Arrhythmias

- It is a simple-dysfunction caused by abnormalities in impulse formation and conduction in the myocardium. The heart is designed in such a way that allows it to generate from the SA node electrical impulses without outside signals. This automaticity comes from the leakage of cations (Na+) in phase 4 of the slow action potential. However sometimes during MI or other conditions that causes death of myocites the SA node stops functioning so an Ectopic Pacemaker (whether a ventricular or an atrial) takes over causing a variety of disorders such as AF , tachycardia.. etc. It could also be caused by an AV block causing the atria and ventricles to beat separately.

- However, in clinic it present as a complex family of disorders that show variety of symptoms, for example, cardiac arrhythmias may cause the heart to:

1. beat too slowly (sinus bradycardia). Like in heart block

2. beat too rapidly (sinus or ventricular tachycardia, atrial or ventricular premature depolarization, atrial flutter).

3. respond to impulses originating from sites other than the SA node. (Ectopic Pacemaker like in MI)

Clinical Definitions

1) Tachycardia : It's a paroxysmal increase in heart rate between 150-250.
2) Flutter : It is a regular increase in heart rate between 250-350.
3) Fibrillation : It is a random (neither paroxysmal nor regular) increase in heart rate above 350, causing no pattern at all on ECG.

Causes of Arrhythmias (2 types)

- **Type 1 Abnormal automaticity :**

Normally the SA node sets the pace of contraction for the myocardium, and underlying pacemakers are depolarized by impulses coming from the SA node.

Now Abnormal Automaticity itself could be caused by two ways :

1) if other cardiac sites show enhanced automaticity (In other words starts to form a slope in phase 4 of the action potential caused by leakage of cations), they may generate competing stimuli, and arrhythmia may occur.

2) Abnormal automaticity may also occur if myocardial cells are damaged, as in the case of MI, in which the damaged cells may stay depolarized during diastolic period (the relaxation period) and reach firing threshold earlier than normal cells. The idea is that these cells remain depolarized (activity zone) and don't reach phase 4 (relaxation zone) of the action potential, this makes it much easier for them to reach the threshold and fire an action potential since they don't get repolarized in the first place.

- **Type 2 Abnormalities in impulse conduction :**

Impulses from pacemaker centers normally conducted divide to activate the entire ventricular surface.

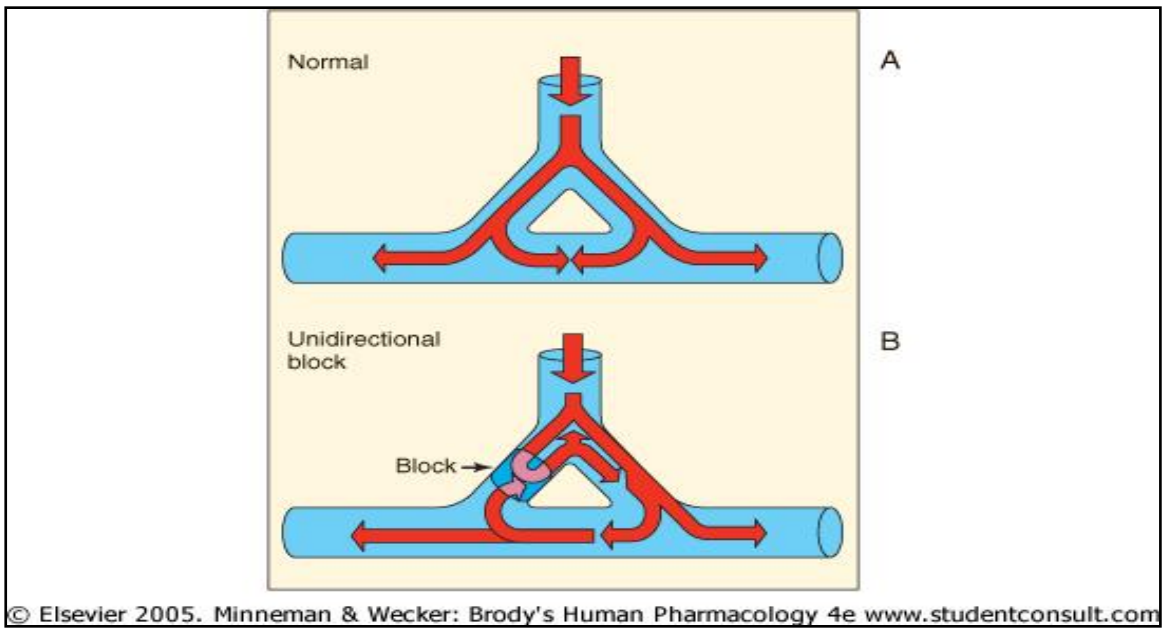
Now if unidirectional block happened, which may be caused by myocardial injury or a prolonged refractory period, this will results in an abnormal conduction pathway, this phenomena called Reentry, Reentry Ventricular Arrhythmia, or Circus Movement.

Reentry is the most common cause of arrhythmia and can occur at any level of the cardiac conduction system.

Now to make this more clear look at the following diagram and read its notes.

General notes about arrhythmia's causes :

1) MI (and also angina) increases susceptibly to arrhythmia 80%
2) Digoxin increases susceptibility up to 25% : It increases Ca inside cells (nodes and other cells) so automaticity increases. so any change or Overload in digoxin concentration may lead to arrhythmia.



In the diagram :

a) Normally (figure A in the diagram) the two impulses after dividing to supply both ventricles converge and meet at the center, thus causing the end of the impulse. In this way the impulse spreads and terminates and the heart beats. It is important to understand that normally the conductivity in the ventricles is faster and depends on Na influx (the depolarization of the normal myocite action potential is caused by Na influx), while SA o AV node depolarization depends mainly on Ca influx.

b) Unidirectional flow (figure B) : When there is an MI for example, and this MI causes weakness or block of conductivity on one side this causes unidirectional flow of impulse. The impulse now can only pass through the normal side. After the impulse passes it will start spreading and converging like its suppose to ; however, there won't be an opposing impulse to end it at the middle and thus will continue spreading and loops back to pass through the blocked side (Reentry) and activate the myocites there which are in the resting state (as you can see in the diagram) this is also called Circus Movement. This results in rapid, arrhythmic, and weak ventricular heart beats, putting also in mind that the SA node is also causing the atria to beat. According to the doctor this is common in Ventricular Tachycardia.

Arrhythmia Consequences

1) Reduces perfusion : could be so severe that it causes collapse of vessels (thus no perfusion) due to severe hypotension , no blood for the heart to pump.

2) Clotting abnormalities in the heart : which is why we give a patient with Atrial Fibrillation Heparin (anticoagulant) .

Remember Na channels undergo three configurations:
1)Active : in phase 0 and half 1
2) Inactive : irresponsive to any stimulus, phase 2 and 3
3) Resting : closed but responcive, phase 4.

Antiarrythmic Drugs

Remember we said that there were two causes of arrhythmia, abnormal automaticity and abnormal conductivity , so now we we'll go through the mechanism of actions and possible ways of these drugs to treat arrhythmia of these two causes.

Effect of drugs on automaticity : There are three ways to deal with abnormal automaticity

1) Reducing the slope

2) Increasing the action potential threshold (making it less negative)

3) Reducing the Resting Membrane Potential (hyperpolarization)

So the idea is to prolong phase 4 of the slow action potential. How? By blocking the activators which are Na and Ca. Examples :

a) Sinus tachycardia : here I'm working on the SA or AV node thus I should use Ca blockers, these will reduce the number of available Ca channels at the upstroke, this will cause reduction of the slope and increase with the threshold.
b) Ectopic pacemaker (myocites) : here I'm working on myocite action potential so I either work on Na or K, but mostly Na. So a Na blocker will also increase the threshold and decrease the slope.

Most of the arrhythmic agents suppress automaticity by blocking either sodium or calcium channels to reduce the ratio of these ions to potassium,

thus result in a reduction in the depolarization and raises the threshold of discharge to a less negative voltage.

Effect of drugs on conduction abnormalities : Conduction depends on 2 things :

1) Na channels.

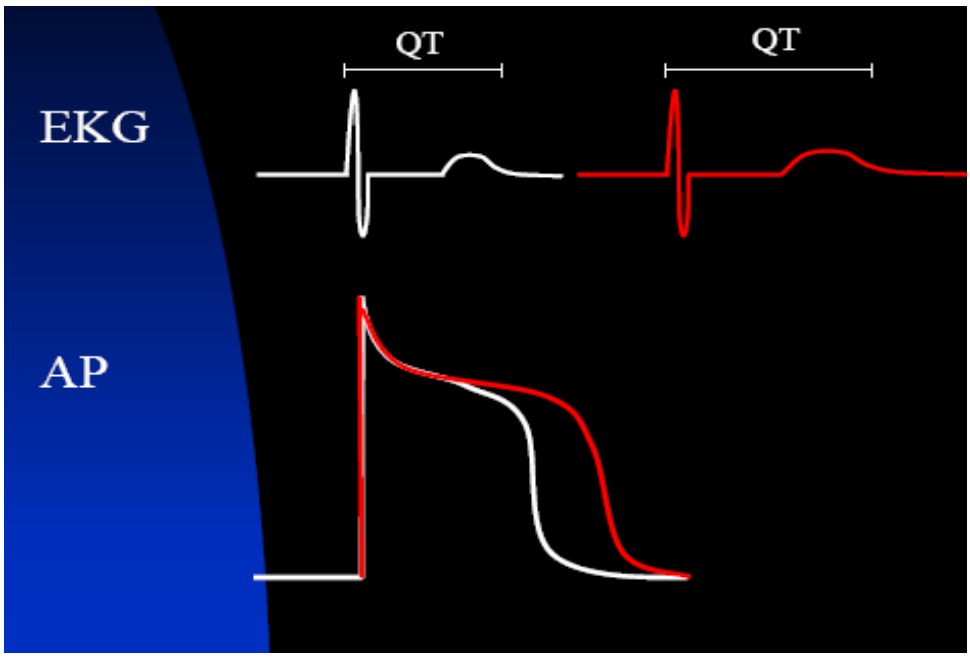
2) refractory period : which is Na channel dependant.

In arrhythmia phase 4 duration is reduced, so my aim is to increase the duration of Na channel inactive state, as it doesn't gets activated. In other words delay reaching to the RMP (phase 4) so the resting form doesn't take over. There are 2 ways to do that :

1) Na blockers : which decreases the number of available resting Na channels and thus lengthens the refractory perios.

2) K blockers : which prolongs phase 2 and 3 (and thus delays phase 4)

This decrease conductivity and prevents reentry by slowing conduction and/or increasing the refractory period.



Now we'll talk about classes and types of drugs: please note that your don't have to know all the drugs in the classes ; just the ones he explained about .

Class I

IA

lengthen AP duration

Intermediate interaction with Na+ channels

Quinidine, Procainamide, Disopyramide

We'll explain about Quinidine :

Quinidine

- It is the first antiarrhythmic drug (oldest)
- Highly toxic yet it's still used. Why? Because it works on both Na and K channels (dual effect)

- 1st effect : It binds to sodium channels and prevent sodium influx, and so slows the rapid depolarization (increases refractory period). Thus can be used in arrhythmia caused by increase automaticity.
- 2nd effect : through K channels, slows repolarization & lengthens AP duration .

→ due to K+ channel blockade with reduction of repolarizing outward current → reduce maximum reentry frequency → slows tachycardia.

Thus can be used in arrhythmia caused by Reentry; when the impulse loops to activate the myocites they will be in refractory state (since the drug lengthened the action potential).

- Thus It Inhibit arrhythmias, which caused by increased automaticity, and also prevent reentry arrhythmias by producing bidirectional block.
- **Therapeutic Uses: according to the doctor it is in all kinds of arrhythmia, mainly :**

1)Atrial flutter & fibrillation

2)Ventricular tachycardia

3) Reentry Ventricular Tachycardia

- **Toxicity : It is nonselective; therefore , many side effects. It's a Na Blocker, K Blocker, and also a Muscarinic Blocker.**

1)Antimuscarinic actions → inh. vagal effects

2)Quinidine syncope (lightheadedness, fainting)

3)Depress contractility & ↓ BP

4)Diarrhea, nausea, vomiting

5)Cinchonism (Headache, dizziness, tinnitus)

IB

shorten AP duration

rapid interaction with Na+ channels

Lidocaine, Mexiletene, Tocainide, Phenytoin

We'll explain about Lidocaine and Mexiletene.

Lidocaine and Mexiletine

- Route : Lidocaine : large first pass effect so not oral, given IV (like nitroglycerine)
  : Mexiletine : given oral (called Oral Lidocaine)
- Selective Na blocker : in nerves (local anesthetic) and in heart (antiarrhythmic).
- local anesthetic that decrease the duration of action potential, unlike quinidine, it suppresses arrhythmia caused by abnormal automaticity like an ectopic pacemaker. (quinidine used to treat arrhythmia caused by increased automaticity).
- It decreases the duration of the action potential
- Uses : Drug of choice in treatment of ventricular arrhythmia arising during myocardial ischemia (experience during myocardial infarction), has little effect on the atrial arrhythmias. If need to be given for a longer period switch to Mexiletine.

✓ *Always remember ALL antiarrhythmic drugs cause Arrhythmia*

✓ *Quinidine causes Cinochonism, while Digoxin causes Xanthopsia.*

- Side Effects :
    1) Hypotension : when given IV
    2) Cardiac arrhythmia may occur
    3) Main side effects are on the CNS, including confusion and convulsions.

- Mexiletine, oral drug, has similar action to Lidocaine and is used for chronic treatments of ventricular arrhythmias with previous myocardial infarction

Class II

- Reduce or block sympathetic nervous system stimulation

β-adrenergic blocking agents :

- B1 receptor : normally increases cAMP, which in turn opens Ca channels and Na channel (both of which effect automaticity) .
- Thus blocking it Depress automaticity and decrease heart rate and contractibility.
- 3 B blockers can be used : propranolol, Esmolol, Satalol. (not atenalol).

Propranolol **:**

- Propranolol being the most widely used. Why? because besides it's B blocker activity it has a membrane stabilizing activity through it's Na stabilizing activity.
- Useful in treating tachyarrhythmias caused by increased sympathetic activity

Esmolol

- *Has membrane stabilizing activity*
- Short acting hence used :
    1) primarily for intra-operative Arrhythmia & other acute arrhythmias.
    2) intra-operative Hypertension.

Sotalol

- Has membrane stabilizing activity as well as a K blocking activity.
- Less side effects than the others therefore : Drug of choice supraventricular (AF or Atrial Flutter) & ventricular arrhythmia in pediatric age group.

Class III

- Prolong repolarization in phase 3

Amiodarone

- **Combines all the effects previously mentioned**
- **Broad spectrum of action on the :**
  1) **Na+ channel blocker : very effective**
  2) **K+ channel blocker : markedly lengthen action potential through them**
  3) **Ca+2 channel blocker : weak**
  4) **Noncompetitive inhibitor of B adrenoreceptors**

- Uses : **it's a powerful inhibitor of abnormal automaticity. (according to the doctor can work on all arrhythmias)**
  - **Approved only in serious Supraventricular & Ventricular arrhythmias due to its side effects**
- **Adverse effect: fatal pulmonary fibrosis**

Adenosine

- **IV Adenosine is the drug of choice for stopping acute superventricular arrhythmia.**

Class IV

Calcium channel blockers

- **Varapamil and dialtiazem :** They slow conduction and prolong the refractory periods.