Cardiac dysrhythmias

By
Dr. Muhammad Zahid

In my previous lectures,we have learnt/Discussed in details

- Definition of Dys/Arrhythemias & their types
- Mechanism of arrhytemias
- Different phases of myocardial actional Potential
- Classification of Anti arrhythemic drugs

Phases of Myocardial Action Potential

Phase 0

Depolarization;(Inflow Of Na+)

Phase 1

Early Repolarization; **(rapid outflow of K+)**

Phase 2

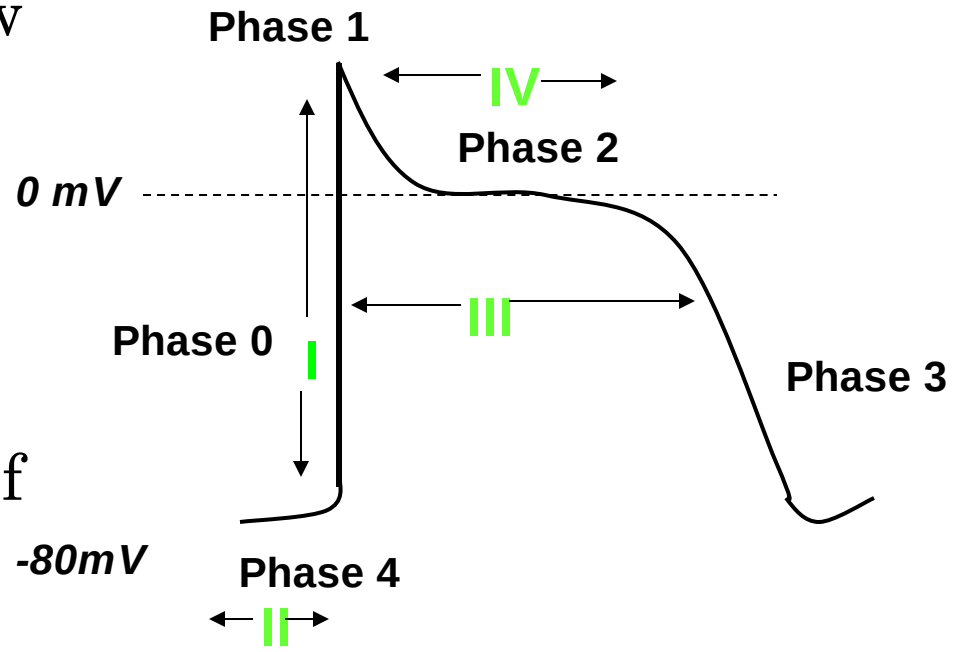
Plateu phase;(Inflow of **Ca++)**

Phase 3

Rapid Repolarization;(K+ outflow)

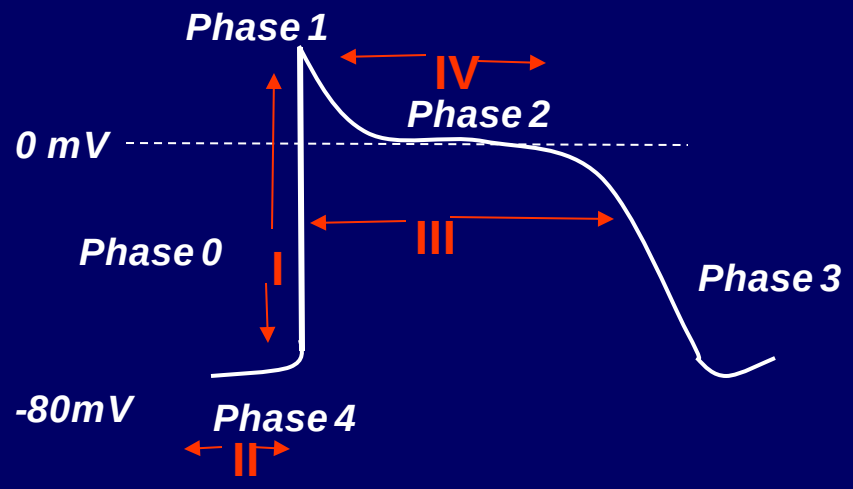
Phase 4 (automaticity):

(Na+ outflow,K+ inflow,Ca++ outflow)



Vaughan Williams classification of anti-arrhythmic drugs

- **Class I**: block sodium channels
  - Ia (quinidine,) ↑AP
  - Ib (lignocaine) ↓AP
  - Ic (flecainide) ↔AP
- **Class II**: ß-adrenoceptor antagonists (atenolol, sotalol)
- **Class III**: prolong action potential and prolong refractory period (suppress re-entrant rhythms) (amiodarone, sotalol)
- **Class IV**: Calcium channel antagonists. Impair impulse propagation in nodal and damaged areas (verapamil)



Let us briefly revise the CLASS 1 anti arrhythemic drugs & their sub classifications.

Then we will discuss in detail

Class 11

Class 111

Class 1V

& miscellaneous group

REVISION

Classification of Drugs & Mode of Action

Therapeutically useful channel blocking drugs have a **high affinity for activated channels** (i.e. during phase 0) or inactivated channels i.e. during phase 2, but low affinity for rested channels.

Class 1 Na+ Channel Blockade.

These drugs **restrict the rapid inflow** of sodium during phase **“ 0 ”** .

& thus slow the maximum rate of depolarization.

Another term for this property is **membrane stabilizing activity ”,** because they have local anesthetic effect as well.

. Class 1(Na+ Channel Blockers) ARE

Sub divided Class 1A,1B & 1C

Due to the reasons-----they differ from kinetic properties although the basic mechanism is the same(Na+ channel blocked)

SO

Sub classification reflects on APD(action potential Duration) & kinetics of Na+ channel

Class 1 A.

e.g Quinidine, procainamide, disopyramide

- They block the Na+ channel.
- These drugs **lengthen action potential** duration(APD), refractoriness & dissociate from the channel with intermediate kinetics

USES.. Effective for supra ventricular & ventricular dysrhythmias.

Class 1 B.

e.g. lignocaine, mexiletine, phenytoin etc.

- They block the Na+ channel.
- The drugs **shorten action potential** duration and refractoriness & dissociate from the channel with rapid kinetics-

How Antiarrhythmic Effect is produced(As APD dec.)

- Though APD decreased but this increases diastole & Extends the time for recovery

USES Effective only in ventricular dys-rhythmias.

Class 1 C.

e.g. Flecainide, Propafenone,

- They act by **blocking the Na+ channel**
- They have negligible effect or no effect on action potential and refractoriness & dissociate from the channel with slow kinetics

USES -Effective for supra ventricular and ventricular dysrhythmias

Class ll.

e.g Sympatholytic especially, β-blockers,

Drugs include those that **reduce adrenergic activity in the heart**,

i.e. they **reduce** the **sympathetic tone** in the heart, reduce automatic discharge (phase 4) and protect against adrenergically stimulated ectopic pacemaker.

Class lll.

_ e.g. Amiodarone, Bretylium

_Drugs that **prolong effective refractory period** by prolonging action potential (no effect on sodium inflow in phase 0).

Prolongation of cellular refractoriness (phase 1, 2, & 3) **beyond a critical** point may prevent a reentry circuit being completed.

They may thereby abolish a re-entrant tachycardia.

Class IV Ca++ Channel Blockade.

e.g verapamil & others

These drugs **depress** the slow **inward calcium current** (phase 2) and slow conduction and **increase refractoriness** in **SA node** and AV node _____ which may explain their effectiveness in **terminating paroxysmal supra – ventricular** tachycardia

Class V (Miscellaneous):

Adenosine

Magnesium sulphate

Digoxin

Ranolazine

Atropine

2. Catheter Ablation:

3. Implantable Cardioversion Defibrillator (ICD):

To day we will start with Class ll (Catecholamine Blockers)

- Blockers are effective because they **counteract** the dysrrythmic effect of catecholamines.
- **Following actions** are produced.

1) The **rate of automatic firing of** SA node is accelerated by β-adrenergic activation and this effect is abolished by β-Blockers.

2) **B-blockers prolong** the refractoriness of the **AV** node which may prevent re-entrant tachycardia at this site.

Many **β-blocking drugs** (propranolol, oxprenalol, alprenolol, acetbutalol, labetalol) possess **membrane stabilizing** properties.

Sotalol prolong cardiac refractoriness (class lll) but has no class 1 effect.

Uses.

1)Effective for a range of **supraventricular tachycardia**, particularly associated with excessive, lotion or hyperthyroidism.

2) Used in **wolf-parkinson white** syndrome & in digoxin induced arrhythmias.

Sotalol ____ used to suppress ventricular **ectopic beats** and ventricular tachycardia.

In emergencies ____ propranolol I/V is given.

Adverse Effects.

Over dosage ____ Heart block precipitated when a patient is dependent on sympathetic drive to maintain output.

Interaction.

Concomitant use with **Ca++ channel blocker** that effect (verapamil, diltazem) increases the **risk** of bradycardia and AV block & depress myocardial conductivity (nifedipine, verapamil) may cause hypotension or cardiac failure.

Class lll

(Lengthening of refractoriness with Sodium Channel)

Amiodarone.

Cardiac Effects

- **Approved only** for **serious** ventricular arrhythmias.
- Amiodarone **prolongs the effective refractory period** of myocardial cells, the AV node and of anomalous pathways.

- Effective in chronic ventricular arrhythmias.

In atrial fibrillation, slows the ventricular response and restores sinus rhythm.

Non-Cardiac Effects.

- Amiodarone causes peripheral vascular dilatation due to

α-blocking effects , β blocking & Ca++ channel inhibiting effects.

Toxicity.

Cardiac.

Amiodarone is effective against all sorts of

Cardiac dysrhythmias.BUT because of its adverse effects, is often **reserved** for cases where other drugs have failed or are contraindicated.

Adverse Effects(Cardiac)

Bradycardia, heart block, induction of vascular dysrhythmias, precipitate heart failure & ⬇ blood pressure.

Extra Cardiac.

Include **fatal pulmonary fibrosis** .

Adverse effects usually increases with the cumulative dose, so limit its use

Amiodarone ____ concentrate in tissues and can be found in every organ.

Corneal Deposits.

The most detected deposits are those in the cornea ____ appear as yellowish brown micro crystals. These may rarely cause visual symptoms except for occasional halos in the peripheral visual field.

Rarely visual acuity develop s which requires discontinuation of treatment.

Skin Deposits.

Photodermitis in 25 % of patients.

Patient should avoid exposure to sun.

5 % develop greyish-blue discoloration.

Neurologic Effects

Paresthesias, tremor, ataxia & headaches.

Thyroid dysfunction.

Amiodarone contains **iodine.** Both hypothyroidism and hyperthyroidism are reported.

So thyroid functions should be done before and throughout the therapy.

Other Effects.

Constipation ____ 20%

Liver ____ hepato-cellular necrosis

Lungs ____ inflammation & fibrosis (pulmonary fibrosis 5-15%)

Drug interactions.

Interaction with **digoxin** (by displacement from tissue binding site) and with warfarin (by inhibiting its metabolism) increases effects of both drugs.

- **β-blockers & Ca++ channel** blockers augment the depressant effect of amiodarone on SA and AV node function.
- Amiodarone raises plasma quinine concentration.

Pharmacokinetics & Doses.

- **Effective when given orally** largely distributed that little remains in the blood.
- stored in fat and many other tissue and t ½ ____ **even 54 days**, after multiple dosing signifies slow release from these sites.

- **Metabolized in the liver** and eliminated via the billiary and intestinal tract.
- If plasma concentration is 1-2 µg / ml, the cardiac concentration is 30 times high.

Loading dose is 0.8 – 1.2 gm daily for 2 weeks, maintenance dose is 200 – 400 mg / daily.

Once daily dose is required because of long half life.

If **toxicity** occurs ____ it may persist for so many days, even the drug is discontinued.

Uses.

- Very effective against supraventricular & ventricular arrhythmias.
- Relatively **low maintenance dose** 100 – 200 mg / day can be used against paroxysmal atrial fibrillation, quite effective in supraventricular arrhythmias in children in which it is safe.

Bretylium

- Was first introduced as an **anti hypertensive** agent.
- It interferes with the neuronal release

of catecholamine but also has antiarrhythmic properties.

It prolongs the cardiac refractory period.

Uses.

For **resistant** ventricular tachycardia especially those complicating myocardial infarction or cardiac surgery.

Main Adverse Effects

Nausea, vomiting, hypotension, and bradycardia.

Other members of this group are sotalol, Ibutilide, dofitilide.

Class lV

Ca++ Channel Blocking Drugs

Ca++ is involved in the **contraction** of cardiac and vascular smooth muscle cell, and in the automaticity of pacemaker cells.

Ca++ & cardiac Cells.

Cardiac muscles are normally depolarized by the fast inward flow of sodium ions, following which there is slow inward flow of Ca++ ions (phase 2),

the consequent **rise** in free intracellular Ca++ ions **activates** the contractile mechanism.

Pacemaker cells in the SA node and AV node rely heavily on the slow inward flow of Ca++ ions (phase 4) for their capacity to discharge spontaneously i.e. further automaticity.

Ca++ channel blockers **inhibit** the passage of ca++ through the membrane channels ___

____ result in myocardial cells is to depress contractility and in pacemaker cells to suppress their automatic activity ____ so have negative ionotropic and chronotropic actions.

Verapamil is the most useful antiarrhythmic.

Verapamil

Blocks both **activated** and **inactivated** Ca++ channels.

Prolongs conduction and **refractoriness** in the AV node and depresses the rate of discharge of the SA node.

It is drug of choice to terminate paroxysmal supraventricular tachycardia.

Adverse Effects.

Cause **peripheral vasodilatation** ___ beneficial to hypertension & peripheral vasospastic disorder.

Nausea, constipation, headache, fatigue, hypertension, bradycardia, heart block & peripheral edema.

Pharmacokinetics & Doses.

Plasma half life is 7 hours.

Extensively metabolized by the liver, after oral administration.

Bioavailability is only 25%.

So should be given with great caution in patients with liver dysfunction.

In adults with heart failure or SA or AV node disease, parenteral verapamil is used to treat supraventricular tachycardia.

Dose of verapamil ___ bolus 5 mg over 2 – 5 minutes, followed by a few minutes later

a second bolus if needed.

Then 5 – 10 mg ___ every 4 – 6 hours or a constant infusion of 0.4 µg / kg / min.

Oral dose ____ higher because of first pass metabolism 120 – 640 mg daily divided into three or four doses.

Uses.

Main indication is supraventricular tachycardia.

Verapamil can also reduce the ventricular rate in atrial fibrillation and flutter.

Diltiazem&Bepridil.

Similar to verapamil in the maintenance of supraventricular arrythmias.

Class V(Miscelleneous)
Adenosine,Digoxin,MgSo4,Ranolazine

ADENOSINE

- Naturally occurring Nucleoside
- At high doses----Dec. Automaticity
  Dec. conduction velocity, Prolongs ERP
- , I/V adenosine-----Drug of choice for Ac.Supra ventricular Arrythmias.

- Short acting(10_15 sec) due to rapid uptake by erythrocytes & endothelial cells.
- TOXIC EFFECTS

Low but Flushing,chest pain, Hypotension

RANOLAZINE

- Anti anginal with Anti arrhythmic effect similar to Amiodarone.
- Main Effect---Dec. APD & shortens repolarization
- Uses Refractory atrial & vent. arrhythmias

Magnesium Sulphate

- Necessary for transport of Na+,Ca++ & K+ across cell membrane.
- Slows the SA Node impulse formation & prolongs conduction time(delay A-V conduction)
- I/V--- used for Arrhythmias ,
- orally not effective.
- Drug of choice for potentially fatal arrhythmias, torsades de pointes & Digoxin induced arrhymias

Interventional strategies For Arrhythemias

Catheter Ablation:

Implantable Cardioversion Defibrillator (ICD):