NOVEL ANTI-ARRHYHTMIC AGENTS

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1. INTRODUCTION

- Approximately 50% of post MI fatalities are due to sudden cardiac death resulting from ventricular tachycardia or ventricular fibrillation.
- It is believed that these arrhythmias are arising from mechanical dysfunction and ischemic events interacting within disordered electro physiologic milieu (1).
- This has prompted active search for safe and effective treatment modalities and their ultimate evaluation in clinical trials.
- Currently ß-blockers are recommended for post MI patients with premature ventricular contraction where as Ca^{2+}channel blockers are not useful and sodium channel blockers are actually harmful.

DRUGS DEVELOPMENT

- In 1970 and early 1980s target or models used in drug development were based on suppression of PVCs recorded in animal models or in patients with PVCs after MI.
- Recently drug development has evolved in two areas

–Amiodarone analogues

–Delayed rectifier k^+ channel blockers

- Remarkable clinical efficacy of amiodarone in the treatment of wide varieties of arrhythmia has lead to search for class-III drugs with better safety profile.

2. PHYSIOLOGY OF CARDIAC MUSCLE (2)

2.1 PROPERTIES OF CARDIAC MUSCLE

1. EXCITABILITY:

- The ability of tissue to give response to a stimulus is called Excitability.
- Initial step is the development of action potential which is followed by contraction of muscle fibres.

2. AUTOMATICITY (RHYTHMICITY):

- The ability of tissue to produce its own impulses regularly is called Rhyhmicity
- All the tissue of the heart possesses the property of rhythmicity
- Automaticity of heart is maintain by pacemaker

PACEMAKER:

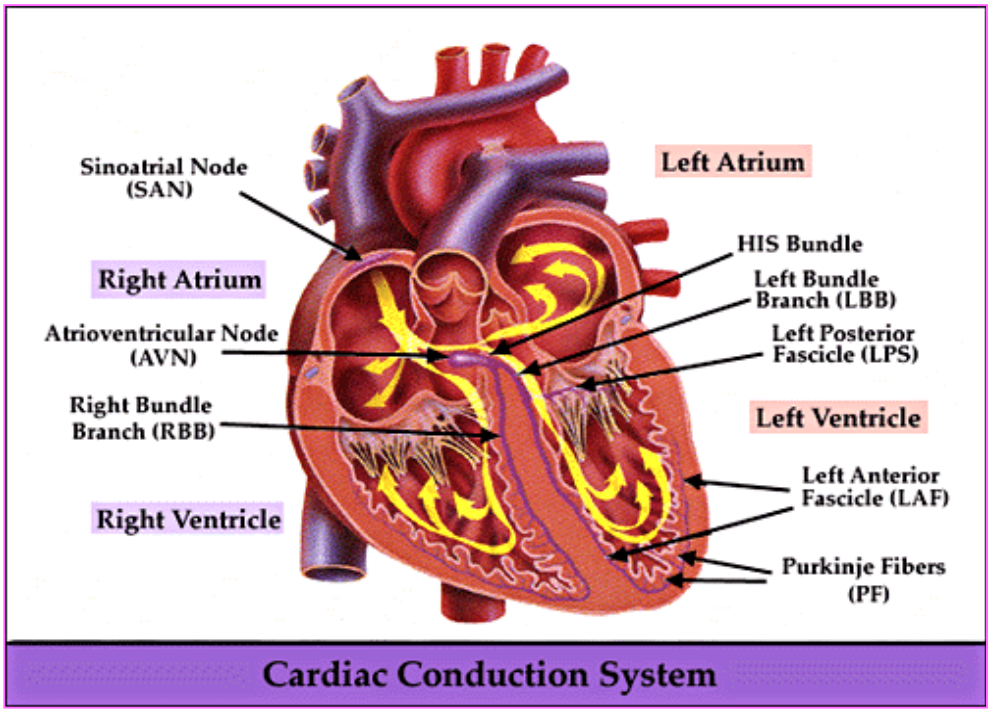
- It is a part of heart from which the impulses for heartbeat are produced normally.

3. CONDUCTIVITY:

Human heart has specialized conductive system through which the impulses produced by SA node are transmitted to all parts of heart.

The conductive system in human heart comprises:

1. AV node
2. Bundle of His
3. Right & left bundle branches
4. Purkinje fibers



4. CONTRACTILITY:

The ability of tissue to shorten in length (contraction) after receiving a stimulus is called **contractility**

-The different contractile properties are as follows.

1. All OR None law

When stimulus is applied to muscle it respond to its maximum OR does not give response at all is called All OR None law

2. Staircase phenomenon

When stimuli are applied at base of the ventricles of quiescent frog heart at interval of two second without changing the strength, for first few stimulus responses are increased & then responses remain unchanged is called Staircase phenomenon

3. Summation of subliminal stimuli

When stimulus with a subliminal strength is applied to muscle it does not give any response but few stimuli with a subliminal strength are applied to ventricles in succession it does response by contraction. It is due to summation of subliminal stimuli.

4. Refractory period

Refractory period is the relative brief period of relaxation of a muscle during which its excitability is depressed. The refractory period of the heart is long & is divided into 3 parts:

1. Absolute Refractory Period:

Coincides the period from the onset of depolarization phase to the repolarization up to threshold potential. During this period even a strong stimulus fails to produce Response. Such a long refractory period ensures enough time for recovery of cardiac muscle & **so *cardiac muscle can't be fatigued***.

2. Relative refractory period:

Begins when transmembrane potential (Vm) has just reached about -60 mV & ends before repolarization phase is ceased.

3. Supernormal Period:

It is time interval from the point of termination of the repolarization to the beginning of slow diastolic depolarization phase.

2.2 ELECTRICAL POTENTIAL IN CADIAC MUSCLE

Resting membrane potential

In individual cardiac muscle fiber, the resting membrane potential is about -80 mV.

In SA node it is -55mV. In purkinje fibers, it is about -90 to-100 mV.

Action potential

The electrical activity that takes place in the cardiac muscle is known as action potential.

Duration of action potential in cardiac muscle is 0.25 to 0.35sec.

1) PHASE O RAPID DEPOLARIZATION

- Nearby -60 mV rapid depolarization occurs by the movement of Na^+ ions through selective channels that are activated in a voltage dependent manner when
- The propagating cardiac impulse or

Spontaneous phase 4 depolarization causes the hypothetical m-gate in Na^+ channel to open.

2) PHASE 1 PARTIAL REPOLARIZATION

- At the peak of upstroke there occurs a rapid repolarization in which membrane potential returns towards 0 mV because of the rapid inactivation of Inward Sodium current
- It occurs also due to activation of short-lived outward current carried by mainly Potassium ions i.e. known as Transient outward current.

3) PHASE 2 ACTION POTENTIAL PLATEAU

- Conductance of all ion channels decreases rapidly giving net balance between inward (depolarizing) &outward (repolarizing) ion currents.
- Increase ICa^{2+} is a major contributor to phase 2 & when membrane is depolarized to -40 mV, opening of voltage dependent Ca^{2+} channels causes increase ICa^{2+}
- Cardiac muscle membrane assists plateau by its special property that is Inward going Rectification – potassium conductance falls to a low level when membrane is depolarized, so Outward K+ current,
- Can't restore resting membrane potential during plateau.

4) PHASE 3 REPOLARIZATION:

- It occurs as the calcium current inactivates &

Outward potassium current activates causing outward potassium current.

- Such potassium current repolarizes the fiber to normal diastolic value of Vm

5) PHASE 4 PACEMAKERS POTENTIAL / DIASTOLIC DEPOLARIZATION

Caused by combination of increased inward & Decreased outward currents during diastole

- Cells having property of Automaticity exhibit spontaneous phase 4 depolarization

- Cells of SA node have Greater background conductance to Na+ ions, so great inward Na+ entry**.**

3. DEFINITION

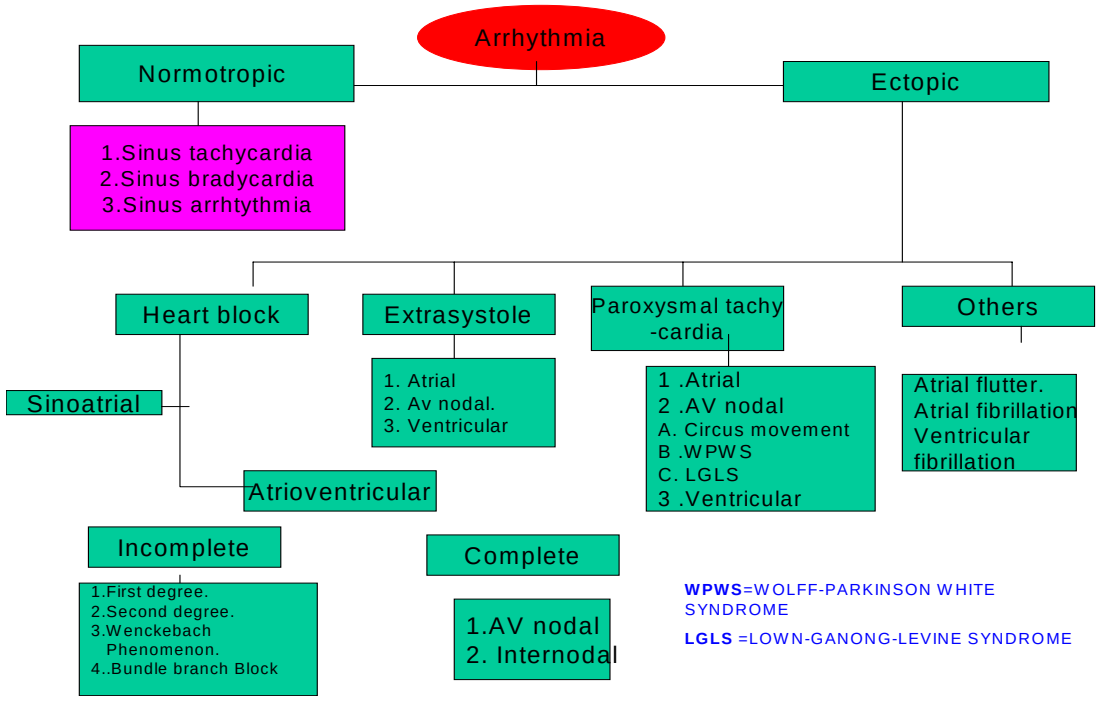
Cardiac arrhythmia:

It is defined as disorder of disturbance in rate, rhythm, origin or conduction of cardiac impulses within a heart.

Drug therapy of arrhythmias depends on

- Presence of arrhythmia and its type.
- Use of anti arrhythmic drugs on basis of mechanism of action (3).

4. CLASSIFICATION OF CARDIAC ARRHTHMIA



5. MECHANISMS OF CARDIAC ARRHYTHMIA

5.1 ABNORMAL PACEMAKER ACTIVITY (4)

- Under some pathological conditions pacemaker activity can arise in other parts of heart than SA node and conducting tissue.
- Predisposing factors are:
- Catecholamines acting on ß1adrenorecepor increase the Rate of depolarization during phase 4 &can cause normally quiescent part of heart to take on a spontaneous rhythm.
- Pain (During myocardial infarction) increased sympathetic discharge releases adrenaline from the adrenal gland.
- Partial depolarization resulting from ischamic damage is caused by decreased activity of electrogenic sodium pump and it will cause abnormal pacemaker activity.
- This mechanism is mainly responsible for Sinus tachycardia, Atrial&Ventricular extrasystoles, and Atrial flutter.

5.2 AFTER DEPOLARIZATION

Under some pathophysilogical conditions, normal cardiac action potential is interrupted or followed by abnormal depolarization if this abnormal depolarization reaches threshold potential it may, in turn give rise to secondary upstrokes which then can propagate and crate abnormal rhythms **(5).**

- These abnormal secondary upstrokes occur can only after initial normal or triggering upstroke & so are termed as triggered arrhythmias (5).

There are two types of After Depolarization.

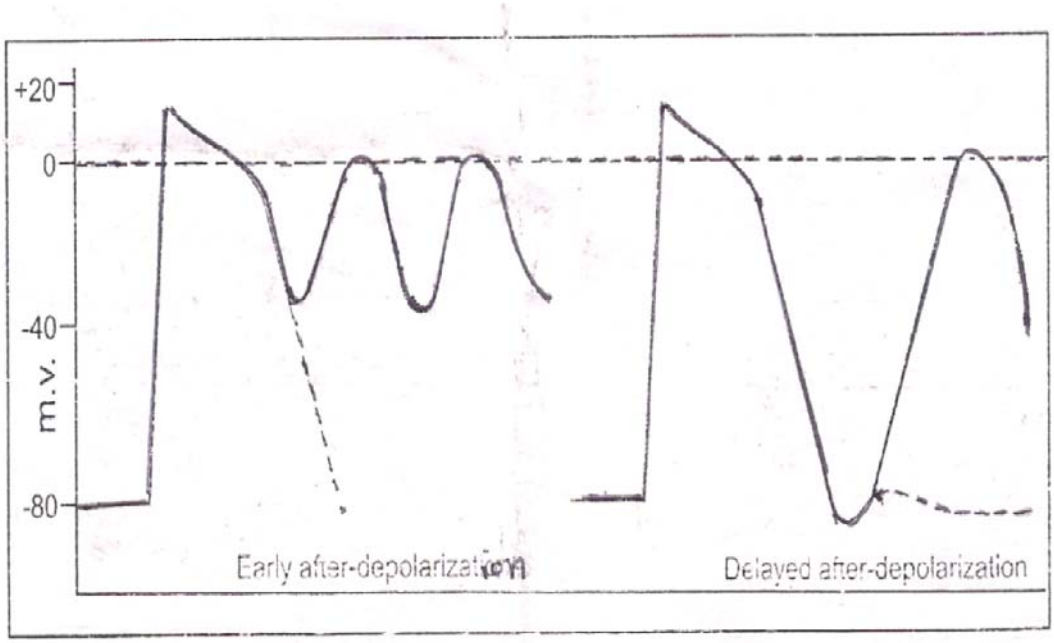
1) Delayed After Depolarization (DAD)

2) Early After Depolarization (EAD)

1) Delayed After Depolarization (DAD)

- A normal action potential may be followed by delayed after depolarization if this reaches threshold a secondary triggered beat can occur.
- It is due to increase in intracellular calcium load in condition like myocardial ischemia, adrenergic stress, digitalis intoxication **.**
- DAD amplitude is increase in vitro by rapid pacing and clinical arrhythmia thought to be correspond to DAD mediated triggered beat are more frequent when underlying cardiac rate is rapid (6).
- It is responsible for train of Extrasystole, Tachycardia, Torsades de pointes (5).

- EAD mediated arrhythmias are common in condition like slow heart rate, low extra cellular calcium and use of class III drugs.
- When cardiac Repolarization markedly prolonged polymorphic ventricular tachycardia with a long QT interval, known as Tosades de pointes syndrome may occur and is thought to be caused by EAD and resultant triggering activity (7).
- The congenital long QT syndrome, a disease in which Torsades de pointes is common is now known to be caused by mutation in the genes encoding the sodium channels underlying the repolazising current IKR and IKS.



- Due to conduction abnormality, impulse may recirculate in the heart and cause repetitive activation without the need for any new impulse to be generated.

Two types of RE-ENTRY

1) Circus movement type

2) Micro-Re entry Circuit.

1) CIRCUS MOVEMENT TYPE (5).

It occur in anatomically define circuit.

A premature impulse is temporary blocked in one direction by refractory tissue and makes only one way transit around an obstacle i.e. natural orifice heart, Infracted myocardium and that will find original spot in advance state of recovery and re excite it

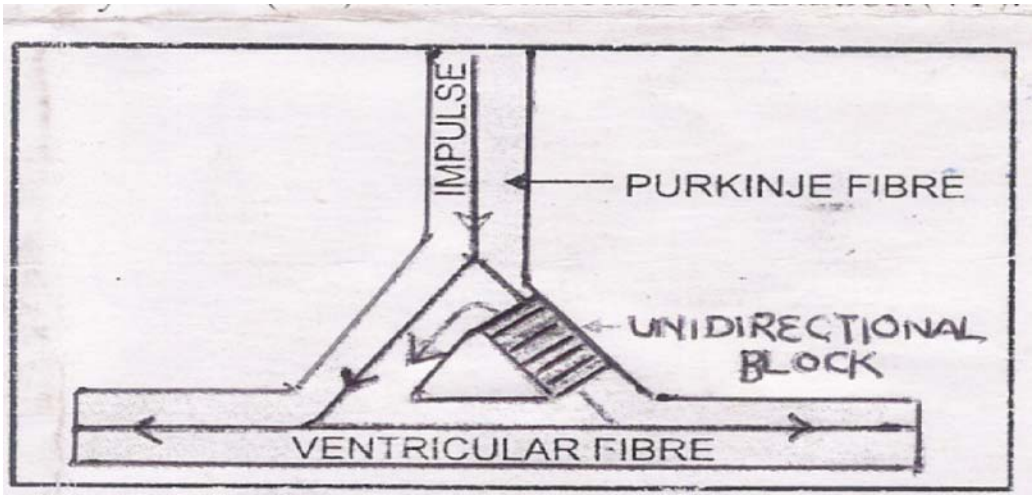
and cause recurrent activation of the adjacent myocardium. This mechanism may cause Atrial flutter, PSVT, Atrioventricular reciprocal tachycardia in Wolff Parkinson White syndrome.

2) MICRO-RE ENTRY CIRCUIT.

- **I**t is formed at a junction of purkinje fibers and ventricular fibers.
- One of the branch of purkinje fibers sufficiently depolarized to cause unidirectional block.
- Extremely slow conduction due to slow channel depolarization and markedly abbreviated, APD and ERP make re-entry possible ventricular Extra-systole, VT and VF.
- For re-entry to occur the pathlength of circuit should be grater than the wavelength (ERP x Conduction Velocity) of impulse.

Slow conduction in re-entrant circuit may be caused by:

- Partial depolarization of membrane-decrease slope of phase 0.
- Cells changing over from fast channel to slow channel depolarization which conducts very slowly when fiber is depolarized to resting membrane potential of about –50mV.Sodium channels are inactivated but calcium channels still able to produce response



3) FRACTIONATION OF IMPULSES

- When atrial ERP is brief & inhomogeneous (under vagal overactivity), an impulse generated early in diastole gets conducted irregularly over atrium i.e. it moves rapidly through fibres with short ERP (which is completely recovered) slowly through fibres with longer ERP (which is partially recovered) and not at all through those still refractory.Thus, cause asynchronous activation of atrial fibres and cause Atrial Fibrillation.
- This arrhythmia must be initiated by premature depolarization but is self sustaining, because passage of an irregular impulse leaves an irregular refractory trace and maintain the inhomogenicity of ERPs.
- Total number of impulses that can be sustained at any moment depends on -

  Average of ERP

  Mass of tissue
- Thus atrial fibrillation is more common in dilated atria (Mitral stenosis).

4) HEART BLOCK

- Even under physiological condition, conduction through SA and AV nodes are tardy.
- It may further slow by ischemia causing partial to complete AV block or Sick sinus.

Two types of Heart block

1) Sinoatrial block.

- When impulses from SA node are not transmitted to AV node due to defective internodal fibers, is called sinoatrial block.

2) Atrioventricular block.

- When impulses from atria are not transmitted to ventricle due to defective conductive system is called atrioventricular block.

a) Incomplete H.block.

- The transmissions of impulses from atria to ventricles are slow down but not blocked completely.

i) First degree (Delayed conduction)

- The conduction of impulses through AV node is very slow**.**

ii) Second degree (Partial H. block)

- In this some of impulses produced by SA node fail to reach to ventricles.

iii) Wenckebach phenomenon

- It is a one type of heart bock characterized by progressive lengthening of conduction time in AV node with ultimate missing of one beat. Afterwards, the conduction of impulses is normal or slightly delayed.

iv) Bundle branch block

- When Left or Right branch Bundle of His is affected then Left or Right Bundle branch block occur respectively. During this, the impulse from atria reaches unaffected ventricle first. Then from here impulse travel into affected side.

b) Complete H.block (Third degree H.block)

- The impulses produced by SA node do not reach the ventricles. So, the ventricle beats in their own rhythm independent of atrial beat. This is called Idioventricular rhythm.

6. GENERAL MECHANISMS OF ANTI-ARRHYTHMIC AGENTS (8)

A single arrhythmia may results from multiple mechanisms e.g. an automatic or triggered beat may results in sustained re-entrant arrhythmia in patient with a potential re-entrant circuit.

- **Anti-arrhythmic agents act by**
  1) Suppressing initiating mechanism
  2) Altering the re-entrant circuit.
- **Drugs slow automatic rhythm by altering one of the four determinants.**
  1) Maximum diastolic potential, which is
     -Increase by Ach and Adenosine.
  2) Slope of phase 4, which is decreased by ß- blockers
  3) Threshold potential, which is altered by class-I and class-IV drugs.
  4) Action potential duration, which is prolonged by class-III drugs.
- Arrhythmia due to after depolarization can be blocked by
  i) Inhibition of development of after depolarization
  ii) Interference with inward current, which is responsible for upstroke

I.e. Arrhythmia due to Digitalis induced DADs can be treated by Verapamil (inhibit the development of DADs) or by Quinidine (blocking sodium channel).

- **EAD induced triggered beat can be blocked by**

  i) Shortening of APD by class-1b drug.

  ii) Use of magnesium.

In patients with congenitally prolonged QT interval, Torsades de pointes often occur with adrenergic stress can be prevented by B blockers as well as rapid pacing.

- **Drugs that prolonged APD can terminate circus movement type re-entry**
- **Drugs that prolonged refractoriness can terminate micro re-entry circuit**

  -- E.g: Class-I&Class-III drug in fast responsive tissue.

Class-IV drugs in slow responsive tissue.

- Conduction usually fails in weak leak in circuit.
- In condition like WPW-related arrhythmia, the weak leak is AV node and drug that prolongs AV nodal refractoriness and slow AV nodal conduction such as class-I, Class-II or digitalis glycosides are likely to be effective.
- Drugs that interfere with cell-cell coupling can also prolong refractoriness in multicellular preparation.

  E.g. Amiodarone exerts this effecting diseased tissue.
- Acceleration of conduction in area of slow conduction could also anti arrhythmic in re-entry.

  E.g. Lidocaine exerts such effect in some experimental condition.

7. CLASSIFICATION OF ANTI ARRHTHMIC AGENTS

CLASS I - Na^+ channel blockers.

class Ia	class 1b	class Ic
-Quinidine	-Phenytoin	- Flecainide
-Disopyramide	-Lignocaine	- Encainide,
-Procainamide	-Mexiletine	- Propafenone

NOVEL CLASS-I AGENTS:

- **SD-3212**
- **AZD 7009**

•**MORICIZINE.**

CLASS II- Anti adrenergic agents.

Propranolol

Bretylium

Esmolol

Sotalol

CLASS III- Potassium channel blockers

Amiodarone

Bretylium

Sotalol

NOVEL CLASS-III AGENTS:

Ibutilide	**Nibentan**	**CX-1**	**Tedisamil**
Dofetilide	**Azimilide**	**AL-275**	
Trecetilide	**Dronedarone**	**AZD-7009**	

CLASS IV- Calcium channel blockers:

Verapamil

Diltiazem

Other agents

Adenosine

Digitalis

Other novel agent:

RSD-1235

Newer techniques

Implantable Cardioverter Defibrillator

Pacemaker

Radiofrequency ablation

Surgery

1.Cryoablation

2.Maze Surgery

Drugs used in Brady arrhythmias

1) Sympathetic agonist: Isoprenaline

2) Parasympathetic antagonist: Atropine

8. NOVEL ANTIARRHYTHMIC AGENTS

A) CLASS- I AGENTS:

1) SD-3212 (levo-semotiadil fumarate):

- It acts by blocking sodium & calcium channels.
- In animal models this drug suppressed Atrial tachyarrhythmias but not ventricular tachyarrhythmias.
- A scientific study indicates that SD-3212 is effective in interrupting canine atrial flutter possibly by suppressing atrial conduction.
- **Use**: It can be used for treatment of **atrial tachyarrhythmias.**

2) AZD-7009:

- It is novel agent in early clinical development for treatment of atrial fibrillation.
- It acts by **blocking sodium & potassium channels**.
- Pre-clinical studies have shown that it is promising drug for converting **AF to Sinus rhythm**.
- An early clinical study shows that I.V AZD 7009 is well tolerated.
- No cases of **'Torsades de-pointes'** are reported.

3) MORICIZINE

- It is a phenothiazine derivative with Class Ic antiarrhythmic properties
- It under goes first pass metabolism.
- **PPB** is 95%, **B.A** is 34-38%.
- Recent clinical studies have shown that moricizine is slightly **less** effective than encainide, flecainide but **more** effective than quinidine & disopyramide in suppressing ventricular premature depolarization.
- It can be **used** in treatment of **VT** &**VF.**
- It has **lower** incidence of serious adverse effects than other **Class- I drugs** (Carnes CA and Coyle JD, 2003**)**.

B) CLASS- III AGENTS

1) IBUTILIDE:

• It is a novel antiarrhythmic drug that was recently marketed for the rapid conversion of atrial fibrillation and atrial flutter into Normal sinus rhythm.

•**M/A**:

•Prolongs action potential duration by activating a slow inward current, largely carried by **sodium ions**.

•Blocks the Rapidly activating component of the delayed rectifier **potassium current**.

• It increases atrial and ventricular refractoriness by action potential prolongation in vivo.

Phamacokinetics: Not given oral route because of extensive first pass metabolism.

Route: Intravenous

t1/2-: 2-12 hrs

Linear kinetics: No

•**Dose:** I.V. 1mg over 10 minute periods in patients weighing 60kg.

Initial dose is 0.01mg/kg with second dose of same strength 10 minutes later in patients weighing less than 60kg.

•**Indication**: Rapid conversion of atrial fibrillation and atrial flutter into sinus rhythm.

•**Contraindication:**

QTc Interval exceeding 440Ms

Bradycardia

Electrolyte disturbances

Other QT-prolonging drugs

• **Adverse effects:**

Torsades de pointes (5.1%)

Premature ventricular complexes (5.1%)

Monomorphic ventricular tachycardia (2.7%)

Hypertension (2%)

Bundle branch block (1.9%)

Nausea (1.9%)

Headache (3.6%)

Bradycardia (1.2%)

2) DOFETILIDE:

•Class III anti-arrhythmic drug.

•M/A: Blocks particular potassium current in heart.

•It is recently approved by U.S. and its effectiveness was shown in large number of clinical trials such as EMERALD and SAFIRE trials.

•These trials showed that patient given dofetilide were more likely to convert **AFor AFL to Normal sinus rhythm.**

•Dofetilide was also evaluated in two large mortality trials known as DIAMOND trial in patients were in hospital with CHF or Heart attack.

•These trial showed that this drug did not increase mortality in either of two patient groups.

•**Dose:** 125,250 or 500mcg twice a day

•**A/E:** Torsades de pointes

•**Contraindication**: Certain drug increases blood level of dofetilide and increase risk of Torsades de pointes.

•E.g. Verapamil, Cimetidine, ketoconazole, trimethoprim, prochlorperazine etc.

•**Uses**: Atrial Fibrillation and Atrial flutter.

3) AZIMILIDE (NE10064):

•Azimilide is an investigational class-III antiarrhythmic that has been developed for treating both supraventricular and Ventricular tachyarrhythmias.

•**M/A:** It mainly **blocks the slowly activating (IKS) and rapidly activating (IKR) Components** which distinguishes it from most of the other potassium channel blockers such as Sotalol and dofetilide, which **block only IKR**.

• Similar to other class-III drugs, azimilide prolongs myocardial depolarization in a dose dependent manner by increasing the action potential during QT interval and effective refractory period.

•In animal models, azimilide has shown to be effective in suppressing both atrial and ventricular tachyarrhythmias, decreasing defibrillation energy requirement and preventing post myocardial infarction, ventricular tachycardia and fibrillation.

It has very predictable pharmacokinetic and has not significant drug interaction with Digoxin or Wafarine.

•**Side effects**

Headache (most frequent)

Neutropenia

Torsades de pointes

4) DRONEDARONE:

•Dronedarone is new class-III antiarrhythmic drug under phase-III development by Sanofi-Aventis for prevention and treatment of atrial fibrillation.

•Evidence of efficacy was first demonstrated in **DAFNE** trial, a phase-II b study that compared dronedarone with placebo for maintenance of sinus rhythm after cardio version for AF.

•Dronrdarone proved effective in preventing recurrences of AF.

•No cases of **Torsades de pointes & Pro-arrhythmias** were reported.

5) TRECETILIDE:

•Trecetilide, a congener of ibutilide, is being evaluated in both IV and Oral preparations for the **termination and prevention of AF and AFL.**

•In addition to **blocking IKR**, It seems to prolong repolarization through other mechanisms that are still being delineated.

•It also significantly prolongs the action potential in animals and repolarization in humans without exerting other electrophysiological effects.

6) NIBENTAN:

-**M/A:** It is a selective potassium channel blocker with class-III antiarrhythmic properties.

•At 0.1-0.25 mg/kg I/V. Nibentan produced dose dependent increases in atrial and ventricular effective refractory periods and the QT interval without significant change in systolic or diastolic atrial or left ventricular pressure, heart rate and left ventricular contractility.

•Nibentan was about 100 times more potent than quinidine and its effect was sustained as long.

CLINICAL STUDIES:

•**Phase-I** clinical trial was performed to evaluate safety of Nibentan in 67 patients with various supraventricular & ventricular tachycardias.

Nibentan produced effects characteristics of class-III drug appearance of additional "U" wave with lowering of T wave amplitude, prolongation of QT interval by 34%.

•It significantly slows down sinus rhythm rate.

•**Phase-II** clinical trial, efficacy of nibentan was studied on 43 patients with cardiac diseases.

•Nibentan produce pronounced antiarrythmic effect in all patient with AFL or SVT & 73% patients with AF

•**Side effect**

•. Torsades de pointes (5.5%)

7) TEDISAMIL:

•Tedisamil (pulzium) differs from other class-III anti arrhythmic agents in that it blocks ITo in addition to IKR.

• Pulzium is an innovative drug for now in later stage of clinical development for treatment of AF.

•Tedisamil has been shown to reduce the incidence of VF and AF in experimental studies.

• Tedisamil is a drug used by cardiologist to treat of rhythm disturbances of heart.

•**S/E**: It produces **bradycardia**, presumably by direct action on SA node, APD and prolongs the QT intervals without affecting QRS complexes.

8) CX-1:

•**C**han**X**press is potent novel antiarrhythinic agent.

•Preclinical invitro test showed that **CX-1** has the requisite properties of a satisfactory antiarrhythmic drug.

•Animal studies have fully established that **CX-1 reverses AF and also prevents recurrence of AF**.

•The safety of drug in human has fully established in phase-I clinical trials.

•Bioavailability of **CX-1** is excellent and It can be given orally and intravenously.

•Drugs similar to **CX-1** for the treatment of **AF** have proven to generate undesirable side effects that limit their efficacy.

•This drug can be used for **treatment of VF & VT**

9) AL-275:

•AL-275 is novel class-III anti arrhythmic drug, which is derivative of dicyclohexylamides of amino carbonic acid.

•It mainly acts by **blocking rapid (IKR) and slow (IKS) activating components of delayed rectifier potassium current.**

•It prolongs ventricular repolarization, lengthens atrial and ventricular ERPs, suppresses sinus node automaticity, does not affect atrio-ventricular and intra-ventricular conduction.

C) OTHER AGENTS

RSD-1235:

•**M/A**: It is a novel, frequency dependent **sodium and early-activating potassium channel blacker** under joint development by Cardiome and its partner.

•The agent is intended as an acute use via intravenous administration to terminate AF and restore SR in AF patients.

•An oral formulation of RSD-1235 is also under development for the long-term maintenance of normal SR following termination of AF.

Safety and side effects:

•During 30 days follow-up period after drug administration, 18.3% patient in placebo group and 13.1% in the RSD-1235 group experienced a Serious Adverse Event (SAE).

•Most of these SAE's were recurrence of AF requiring hospitalization

•There were no cases of drug related **Torsades de pointes.**

•During first 24 hrs after study drug infusion, the most common non-cardiac side effects associated with RSD-1235 were,

Disgeusia (30%)

Paresthesia (11%).

Sneezing (16%).

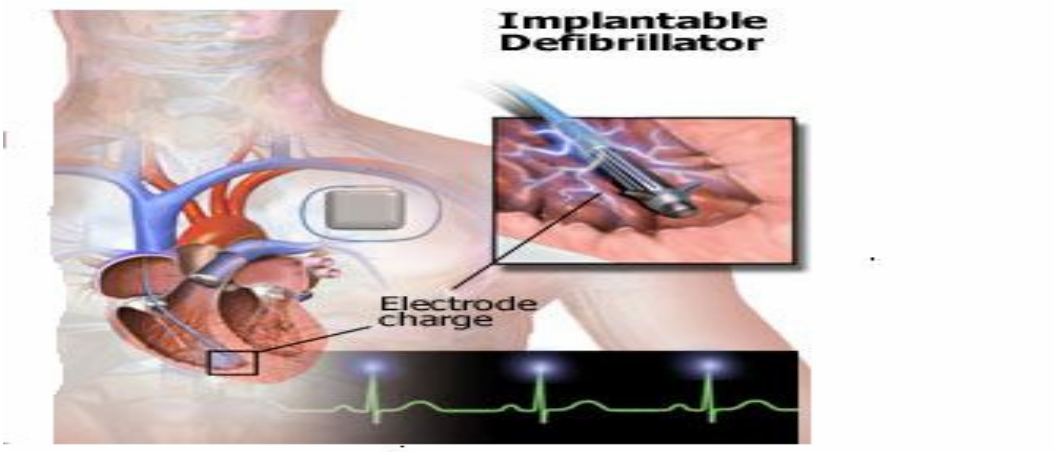
Nausea (9%)

Cough (5%).

D) Newer techniques to treat arrhythmias

1.Implantable Cardioverter Defibrillator

- This is a device that applies electric impulses or, if needed, a shock to restore a normal heartbeat.



The device's power source is implanted in a pouch beneath the skin of our chest or the area above your stomach and connected to patches placed on our heart.

Use: Ventricular tachycardia and Ventricular fibrillation

Newer implantable devices are inserted through a blood vessel, which means that you do not need open-chest surgery.

2.Pacemaker

A pacemaker is a matchbox size device that is run by a battery.

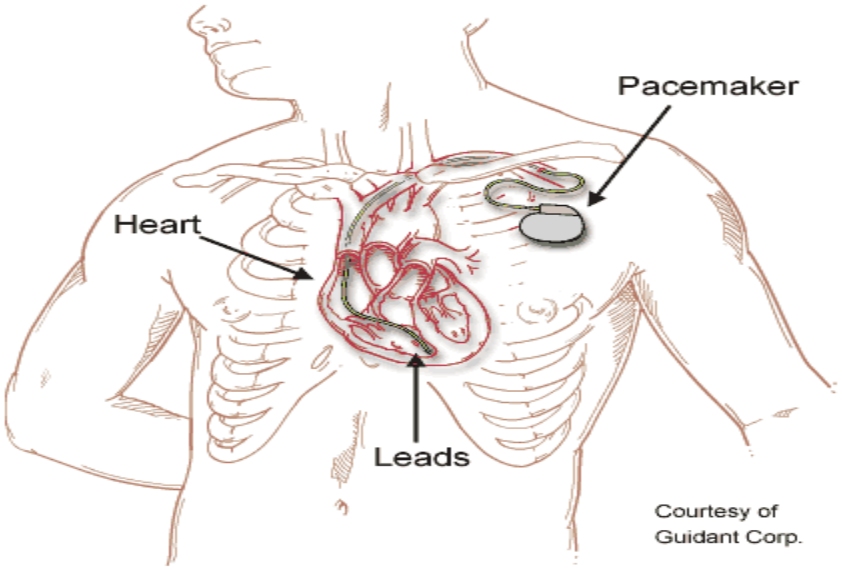
It is made up of two parts:

1. A pulse generator, which includes the battery and several electronic circuits.
2. Wires, called **leads**, which are attached to the heart wall.

Depending on the type of pacemaker you need, there may be one or two leads.

- If only one lead is needed, it is placed inside the lower-right chamber (the right ventricle). If two leads are needed, the other is placed in the upper-right chamber (the right atrium). The leads are then attached to the pacemaker.
- The pacemaker is surgically implanted near the bone below your neck (the collarbone).
- If only one lead is needed, it is placed inside the lower-right chamber (the right ventricle). If two leads are needed, the other is placed in the upper-right chamber (the right atrium). The leads are then attached to the pacemaker.
- Most pacemaker surgery is done under local anesthesia.

- Once the pacemaker is implanted, the leads carry signals back from the heart. The pulse generator "reads" these signals and the batteries send electrical impulses to the heart to help pace it.
- Most pacemakers can sense the heart's rhythm and turn themselves off when the heartbeat is above a certain level.
- They will turn on again when the heartbeat is too slow. These types of pacemakers are called demand pacemakers.
- The pacemaker's batteries supply the electrical energy that acts like your heart's natural pacemaker.



Uses:

- Pacemakers can help pace the heart in cases of slow heart rate, fast and slow heart rate, or a blockage in the heart's electrical system.
- A pacemaker can pace the heart's upper chambers (the atria), the lower chambers (the ventricles), or both.
- Pacemakers may also be used to stop the heart from triggering impulses or from sending extra impulses.

3. Radiofrequency ablation

- It is a procedure that uses a catheter and a device for mapping the electrical pathways of the heart.
- After you are given medicine to relax you, a catheter is inserted into a vein and guided to your heart, where doctors use high-frequency radio waves to destroy (ablate) the pathways causing the arrhythmia.

4.Surgery

1. Cryoablation

- Using computerized mapping techniques, surgeons can find out which cells are "misfiring."
- Then **cryoablation** can be used to eliminate tissue with a cold probe and destroy the "misfiring" cells.

2. Maze Surgery

- Maze surgery may be recommended if you have atrial fibrillation that has not responded to medicines or electrical shock (cardioversion therapy).

Surgeons create a "maze" of new electrical pathways to let electrical impulses travel through your heart without being blocked.

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