بسم الله الرحمن الرحيم

Pharmacology of CVS
Lecture 1: Cardiac arrhythmias: Types, mechanisms and drugs

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Introduction

Conducting system vs contractile tissue of the heart

Conducting System:

SA node, AV node, Purkinj fibers

Contractile tissues

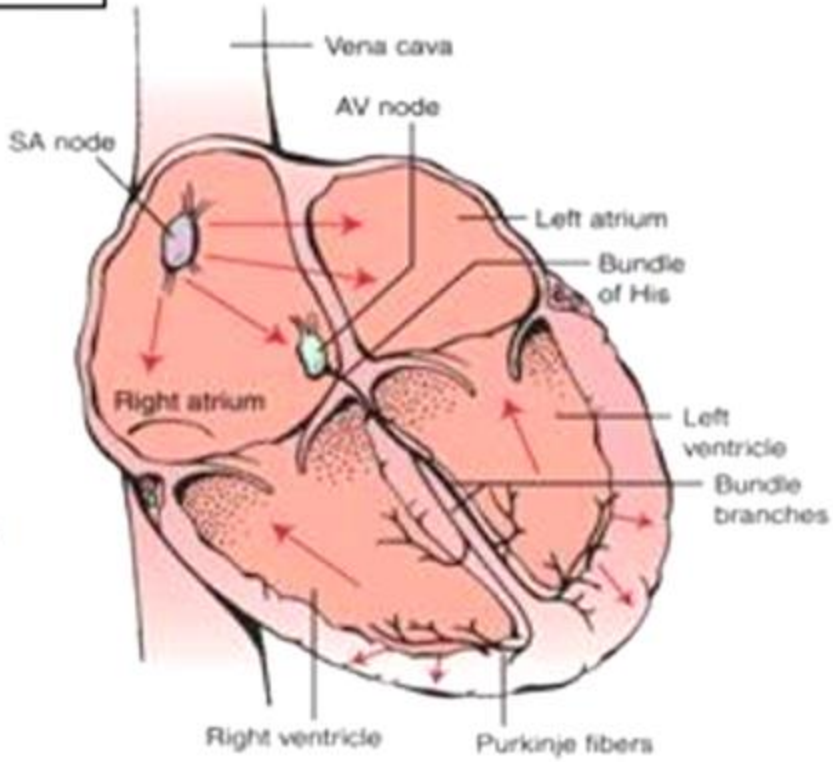
Atrial & Ventricular muscles

Impulse Propagation:

- SA node → AV-node → Bundle of His → Purkinje fibers → ventricle.

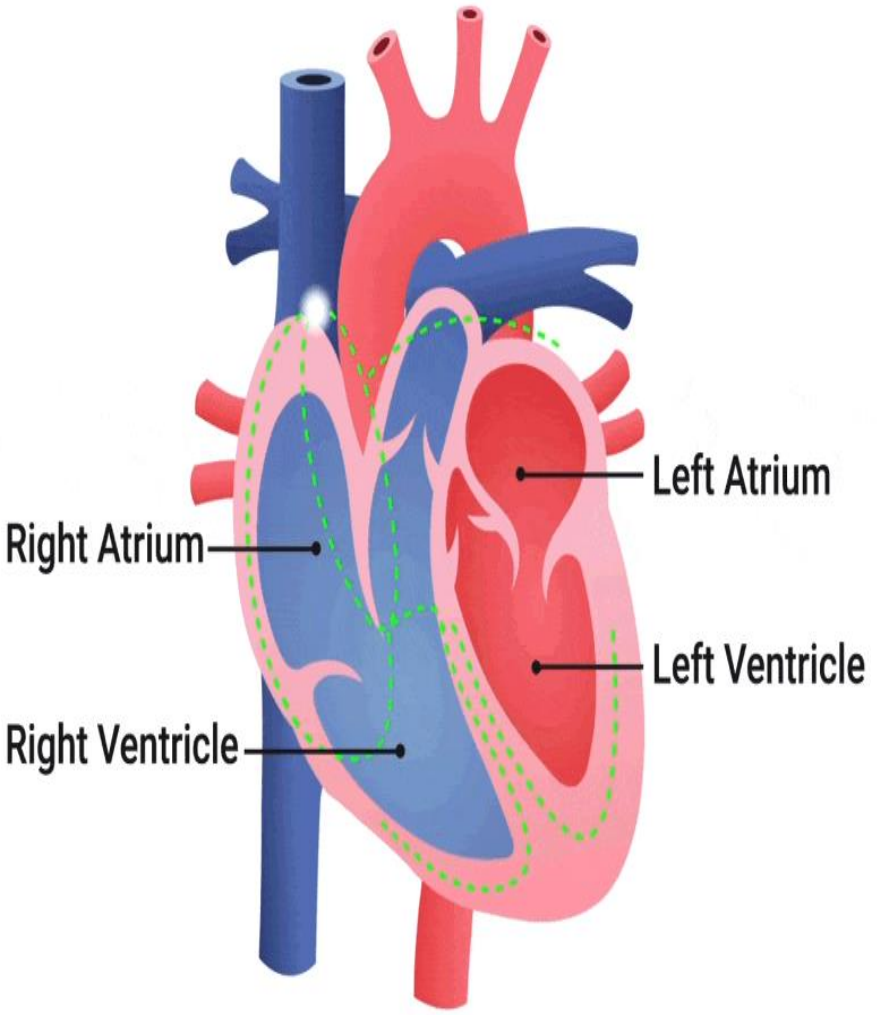
- SA node is the initial pacemaker.

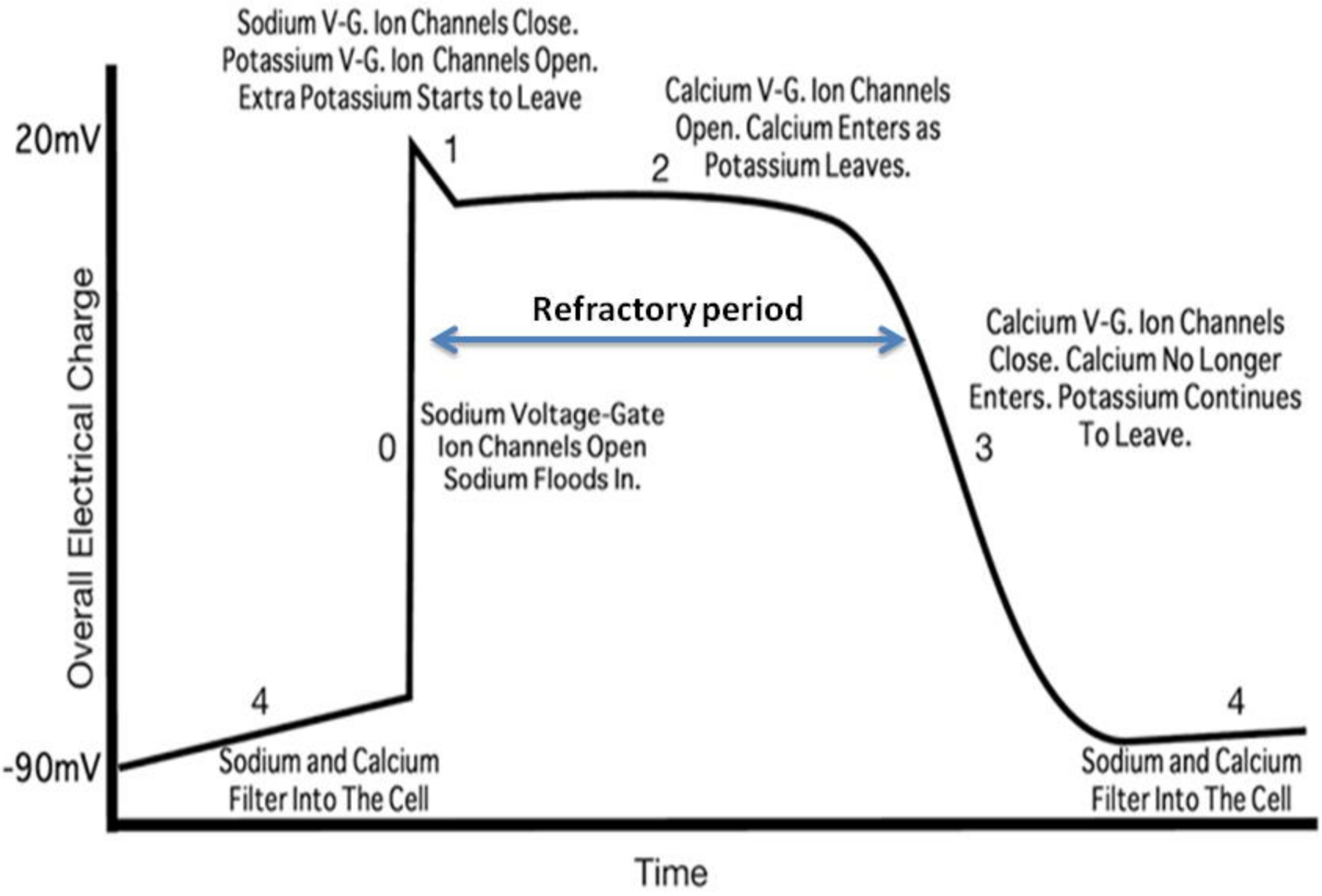
- To understand the action of antiarrhythmics, electrophysiology of the heart must be reviewed.



Cardiac properties in relation to the phases of action potential

1. **Automaticity:** is represented by spontaneous depolarization (phase 4).
2. **Conduction**: represented by phase 0 (maximal rate of depolarization or Vmax).
3. **Effective refractory period** (ERP): is represented by phase 1, 2, 3 until the membrane is repolarized to -60 mV. It is represented by the width of depolarization. During ERP, cardiac cells cannot respond to a new conducted stimulus.




Sodium V-G. Ion Channels Close.
Potassium V-G. Ion Channels Open.
Extra Potassium Starts to Leave
1
Calcium V-G. Ion Channels
Open. Calcium Enters as
2 Potassium Leaves.
20mV
Overall Electrical Charge
Refractory period
Calcium V-G. Ion Channels
Close. Calcium No Longer
Enters. Potassium Continues
To Leave.
3
0
Sodium Voltage-Gate
Ion Channels Open
Sodium Floods In.
4
4
-90mV
Sodium and Calcium
Filter Into The Cell
Sodium and Calcium
Filter Into The Cell
Time

Cardiac arrhythmias

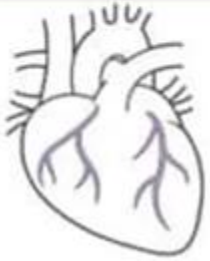
- **Arrhythmias**: are **abnormal heartbeat** (abnormalities in **rate**, **rhythm** or **both**) due to abnormality in **automaticity** (ectopic beats), abnormality in **conductivity** (reentry) or abnormality in **both**.
- **In arrhythmias,** cardiac depolarization deviate from normal in one or more aspects: abnormality in the **site of origin of the impulse**, its **rate** or **regularity**, or its **conduction.**
- **Anti-arrhythmic drugs** are those drugs that **suppress** the abnormality of cardiac rhythm by **blocking specific ion channels** (Na^+, Ca^{++} and K^+) or by **altering autonomic functions**.

Causes of Arrhythmia

1. Electrolyte disturbance as hypokalemia and hypocalcemia.
2. Myocardial ischemia, hypoxia and Myocardial Infarction.
3. Acidosis or alkalosis.
4. Excess catecholamine.
5. Hypoglycemia.
6. Overstretching of cardiac fibers.
7. Drug toxicity (as digitalis and anti-arrhythmic drugs).

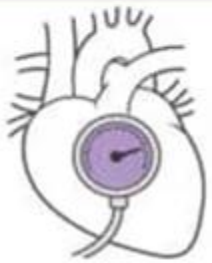
Arrhythmia occurs in **25 % of patients** with **digitalis** therapy and in **70 %** of the cases of acute **myocardial infarction** (MI).

Risk factors for cardiac arrythmias and cardiac arrest



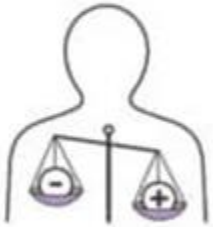
Coronary artery disease

Heart valve disorders

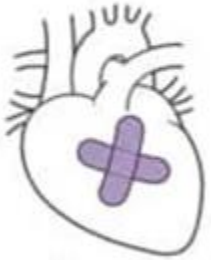


High blood pressure

Alcohol abuse



Electrolyte imbalances in the blood



Trauma or injury to the heart due to surgery, infection, or previous heart attack

Electrocution

Cardiomyopathy and changes in the heart muscle

Drugs and medication

Genetic disorders

Congestive heart failure

Congenital heart defects

Types of cardiac arrhythmias

A. Supraventricular (atrial) arrhythmia:

1. Sinus tachycardia (pulse more than 100 beats / min.).
2. Sinus bradycardia (pulse less than 60 beats / min.)
3. **Supraventricular tachycardia,**
4. **Atrial flutter (regular fast)**
5. **Atrial fibrillation (irregular fast)**

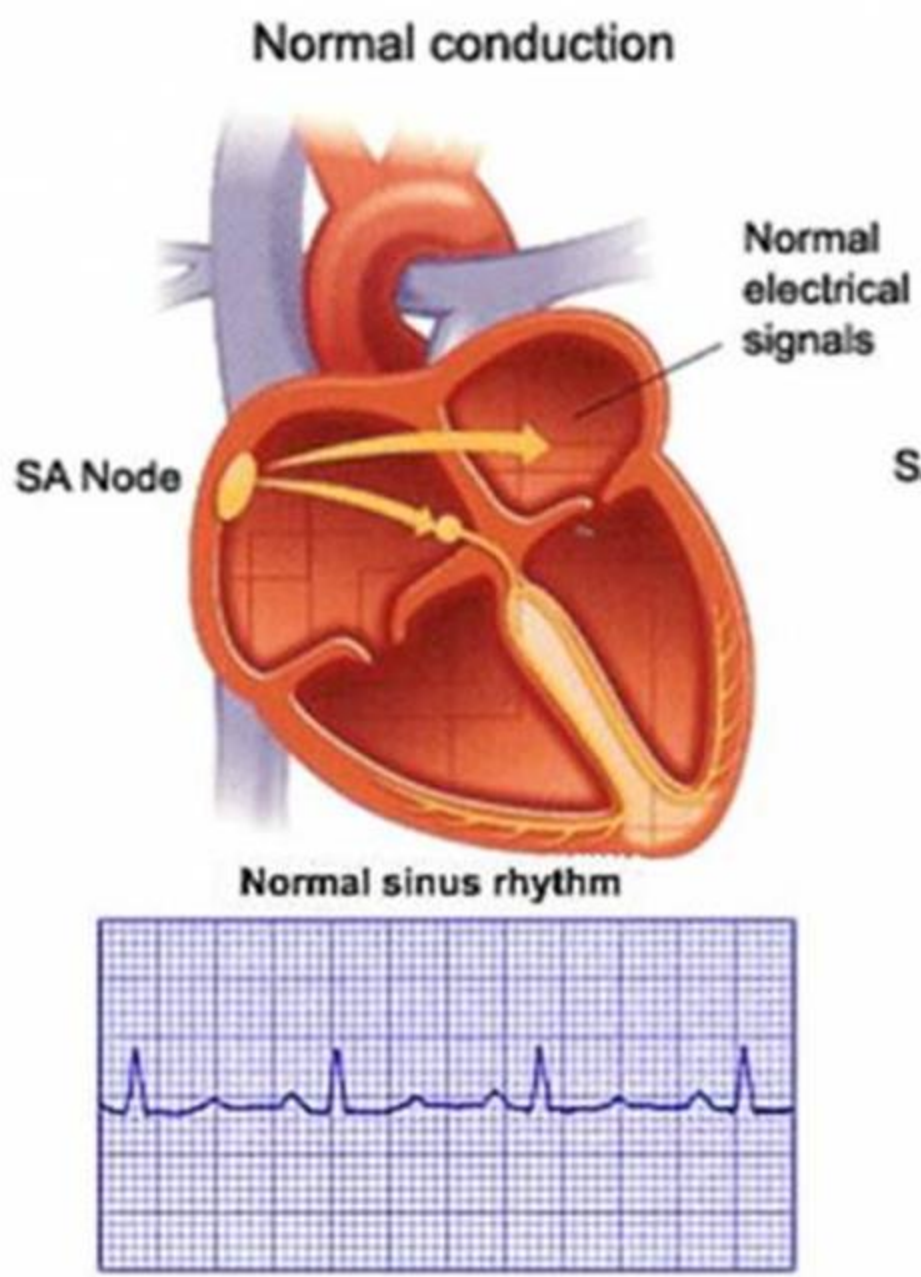
B. Ventricular arrhythmia:

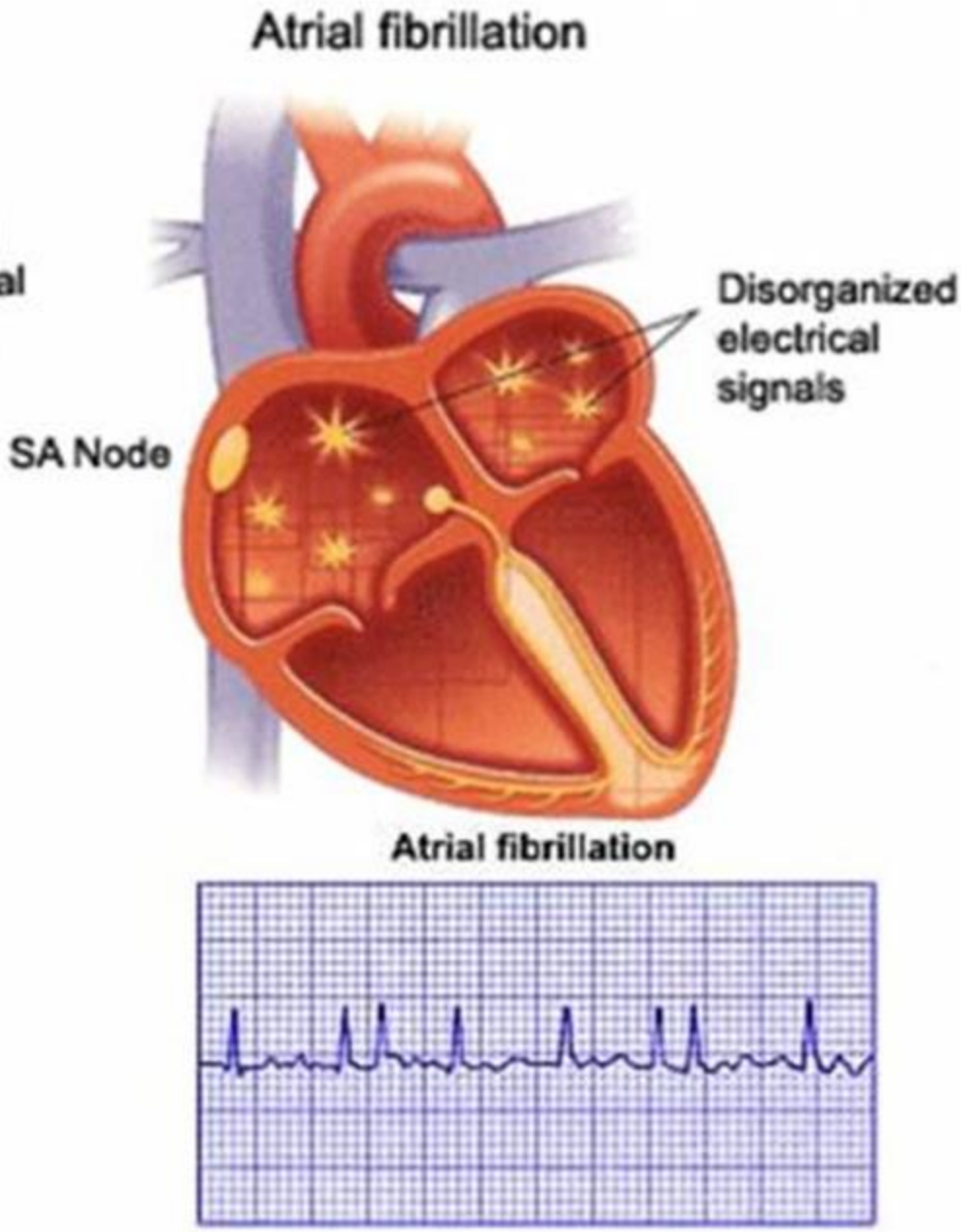
i. **Ectopic beats: ventricular premature contractions.**
ii. **Ventricular tachycardia (monomorphic or poly morphic).**
iii. **Ventricular fibrillation.**
iv. **Torsade de pointes and asystole**

C. Partial and complete AV conduction block

N.B. Ventricular arrhythmias are life-threatening.
N.B. Underlined disorders are due ectopic rhythms (away from SA node)

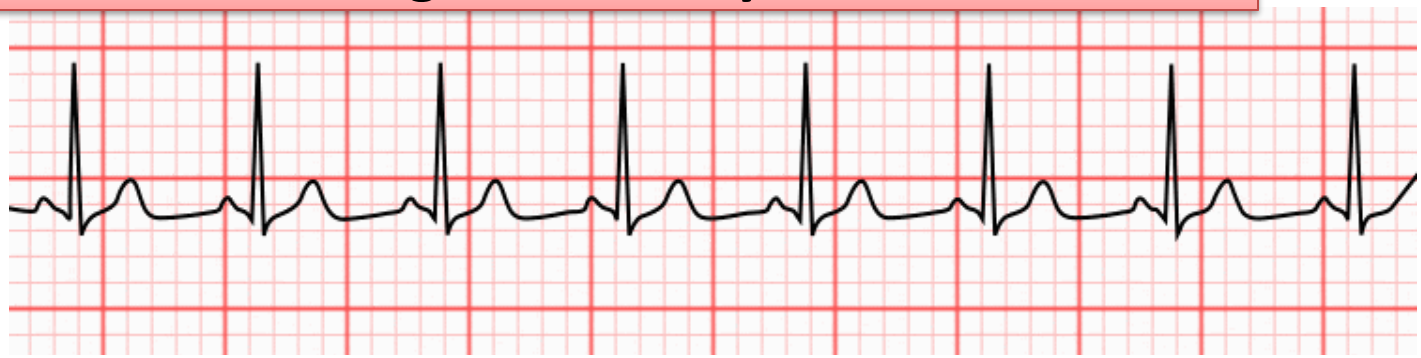
ECG for diagnosis of arrythmias



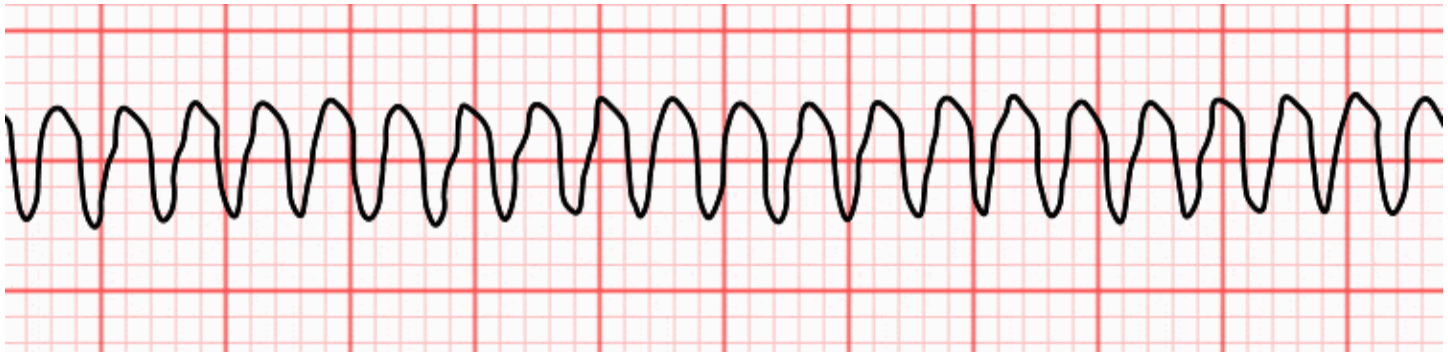


ECG for diagnosis of arrythmias

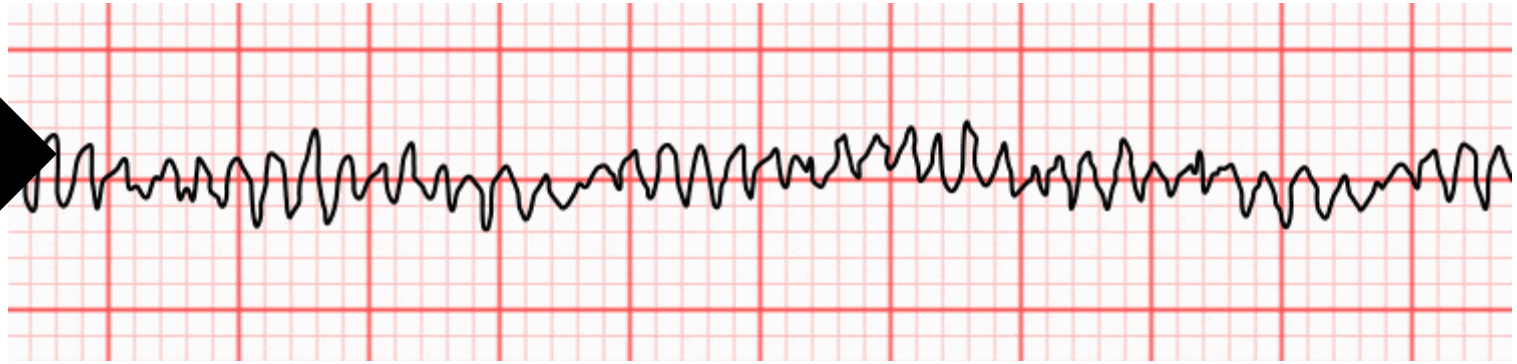
Normal sinus rhythm



VTC



VF



VTC= ventricular tachycardia; VF= ventricular fibrillation

Goals of treatment of arrhythmias

- To **terminate** already present arrhythmias.
- To **prevent recurrence** of arrhythmias in susceptible patients.
- To **protect ventricles** against arrhythmias during atrial arrhythmias.
- To **Restore** normal sinus rhythms.

Management of cardiac arrhythmias

1- Non-pharmacological approach:

Pacemaker *or catheter ablation,* ***Implantable cardioverter/ defibrillator*** , Direct current (**DC**) electrical shock (***cardioversion***).

2-Avoid and treat predisposing factors

3- Using Antiarrhythmic drug therapy.

Class	Mechanism	Example
I	Na channel blockers Membrane Stabilisers	Lignocaine
II	Beta Blockers	Metoprolol
III	K channel blockers	Amiodarone
IV	Ca channel blockers	Verapamil
Other	Digoxin. Adenosine. MgSO4. Atropine	

Classification of anti-arrhythmic drugs

Type IA
- Disopyramide
- Procainamide
- Quinidine

Type IB
- Lidocaine
- Mexiletine

Type IC
- Flecainide
- Propafenone

Type II
- Beta blockers (e.g., propranolol)

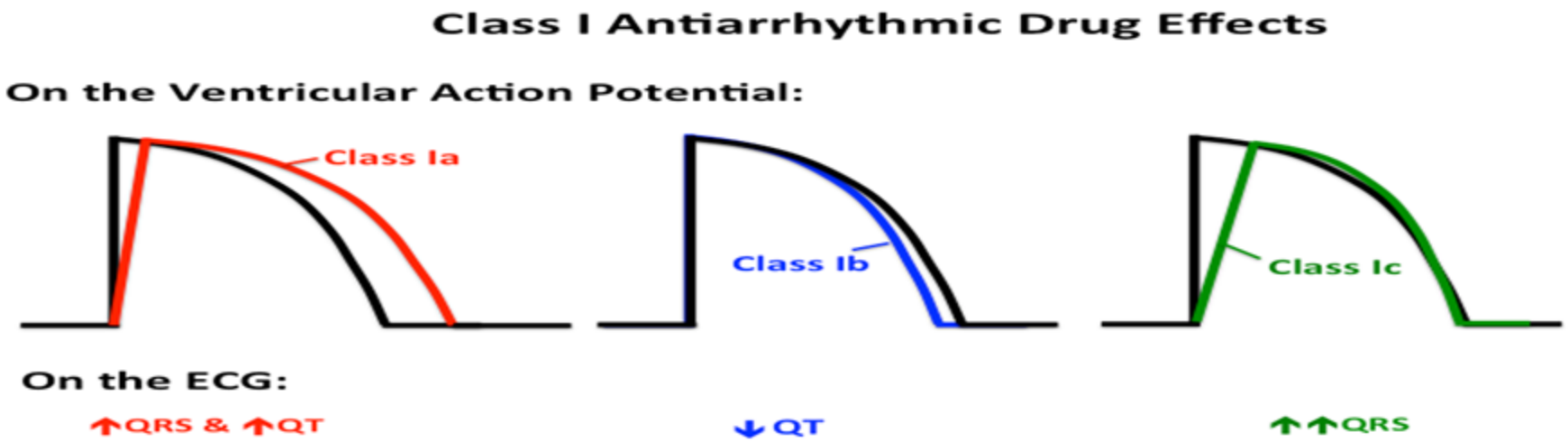
Type III
- Amiodarone
- Bretylium
- Dofetilide
- Ibutilide
- Sotalol

Type IV
- Nondihydropyridine calcium channel antagonists (verapamil and diltiazem)

SUBGROUP 1A

1-quinidine

1. **Blocking Na+ channels:**
   1. Suppresses ectopic activity and terminating abnormal automaticity.
   2. Depresses conduction velocity and terminate abnormal reentry.
2. **Blocking K+ channels:** Prolonging AP duration and ERP in ventricular muscles (i.e. increases refractoriness).
3. **Additional autonomic actions:**
   A. atropine like action.
   B. Alpha adrenergic blocking action.



Therapeutic uses: orally

1- Supraventricular arrhythmias:

- Treatment of paroxysmal Supraventricular tachycardia.
- Prevention of recurrence of atrial fibrillation and atrial flutter after **cardioversion** (direct current will restore sinus rhythm) and quinidine will prevent the recurrence of ectopic pacemakers.
- **Co-medications** with quinidine in case of AF (**Anti-coagulants** + **verapamil** or **Beta blockers**).

2-Ventricular arrhythmias:

- Treatment of ventricular extrasystole.
- Prevention of recurrence of paroxysmal ventricular tachycardia after cardioversion.

N.B. **I.V. quinidine** may be used in the treatment of ***acute malaria***.

Treatment of atrial fibrillations (AF)

A) Before treatment of atrial fibrillation, we need to:

1. Decrease A-V nodal conduction by β-blockers (as esmolol), or Ca^{++} channel blockers (as verapamil) or digoxin to protect the ventricles from receiving rapid atrial impulses.
2. **Use of anticoagulant drugs** as AF is usually associated with stagnation of blood with thrombosis in the atrium.

B) Termination of atrial fibrillation: **cardioversion will restore sinus rhythm.**

C) ***Prevention of recurrence of atrial fibrillation:***

After correction of atrial fibrillation, the sinus rhythm is maintained using quinidine, amiodarone or dofetilide.

Adverse effects of quinidine

i- Cardiac toxicity (CVS depression)

1- Quinidine syndrome or syncope (Torsade de pointes):

- *Manifested by recurrent light headedness and syncope.*
- *Polymorphic & disorganized **ventricular tachycardia** and can leads to sudden death.*
- Torsade de pointes is due to blocking of K^+ channels.

2- Embolism with old standing AF: intra-arterial thrombi → which become dislodged on conversion to sinus rhythm by quinidine.

3- Decrease the myocardial contraction: worsen **heart failure.**

4- Hypotension especially with I.V. quinidine.

5- A-V nodal block and S-A nodal block.

ii- Atropine- like actions

In some individuals, quinidine may increase the ventricular rate producing ***paradoxical ventricular tachycardia.***

iii- Extracardiac toxicity

1. ***GIT toxicity***: nausea, vomiting & diarrhea (occurs in 20%).

2. ***Cinchonism:*** as it is obtained from cinchona plant (**tinnitus**, **hearing loss**, **blurring of vision**, headache, diplopia, **photophobia**, confusion and **psychosis**).

3. ***Hypersensitivity reactions***: fever, thrombocytopenia and hepatic dysfunction.

N.B. Quinidine ***Increase the level serum digoxin and enhance its toxicity***: due to its displacement from tissue binding and by decreasing its renal excretion.

This is a dangerous drug-drug interaction.

Contraindications of quinidine

1. AV conduction block (worsen).
2. Hypotension (worsen).
3. History of embolism.
4. Old standing atrial fibrillation.
5. Congestive heart failure (negative inotropic worsen the case).
6. Arrhythmias due to digitalis intoxication.
7. Myasthenia gravis: aggravate the condition

2- Disopyramide

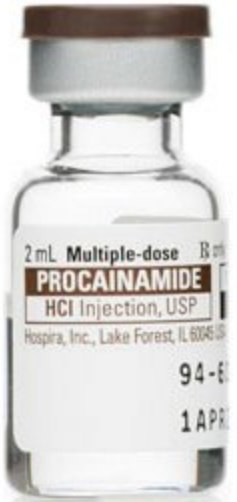
It is like quinidine but differ in

1. It has **no α-adrenergic receptors blocking activity**.
2. It has **more anti-cholinergic activity** (can cause dry mouth, blurred vision, glaucoma and urinary retention).

3-Procainamide

Like quinidine in pharmacological effects and uses but differ in:

- It lacks the atropine-like action of quinidine.
- It is better tolerated than quinidine when given I.V. infusion in emergencies.
- It causes more hypotension due to blocking of α-adrenergic receptors and autonomic ganglia.
- It **does not cause Cinchonism.**
- It is metabolized in the liver by acetylation and there are fast and slow acetylators.
- It may cause SLE-like syndrome in 30 % of patients, more common in slow acetylators as it is dose-dependent side effect.



SUBGROUP 1 B

Lidocaine

-It is a local anesthetic and anti-arrhythmic drug.

Mechanism : blocking of activated and inactivated Na+ -channels.

- ✓ It decreases conduction velocity (terminate reentry).
- ✓ Highly effective in **suppressing arrhythmias associated with ischemia and digitalis toxicity** but relatively ineffective against atrial flutter and atrial fibrillation.
- ✓ **Lidocaine is effective in ventricular arrhythmias only.**
- ✓ Group 1 B causes shortening of ERP.
- ➢ Therapeutic doses **do not affect contraction** or vascular resistance.
- ➢ Lidocaine is the least cardiotoxic & hypotensive anti-arrhythmic drug.

Pharmacokinetics:

1) It has an extensive first-pass metabolism in the liver, so it is used **only I.V**. for antiarrhythmic applications.
2) It crosses BBB producing CNS excitation.
3) It has rapid onset and short duration of action ($t_{½}$ is 2 h.), so suitable in emergent ventricular arrhythmia.

Therapeutic uses in arrythmia:

Lidocaine (I.V.) is used in ventricular arrhythmias caused by Myocardial infarction, Open heart surgery and Digitalis intoxication.

- **Adverse effects of lidocaine**

1. ***CNS stimulation:*** confusion, tremors, convulsion & then CNS depression.
2. **Hypersensitivity reactions**.
3. **Hypotension if given by large doses**.

2- Tocainide

- It is a **lidocaine analog**, but it is **used only orally.**
- The major adverse effects are **tremor and nausea**.
- It is rarely used now (it may cause fatal bone marrow aplasia and pulmonary fibrosis).

3- Mexiletine

- It is like lidocaine in actions and uses but given only ***orally***.
- May cause CNS symptoms (dizziness, light headedness and tremors) and GIT symptoms (nausea and vomiting).

4- Phenytoin

- It is antiepileptic and antiarrhythmic drug
- It **blocks** the inactivated **cardiac Na^+ channels.**
- It has a **depressant effect on the sympathetic centers** in CNS especially in cases of **digitalis toxicity.**

SUBGROUP 1C

1-Flecainide 2-Propafenone (related to propranolol). 3- Moricizine

- They are the most potent antiarrhythmic drugs (blocking Na –channels) in all cardiac cells including anomalous in A-V pathway which causes Wolff Parkinson White Syndrome (WPWS).

Therapeutic uses: Severe life-threatening ventricular tachyarrhythmia & WPWS.

Side effects:

1. They may aggravate preexisting arrhythmia or induce new one.
2. Increase the incidence of sudden death in patients taken drug than the placebo (non-taken).

Group 2 (beta-adrenergic blockers)

- **Propranolol**, metoprolol and esmolol, carvedilol and others.

Mechanisms: They block beta adrenoceptors in cardiac tissues; propranolol also blocks sodium channels (quinidine-like action).

Uses in arrythmias

1. They are used in supraventricular arrythmias to decrease AV conduction and protect the ventricles from high atrial rates.
2. They are used in treatment of sinus tachycardia especially when sympathetic over activity exist
3. Treatment of ventricular arrythmias and vent. Extrasystole.

Adverse effect:

1 A-V block and bradycardia.

2- Cardiac failure.

3-Bronchospasm.

4- Potentiate hypoglycemia of insulin.

Group 3 (K^+ CHANNEL BLOCKERS)

General characters:

1. They **prolong repolarization** and increase action potential duration due to blocking of K channel. They **Prolong Q-T interval in the ECG**.
2. They **block other channels** or **autonomic functions** except **dofetilide** which is a **pure potassium channel blocker**).

1- Amiodarone

Pharmacological effects:

- It **blocks K^+-channels, Na+-channels**, **Ca++ channels**, **beta and α-adrenergic receptors** causing:

1. Marked prolongation of action potential duration **& ERP of atrium, ventricle and A-V node**.
2. **Decrease in the conduction** of A-V node.
3. **Reduction of both normal** and abnormal **automaticity.**
4. Peripheral **vascular dilation** due to Ca^{++} and α-blocking activity.

- **It has Structural analog to thyroid hormone.**

Pharmacokinetics:

Used orally, has delayed onset and long duration; **t ½ (25-60 days),** so it is used in **high loading dose** for 2 weeks, followed by low maintenance dose once/day.

Therapeutic uses: in both atrial and ventricular arrhythmias.

1. It is used to maintain sinus rhythm in patients with atrial fibrillation.
2. Treating ventricular fibrillation "if resists Lidocaine & cardioversion".
3. Recurrent unstable sustained ventricular tachycardia.

Side effects:

1. **Corneal microdeposits** (due to deposition of drug in cornea).
2. **Thyroid dysfunction**: hypothyroidism or hyperthyroidism.
3. Reversible **pulmonary fibrosis** which may be fatal.
4. **Cardiac toxicity**: bradycardia, A-V block, paradoxical ventricular arrhythmia (Torsade de pointes, but unusual) + heart failure & hypotension.
5. **Hepatic injury.**
6. **Photosensitivity** due to deposition of the drug in the skin.

Dronedarone (non-toxic amiodarone)

- **Dronedarone** is a structural analog of amiodarone in which the iodine atoms have been removed.
- So, dronedarone is free of thyroid dysfunction or pulmonary toxicity.
- The drug has a **half-life of 24 hours.**
- Dronedarone absorption increases twofold to threefold when taken with food.
- Dronedarone is both a **substrate and an inhibitor of CY3A4.**

2- Sotalol

- Sotalol is a non-selective beta-adrenergic blocker that prolongs the cardiac action potential due to K^+-channel blocking activity.
- It can be used in **atrial and ventricular arrhythmias.**
- Side effects as beta-blockers (bradycardia, A-V block and heart failure) and torsade de pointes only with high doses or in presence of **renal dysfunction**.

3- Bretylium

It is a norepinephrine release inhibitor (adrenergic neuron blocker) and K channel Blocker; It is used for the prophylaxis and therapy of ventricular fibrillation, as well as the treatment of life-threatening ventricular arrhythmias.

4- Dofetilide

- **it is a pure K^+-channel blocker,** used to maintain sinus rhythm after cardioversion correction of atrial flutter or fibrillation.
- The main side effect is the risk of torsade de pointes (polymorphic ventricular tachycardia), as it can cause dose-related Q-T interval prolongation.

5- Ibutilide

It is a Class III antiarrhythmic agent available in **intravenous formulations**. It is indicated for the **conversion of acute atrial flutter and recent onset atrial fibrillation to normal sinus rhythm .**

Group 4 (Ca^{++} channel blockers)

The non-dihydropyridine calcium channel blockers (**verapamil**) exhibit antiarrhythmic effects predominately at the **AV-node** via blocking of slow inward Calcium current.

Uses

1- to protect ventricles from **supraventricular arrythmias.**

2- the utility in **ventricular tachycardia** is less clear; they could be adjunctive to other medications.

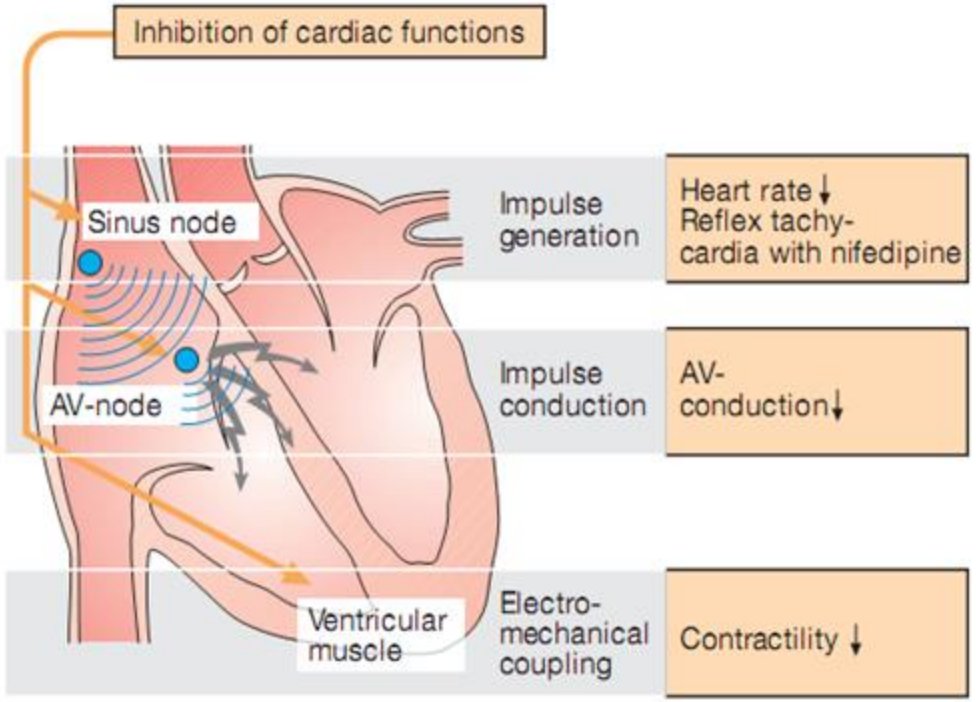
Adverse effects:

1- Bradycardia.

2- AV block.

3- Cardiac failure.

4- Constipation with verapamil.



Group 5 (Miscellaneous antiarrhythmic drugs)

1- Adenosine

- It is an endogenous purine nucleotide that binds to adenosine receptors type 1 (A1) which is G-protein coupled receptor causing **inhibition of cAMP-mediated Ca^{++} influx** in atrial and nodal tissues

Therapeutic uses:

1. Effective **only in atrial arrhythmia**, it is the ***drug of choice*** in treatment **of paroxysmal supraventricular tachycardia** (due to its short duration and less myocardial depression).
- It is used by ***bolus I.V.*** injection, it has very short duration of action ($t_{½}$ is less than 10 seconds) due to rapid metabolism. If it is given slowly, it will be metabolized before reaching the heart.

1. It is used to induce controlled hypotension during surgery.
2. It is used for diagnosis of coronary artery disease.

Side effects:

1. Flushing and chest pain in 20 %
2. Theophylline and caffeine block its receptors, so they decrease its effect

2- Magnesium

- I.V. Mg SO_4 is effective in:

1-Digitalis induced arrhythmias if hypomagnesemia is present.

2- Some cases of torsades de pointes and acute myocardial infarction even if serum Mg^{++} is normal.

3- Digoxin

- It inhibits Na+/K+ATPase. Used in treatment of heart failure.
- Used to protect ventricles from atrial fibrillations.

4- Ranolazine

- Anti-anginal drug.It is a a new agent in the control of AF.

5- Ivabradine

Ivabradine functions in a use-dependent fashion at the **SA node**, and lowering heart rate (bradycardic drug) without affecting inotropy or vascular resistance.

The adverse effects of ivabradine are related to symptomatic bradycardia.

Remember

- **Atropine is the first line drug for treating bradycardia and AV block.**
- **Also, Administration of isoproterenol may facilitate both normal and depressed conduction in the A-V node and His-Purkinje system.**
- **However, Permanent pacing is the therapy of choice in patients with symptomatic atrioventricular (AV) block with bradycardia.**


THANK
YOU