!! JAY AMBE !!

2. ANTI ARRHYTHMIC DRUGS

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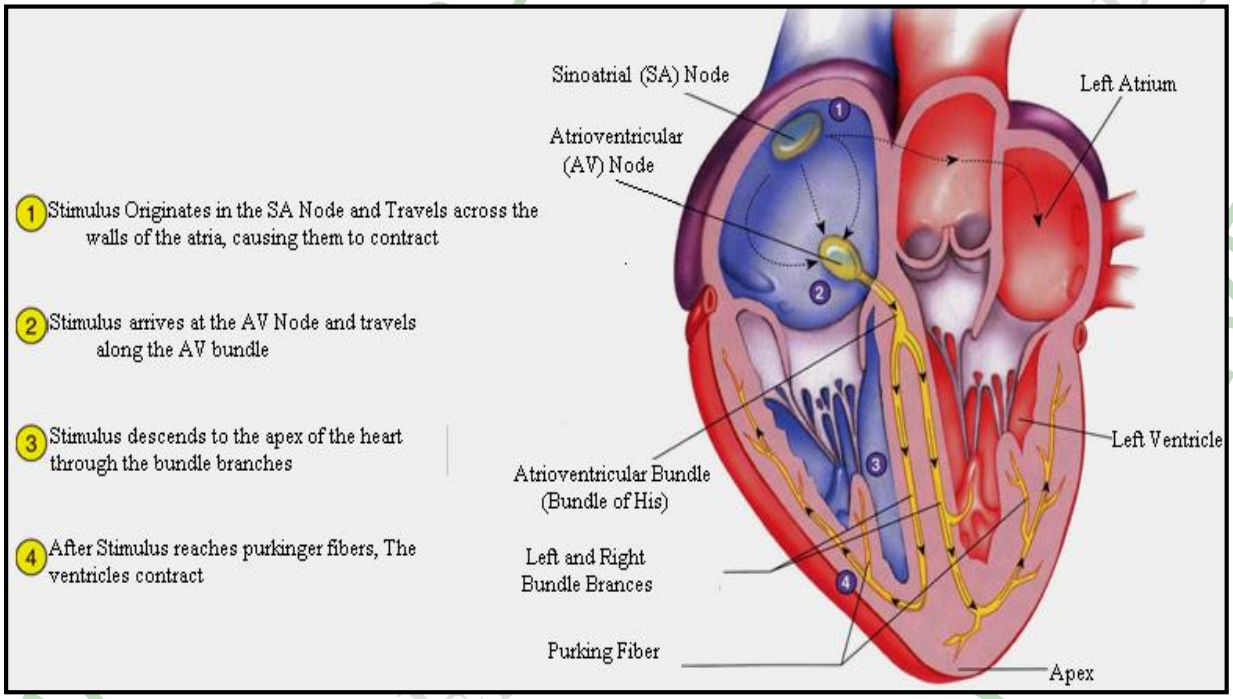
ARRHYTHMIA

Introduction:

An arrhythmia is an irregular heartbeat - the heart may beat too fast (tachycardia), too slowly (bradycardia), too early (premature contraction) or too irregularly (fibrillation). Arrhythmias are heart-rhythm problems - they occur when the electrical impulses to the heart that coordinate heartbeats are not working properly, making the heart beat too fast/slow or inconsistently.

Heart conduction system:

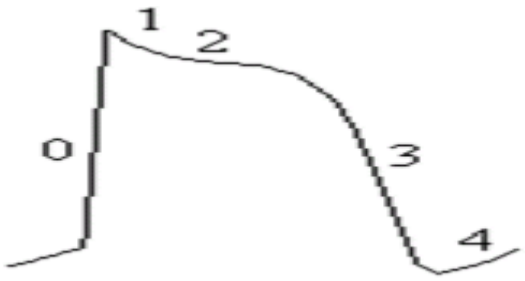


- The Sinoatrial node (SAN), located within the wall of the right atrium (RA) just inferior to the opening of the superior vena cava, normally generates electrical impulses (Action Potential) that are carried by special conducting tissue of both atria to the atrioventricular node (AVN).
- Upon reaching the AVN, located between the atria and ventricles, the electrical impulse is relayed down conducting tissue (Bundle of HIS) that branches into pathways that supply the right and left ventricles. These paths are called the right bundle branch (RBBB) and left bundle branch (LBBB) respectively that course through the interventricular septum towards the apex of the heart. The left bundle branch further divides into two sub branches (called fascicles).
- Finally, large diameter conduction myofibers (Purkinje Fibers) passes electrical current to the apex of the ventricular myocardium and then upward to the remainder of the ventricular myocardium.

2. ANTI ARRHYTHMIC DRUGS

SA-node➔ AV-node➔ AV bundle➔ Right & Left Bundle braches➔ Purkinje fibers

Action potential:



Phase 0: Rapid Depolarization	Rapid entry of Na^+	
Phase 1: Rapid Repolarization	Exit of K^+	
Phase 2: Slow Repolarization	Slow entry of Ca^+	
Phase 3: Rapid Repolarization	Exit of K^+	
Phase 4: Resting Phase or Platue Phase	Return to initial state	K^+ Na^+, Ca^+

Classification of arrhythmias:

Arrhythmias are classified according to two factors:

- Where they originate - the atria or ventricles.
- The heart rate - fast (tachycardia - over 100 beats per minute), slow (bradycardia - less than 60 beats per minute).

A. Tachycardia in the atria:

a. **Atrial fibrillation:** It is a rapid, continuous, chaotic and irregular beating in the localized area of atria.

b. **Atrial Flutter**: It is a rapid irregular atrial pulsation (180-300 beats/min.) where in ventricle fails to follow atria.

c. **Supraventricular tachycardia (SVT):** A regular, abnormally rapid heartbeat caused by rapid firing of electrical impulses from a focus above the atrioventricular node (in the heart). It is called SVT because the rapid heartbeat originates above the ventricles of the heart. The patient experiences a burst of accelerated heartbeats that can last from a few seconds to some hours.

d. **Wolff-Parkinson-White (WPW) syndrome:** There is an extra electrical connection inside the heart that acts as a short circuit, resulting in an abnormally fast heart beat (sometimes irregular). This syndrome can be life-threatening, although it is unusual.

B. Tachycardia in the ventricles:

a. **Ventricular tachycardia:** Abnormal electrical impulses that start in the ventricles cause abnormally fast heart beating. Typically, the heart will have a scar from a previous heart attack, which forces the electrical signal to travel around it. Usually, the ventricle will contract more than 200 times a minute.

b. **Ventricular fibrillation:** It is a rapid, continuous, chaotic and irregular beating of ventricles. The ventricles do not pump blood properly (they quiver uselessly instead). Blood pressure drops dramatically, depriving vital organs, including the brain, of their essential blood supply. The majority of patients loses consciousness fairly quickly and requires emergency medical assistance, including CPR (cardiopulmonary resuscitation).

C. Bradycardia (heart beats abnormally slowly):

– A slow heartbeat (under 60 beats per minute) does not necessarily mean there is a problem.

a. **Sick sinus**: A problem with the sinus node of the heart. The sinus node is the heart's natural pacemaker. If it does not function properly the patient's resting heart rate may be abnormally low (bradycardia). If the sinus node functions properly, sick sinus may be caused by scarring near the sinus node which undermines the movement of electrical impulses.

b. **Conduction block**: A block of the electrical pathways of the heart. This can occur in or close to the atrioventricular node, located on the pathway between the atria and the ventricles. The block may be along the other pathways to each ventricle. The electrical impulses between the upper and lower halves of the heart may be slowed or blocked; this depends on the type of block and where it is. If the signal is totally blocked, some cells in the atrioventricular node or ventricles can make a steady but slower heartbeat. The patient may experience skipped heartbeats or bradycardia - sometimes there are no symptoms at all.

c. **Premature heartbeats**: This occurs in the ventricles and comes before the ventricles have had time to fill with blood after a regular heartbeat. A premature heartbeat occurs between two normal heartbeats. However, the patient will feel he/she has skipped a heartbeat. In most cases the occasional premature beat is nothing to worry about.

However, it can trigger a longer-lasting arrhythmia - this is especially the case if the patient has heart disease.

CLASSIFICATION OF ANTI ARRHYTHMIC DRUGS:

Group I: Drug which blocks voltage sensitive sodium channels and thus reduces excitability of non-odal region of heart.

a. **Class Ia**

Class Ia antiarrythmics, in addition to their effect on the voltage-gated sodium channels, slow repolarization by inhibiting potassium efflux. They are quinidine, hydroquinidine, disopyramide.

b. **Class Ib**

The drugs of the Ib class, in addition to their effect on the sodium voltage-gated channels, accelerate cellular repolarization by increasing potassium efflux, and decrease the duration of the action potential and the refractory period. They are lidocaine, phenytoin and mexiletine.

c. **Class Ic**

Class Ic antiarrythmics inhibit the voltage-dependant sodium channels and prolong the depolarisation phase, have little effect on the repolarization phase. They are flecainide, propafenone and aprindine.

Group II: Drug acting inhibiting of sympathetic nerve (β-Blocker).

Eg: Propranolol, Practolol, Sotolol, Bretlylium, Esmolol etc.

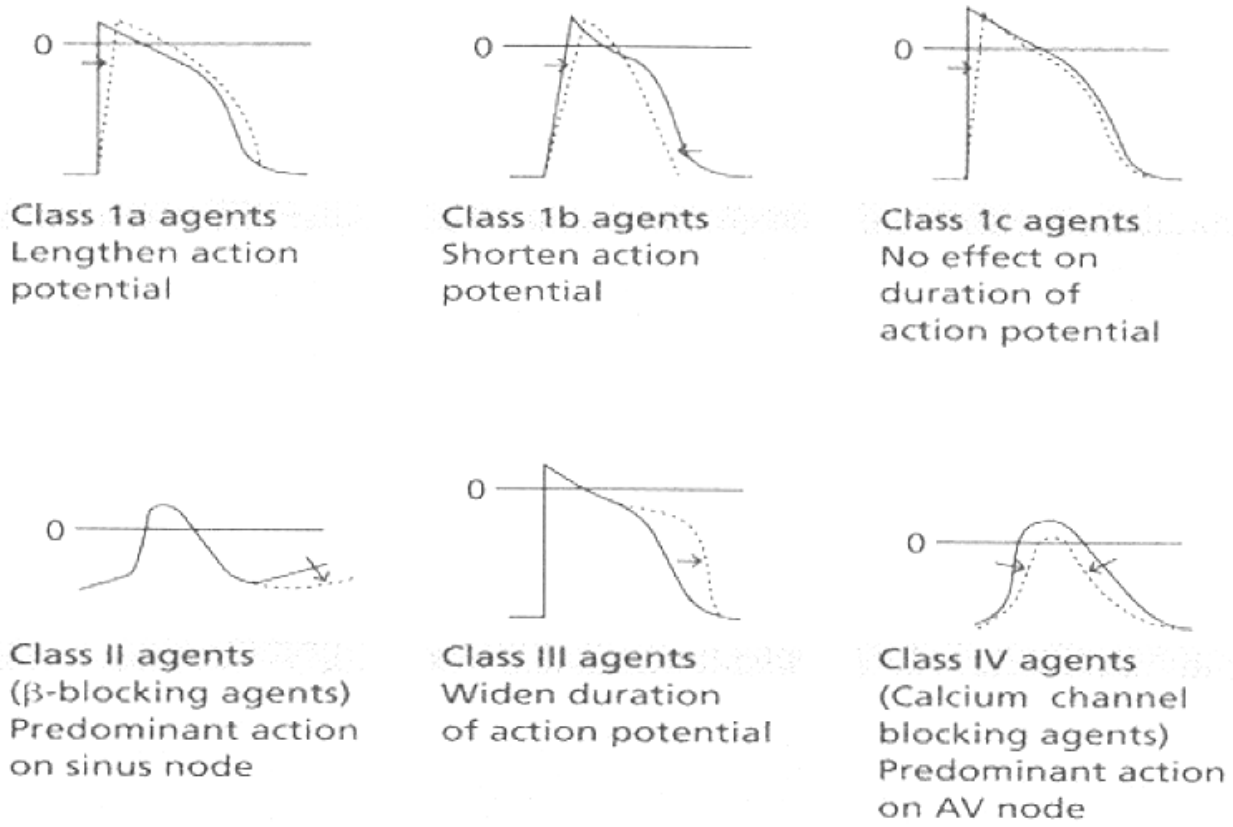
Group III: Potassium Channel Blockers.

Drug that prolong action potential and repolarization.

Eg.: Sotololo, Dofetilide

Class IV: Calcium channel blockers.

Eg.: verapamil, Nifedipine, Diltiazem etc



Class Ia antiarrythmics:

A. Quinidine:

- It is a stereoisomer of quinine, originally derived from the bark of the cinchona tree.
- The drug causes increased action potential duration, as well as a prolonged QT interval.
- Moderate reduction in phase 0 slope and increase ERP.

Mechanism of Action:

- Quinidine primarily works by blocking the fast inward sodium current (I_{Na}). Quinidine's effect on I_{Na} is known as a 'use dependent block'.
- This means at higher heart rates, the block increases, while at lower heart rates, the block decreases. The effect of blocking the fast inward sodium current causes moderate reduction in phase 0 slope.

Side Effects:

Cardiac:

- Bradycardia, Ventricular tachycardia, Ventricular fibrillation, Hypotension etc.

Extra Cardiac:

- Skin rashes, Fever, cinchonism (blurred vision, tinnitus, headache, psychosis); cramping and nausea.

Combination with other drugs:

- Quinidine is also an inhibitor of the cytochrome P450 enzyme 2D6, and can lead to increased blood levels of lidocaine, beta blockers, opioids, and some antidepressants.
- Quinidine also inhibits the transport protein P-glycoprotein and so can cause some peripherally acting drugs such as loperamide to have central nervous system side effects, such as respiratory depression, if the two drugs are coadministered.

Use:

- Atrial fibrillation, Atrial flutter, Paroxysmal tachycardia, Ventricular fibrillation, Malaria.

B. Procainamide:

- It is safer than quinidine for IV use.

Mechanism of action:

- It is a sodium channel blocker which blocks open sodium channels and prolongs the cardiac action potential (outward potassium (K+) currents may be blocked).
- This results in slowed conduction, and ultimately the decreased rate of rise of the action potential, which may result in widening of QRS on electrocardiogram.

Side effects and use is similar to quinidine.

C. Disopyramide:

Mechanism of action:

- Disopyramide's Class 1a activity is similar to that of Quinidine in that it targets sodium channels to inhibit conduction.
- Disopyramide depresses the increase in sodium permeability of the cardiac Myocyte during Phase 0 of the cardiac action potential, in turn decreasing the inward sodium current. This results in an increased threshold for excitation and a decreased upstroke velocity
- Disopyramide prolongs the PR interval by lengthening both the QRS and P wave duration and it slows the action potential propagation through the atria to the ventricles.

Side effects:

Cardiac:

- Acute heart failure
- Severe hypotension

Extracardiac effects

- Dry mouth, Constipation, Urinary retention, Blurred vision, Glaucoma, Rash Agranulocytosis, Additionally, disopyramide may enhance the hypoglycaemic effect of gliclazide, insulin, and metformin

Class Ib antiarrythmics:

A. Lignocaine:

It is a common local anesthetic and antiarrhythmic drug. Lidocaine is used topically to relieve itching, burning and pain from skin inflammations, injected as a dental anesthetic or as a local anesthetic for minor surgery.

Mechanism of action:

- It act mainly by inhibiting sodium influx through sodium-specificion channels in the neuronal cell membrane, in particular the so-called voltage-gated sodium channels. When the influx of sodium is interrupted, an action potential cannot arise and signal conduction is inhibited.
- Depress the automaticity in ventricular tissue. No action on SA node, AV node or Atria.

Side effects:

- Nerve damage, neurotoxicity due to allergenic reaction, excessive fluid pressure in a confined space, severing of nerve fibers or support tissue with the needle/catheter, convulsion, confusion, numbness or tingling of lips or tongue.

Use:

- Ventricular arrhythmias in myocardial infarction.

B. Phenytoin:

- Phenytoin is believed to protect against seizures by use- and voltage-dependent block of voltage-gated sodium channels.
- Phenytoin has low affinity for resting sodium channels at hyperpolarized membrane potentials.
- Use:
- Digitalis induces arrhythmias because it does not increase AV block, Supravaetricular and ventricular tachycardia, Epilepsy.

Class Ic antiarrythmics:

A. Flecainide acetate:

- It is a class Ic antiarrhythmic agent used to prevent and treat tachyarrhythmias (abnormal fast rhythms of the heart).
- It is used to treat a variety of cardiac arrhythmias including paroxysmal atrial fibrillation (episodic irregular heartbeat originating in the upper chamber of the heart), paroxysmal supraventricular tachycardia (episodic rapid but regular heartbeat originating in the atrium), andventricular tachycardia (rapid rhythms of the lower chambers of the heart).

Mechanism of Action:

- It blocking the sodium channel in the heart, causing prolongation of the cardiac action potential.
- This thereby slows conduction of the electrical impulse within the heart. The greatest effect is on the His-Purkinje system and ventricular myocardium. The effect of flecainide on the ventricular myocardium causes decreased contractility of the muscle, which leads to a decrease in the ejection fraction.

Use:

- Flecainide is used in the treatment of many types of supraventricular tachycardias, including AV nodal re-entrant tachycardia (AVNRT) and Wolff-Parkinson-White syndrome (WPW). This is because of the action of flecainide on the His-Purkinje system.