potential duration)**

Why does QT prolongation increases risk of arrhythmia?

Basically when they prolong the APD ,the points of time at which the cell is in the relative refractory period increase, and so they have a higher probability of getting stimulated again, a thing called (early after depolarization) or (premature beats), those abnormal messages usually occur at the end of phase 3 (during or in the end of repolarization)

- Includes: quinidine, procainamide, disopyramide
- Clinical application: supraventricular tachyarrythmias (atrial fibrillation) and ventricular tachycardia **(except for when this ventr. Tachycardia is caused by a drug that causes QT prolongation , in such case we don't give Class 1A)**

We don't give with drugs that prolong QT interval such as ranolazine….etc



Side effects

- **Quinidine:**
  - Torsades de pointes with QT interval prolongation
  - GIT side effects: diarrhea, nausea, vomiting
  - Cinchonism: a syndrome of headache, dizziness and tinnitus(it means “hearing” a continuous ring in ur ear)
  - May increase the plasma concentration of digoxin leading to digitalis toxicity
- **Procainamide:**
  - Torsades de pointes with prolonged QT interval
  - Lupus-like syndrome: rash, small joint arthralgia, and arthritis
  - Pleuritis and pericarditis
  - Hypotension
  - Nauses, vomiting, fever, hepatitis

We don’t give quinidine to patients with QT prolongation, either due to hereditary long QT syndromes, or from other acquired reasons such as drugs

Torsades de pointes:

The doctor didn't want to explain this very much , because Torsades de pointes is truly a complex and very difficult phenomena but here is what he said:

- **We have no P wave on the ECG , what happens is like atrial fibrillation , many small waves, we have an early after depolarization and delayed after depolarization, I have the message coming from everywhere in the ventricles, it starts flipping on the ECG , some waves give a positive deflection and some give a negative deflection.**

***EXTRA*: Torsades de pointes means (twisting of points) , what happens basically is that there is a premature beat(early after depolarization, which is simply a beat that happens in the period between 2 normal beats ,it happens prematurely due to all the factors and causes we mentioned throughout the lecture) and this wave will stimulate a cell that is still in its repolarization phase , in the relative refractory period , because of the prolonged QT interval , so what would happen is that the R wave of this premature beat will be continuous and superimposed on the T wave of the already repolarizing myocyte, that is what is called the "R on T phenomena", this as you know might cause a circus rhythm, and we will have an arrythmia with many different small and enormous amount of waves but they are kind of continuous , those waves will have different deflections, some giving positive deflections some giving negative deflection, if I can maybe put it in simple terms, its like the chain reaction I mentioned before , but its much more organized and continuous.**
I can't ever explain this properly , even the book and the articles on the internet don't explain it very well , its really a mystery and a very complex phenomena.

Class Ib

Contraindicated in patients with arrhythmias that cause QT shortening, and decreased APD

- 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 **(we normalize the frequency of (we hold the rhythm properly here).**

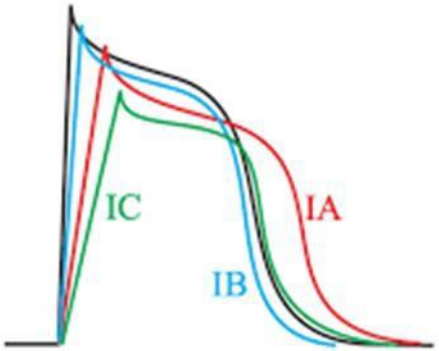
They're used in such cases where ventricular tachyarrhythmias are caused by drugs that cause QT prolongation , such as Class 1a anti arrhythmics, opioids, anti emetics (ondansetron etc..), anti fungals, anti depressants, ranolazine, etc…

As you see they don't induce a big change.

- Includes: lidocaine
- Clinical applications: Ventricular tachyarrhythmias

(ventricular tachycardia, ventricular fibrillation) **(Because early after depolarization and prolonged QT interval most commonly occur in the ventricles more than the atria)**

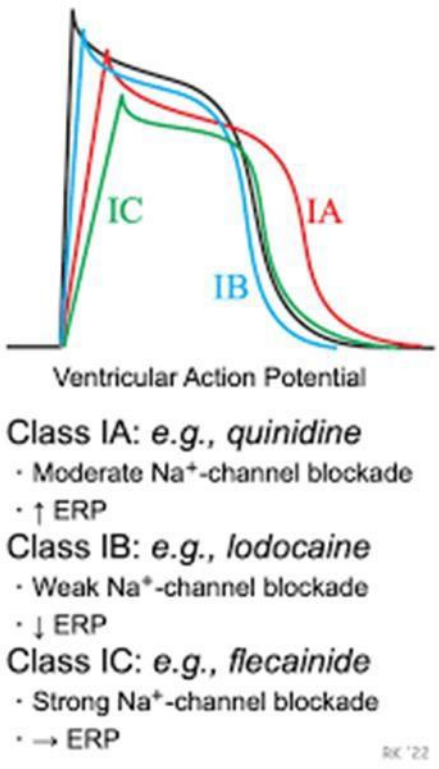
- **Side effects**: CNS effects (slurred speech, drownsiness, dizziness, muscle twitching, seizures)



Class Ic

- Also bind to the inactivated Nav1.5, from which they dissociate more slowly, over τ >10 seconds (marked block)**(we heavily decrease the slope)**
- Reduce AP conduction velocity
- Maintain normal ERP and APD
- Include: propafenone, flecainide
- Clinical applications:
  - Supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter, atrial fibrillation);

    Drug of choice in many of those cases
  - Ventricular tachyarrhythmias resistant to other treatment



Class Ic Side effects

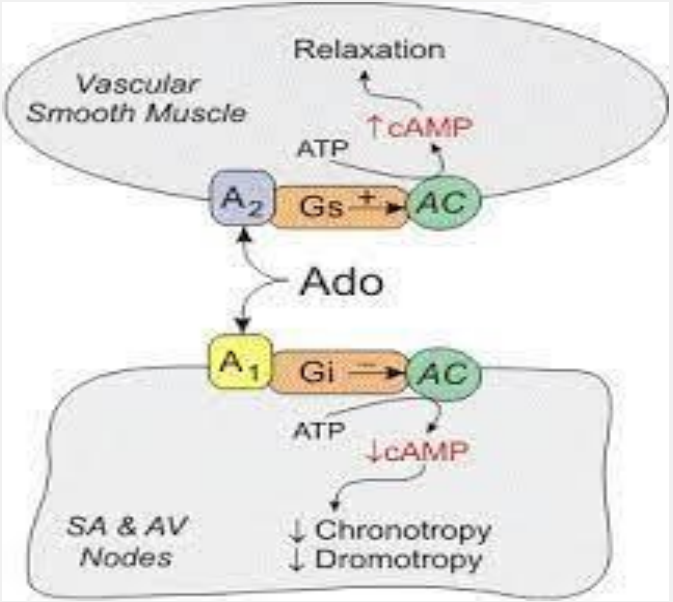
- **Flecainide:**
  - Ventricular tachycardia in presence of ischemic heart disease or old MI **(contraindication)**
  - Vision problems
  - Headache, dizziness
  - Has been shown to have teratogenic effects
- **Propafenone:** **(important)**
  - Ventricular tachycardia in presence of ischemic heart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

Class IIe (*they're not actually class II,doctor said that theyr'e called miscellaneous anti arrhythmics*)

If we lost control of the arrhythmia and it became serious , such as vent. Fib or vent.flutter, and we don't want to give DC shock , we give adenosine

- Adenosine A1 receptor activators

A1 is a GPCR(G protein coupled receptor) produces an inhibitory affect by the subunits of the G protein Alpha , beta , and gamma , the alpha and beta subunits decrease ca+2 release and the gamma subunit activates potassium channels, causing hyperpolarization (action potential is less negative than -90) which causes a negative chronotropic effect and dromotropic effect



- 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

Usually used for atrial problems, exceptionally used in VTs when its cAMP mediated

The drug suppresses the heart beating completely for almost 30 seconds, it works and finishes very fast, works in 30 seconds and finishes in 30 seconds

The doctor here focused mainly on the first side effect.

Adenosine side effects

- Sinus bradycardia, sinus arrest or AV block
- 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.

Class IId

It is written that Digoxin and Adenosine are class II drugs, but the doctor told us that they're not , they're called miscellaneous anti arrhythmic drugs

- Muscarinic M2 receptor activators (indirectly by increasing vagal stimulation)
- Examples: **digoxin**
- Digoxin has *two principal mechanisms of action*, which are selectively employed depending on the indication:

1. **Positive inotropic**: 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 **such as what happens when we have an AV nodal or atrial ectopic foci**

Dixogin increases acytelcholine release and action on M2 receptors, they are GPCR (Gi), having alpha and beta and gamma subunits, the alpha and beta decrease ca+2 release, and the gamma subunit activates potassium channels, but its not as strong of a negative effect as adenosine, they don't completely zero out the beats

Digoxin adverse effects

- Visual changes (blurring, photophobia, disturbance in vision color aka xanthopsia)
- GI toxicity: anorexia, nausea, vomiting
- Gynaecomastia, skin rashes
- Cardia adverse effects:
  - Bradycardia
  - AV block
  - Paroxysmal atrial tachycardia
  - Sino atrial arrest
  - Ventricular tachycardia

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

Ones in red are the most important

Amiodarone (oral) also has an effect of blocking sodium channels

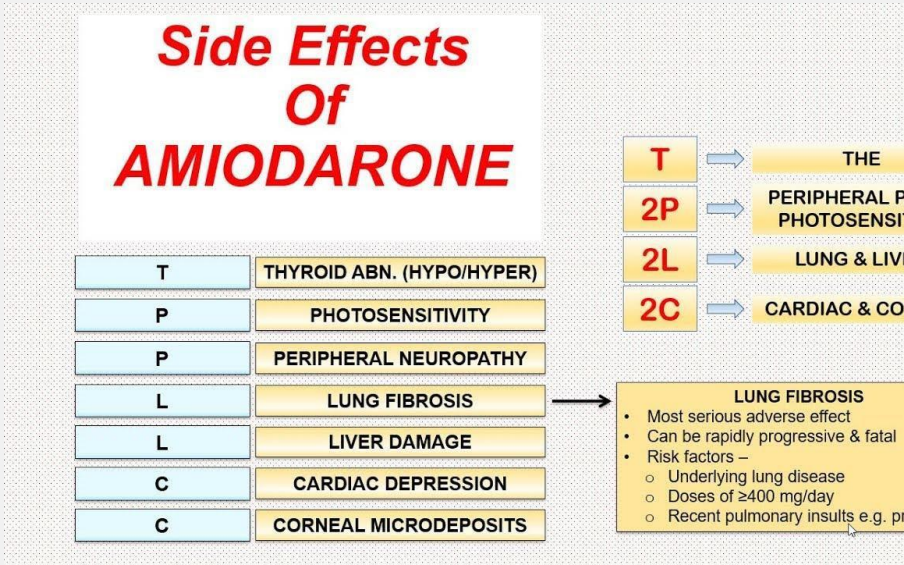
Sotalol has an effect on B1 and on K+ (inhibitory)

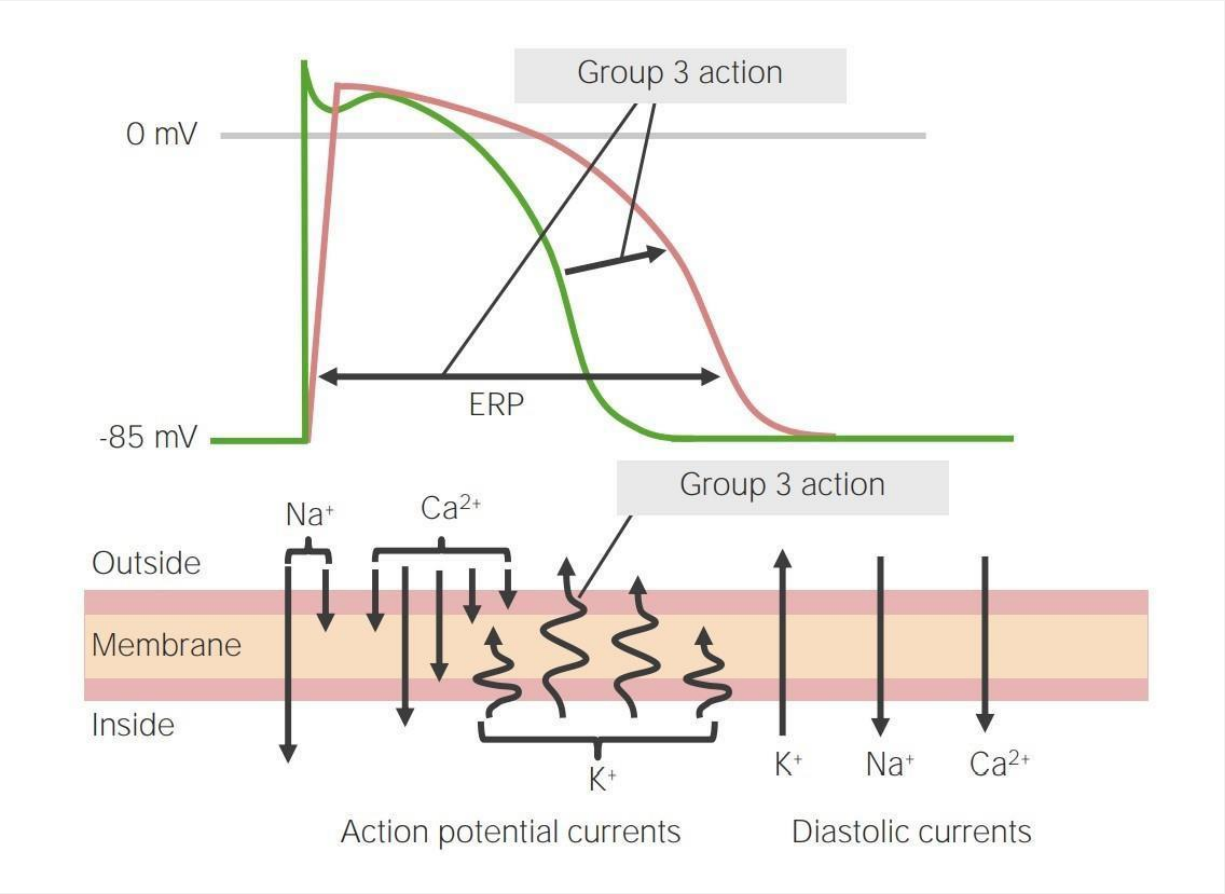
- They block multiple K+ channel targets resulting in prolonged atrial, Purkinje, and/or ventricular myocyte AP recovery, increased ERP, and reduced repolarization reserve , **decreased conductivity and velocity and QT prolongation**

- **Sotalol is a drug of choice in pediatric arrhythmias**
- **Amiodarone is mainly a drug of choice in many ventricular arrhythmias, except those that come with a prolonged QT**

Class III side effects

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





QT prolongation more than Class 1a

اللهم عليك بأعدائك أعداء الدين، اللهم رد عنا كيدهم وقلل حدهم وأزل دولتهم واذهب عن أرضك سلطانهم ولا تدع لهم سبيلاً على أحد من عبادك المؤمنين.

Thank You