بسم الله الرحمن الرحيم

Pharmacology of CVS

Lecture 1: Cardiac arrhythmias: Types, mechanisms and drugs

By

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Introduction

Conducting system vs contractile tissue of the heart

Conducting System:

SA node, AV node, Purkinj fibers

Contractile tissues

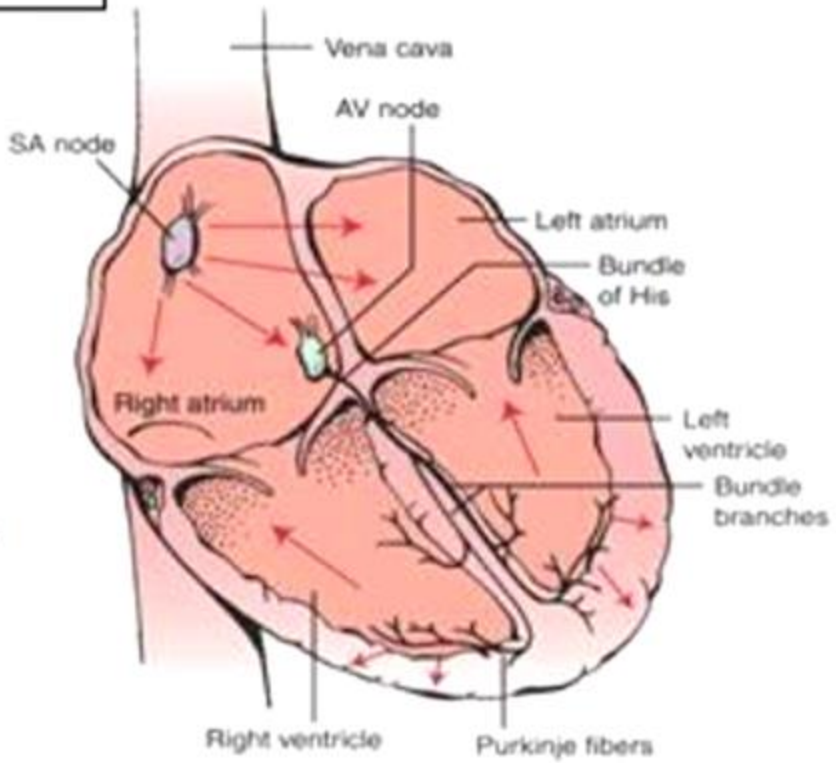
Atrial & Ventricular muscles

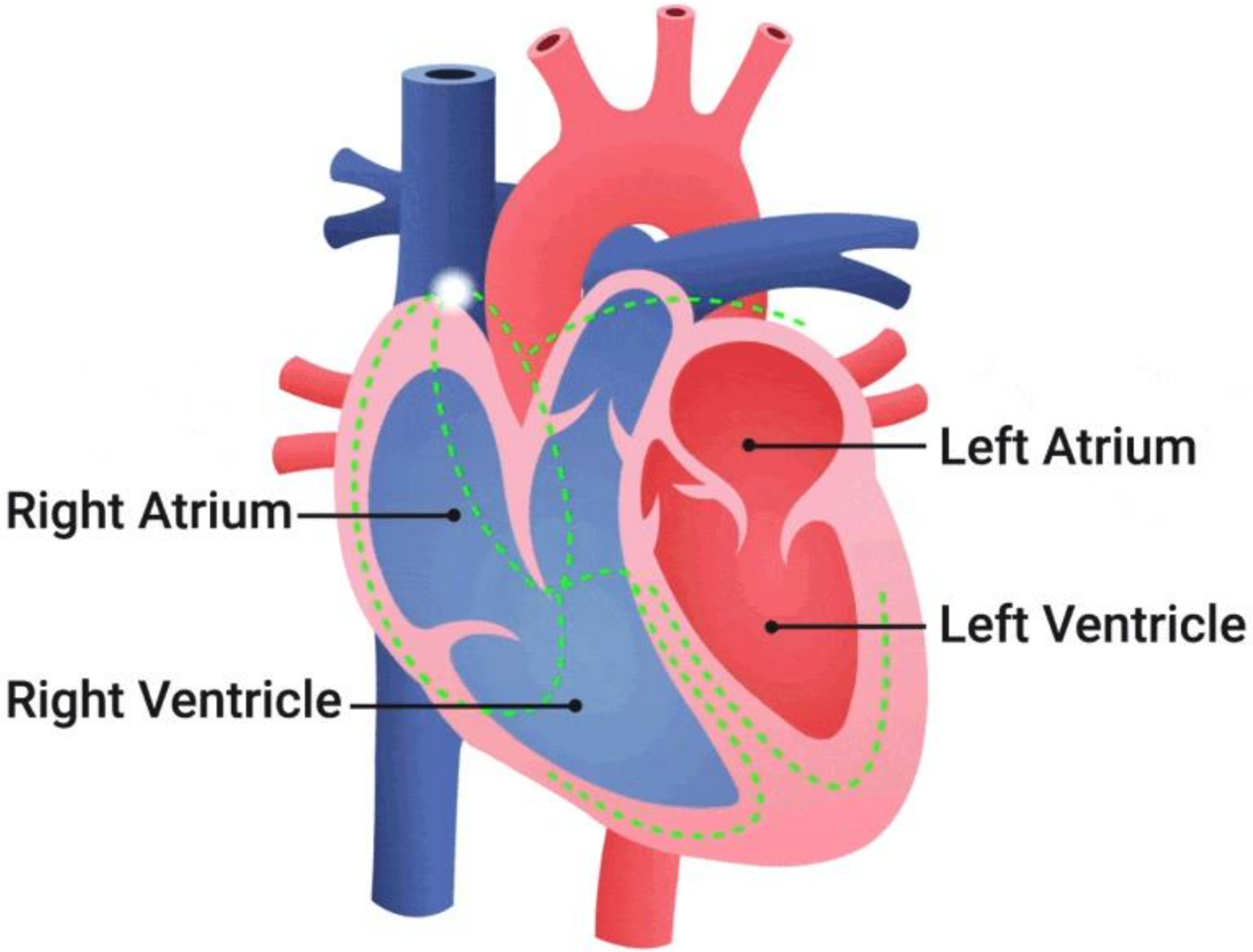
Impulse Propagation:

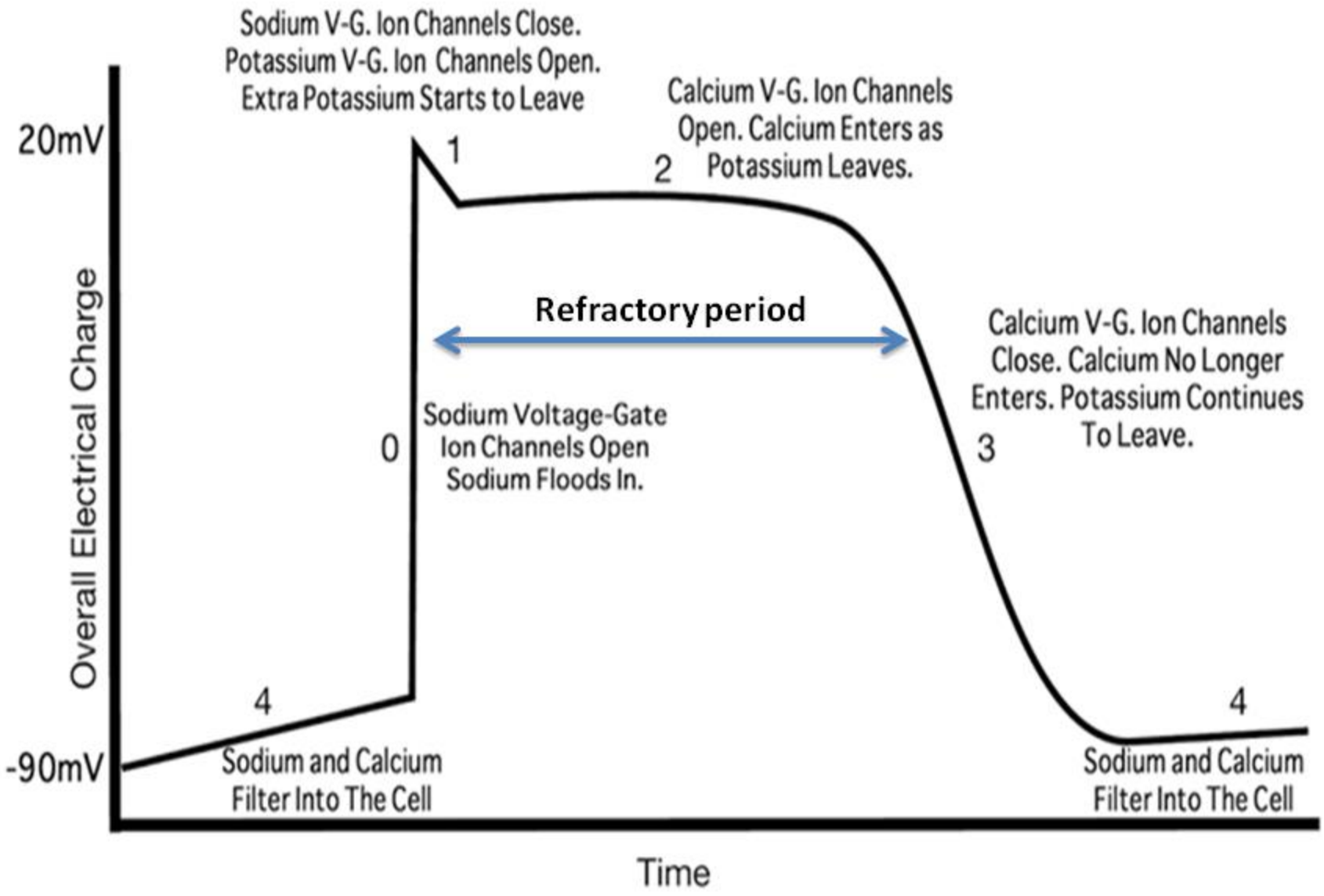
- SA node → AV-node → Bundle of His → Purkinje fibers → ventricle.

- SA node is the initial pacemaker.

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




Left Atrium
Right Atrium
Left Ventricle
Right Ventricle


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 properties in relation to the phases of action potential

1. **Automaticity:** is represented by spontaneous depolarization (phase 4).

2. **Conduction**: is 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.

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 like 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).

Types of cardiac arrhythmias

A. Supraventricular (atrial) arrhythmia:

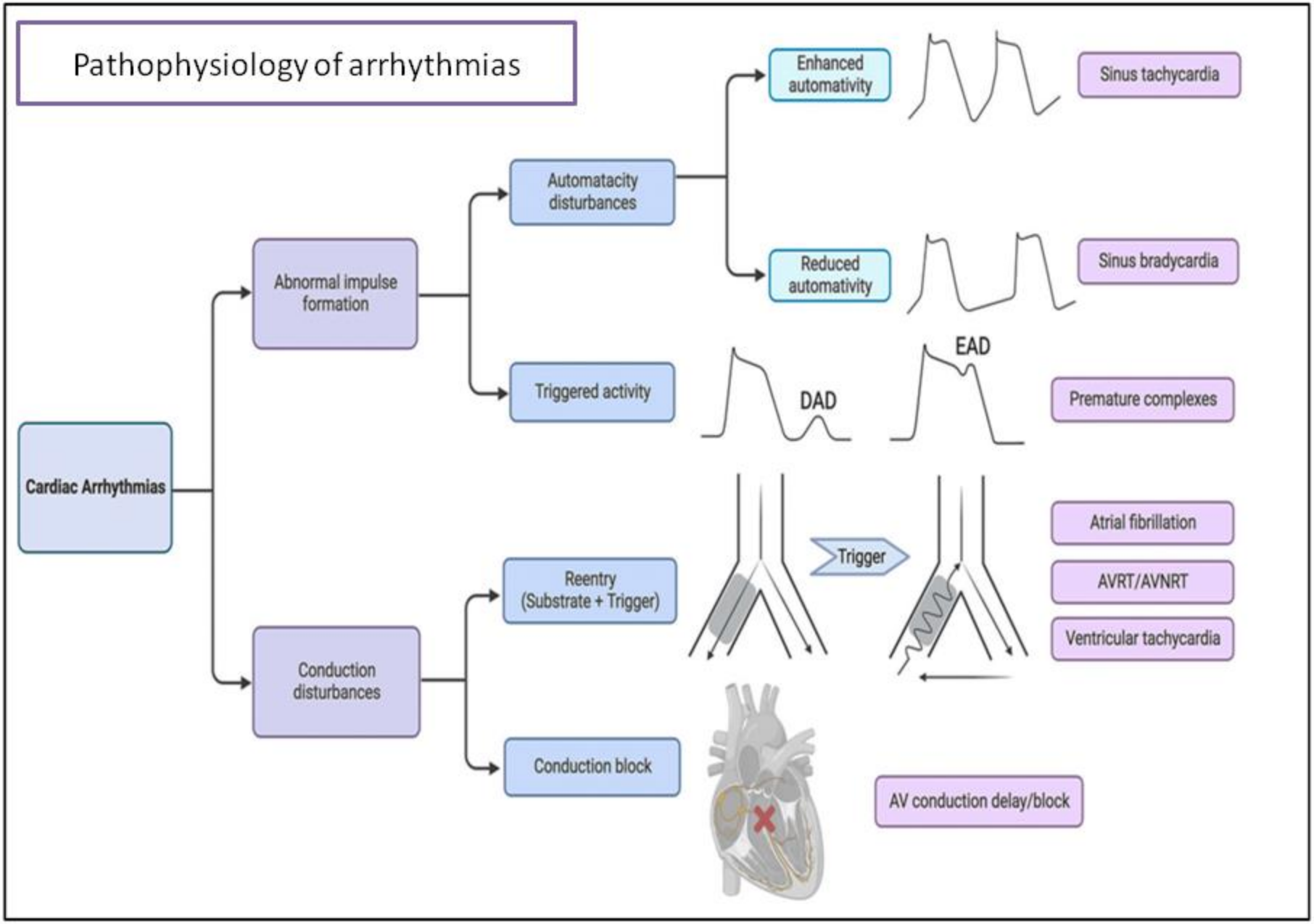
1. Sinus tachycardia (pulse more than 100 beats / min.).
2. Sinus bradycardia (pulse less than 60 beats / min.)
3. **Supraventricular tachycardia,**
4. **Atrial flutter (regular fast)**
5. **Atrial fibrillation (irregular fast)**

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)



DAD= delayed after depolarization

EAD= Early after depolarization

AVRT =Atrioventricular Re-entry Tachycardia

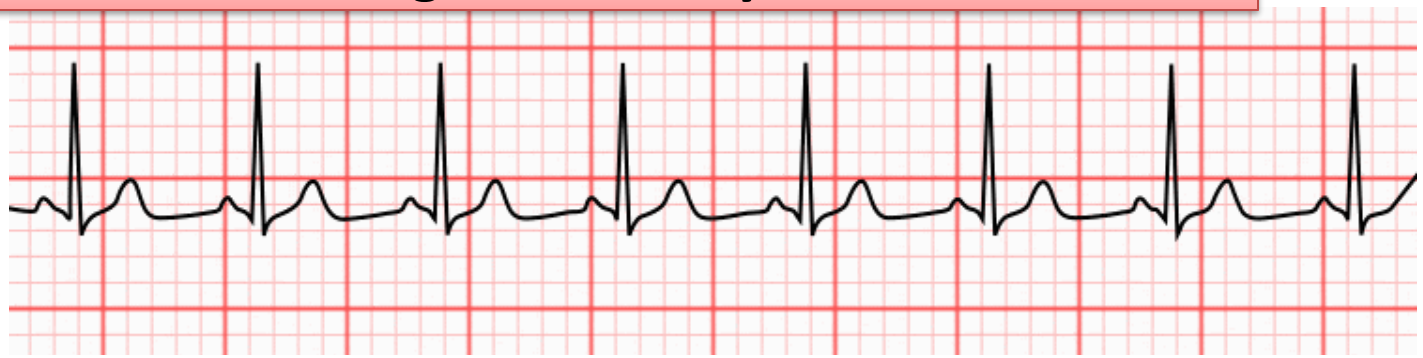
AVNRT= Atrioventricular nodal reentrant tachycardia

5 Symptoms of Cardiac Arrhythmia

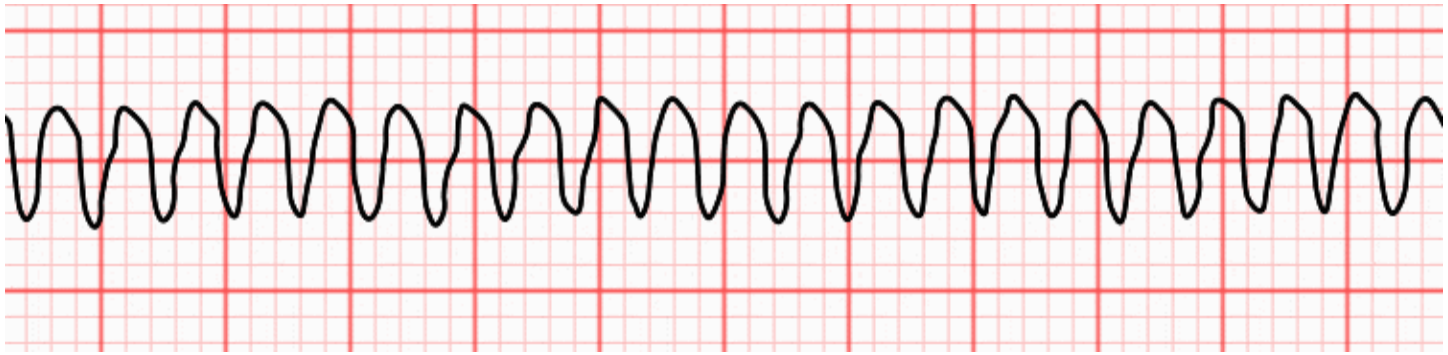
- Palpitations, heart pounding
- Panting
- Chest pain
- Dizziness
- Fainting or falling unconscious

ECG for diagnosis of arrythmias

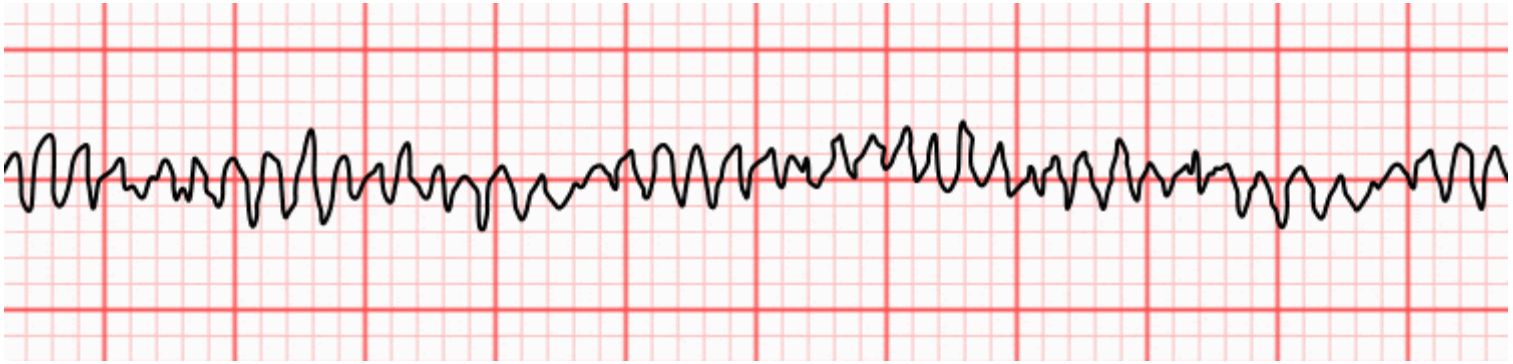
Normal sinus rhythm



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 sinus rhythm.**

Management of cardiac arrhythmias

1- Non-pharmacological approach:

i. ***Pacemaker*** *or catheter ablation.*

ii. ***Implantable cardioverter / defibrillator*** *(ICD).*

iii. Direct current (DC) electrical shock (***cardioversion***).

2-Antiarrhythmic drug therapy.

3- Avoid and treat predisposing factors.

Disadvantages of antiarrhythmic drugs:

1. Most of antiarrhythmic drugs have **limited efficacy**
2. **They** may be **pro-arrhythmic**
3. They may increase the mortality rate in some patients.

✓ For these reasons, it is better to start with non-pharmacological therapy alone or with antiarrhythmic drugs.

Classification of anti-arrhythmic drugs into classes, groups or types

Vaughan-Williams Classification

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

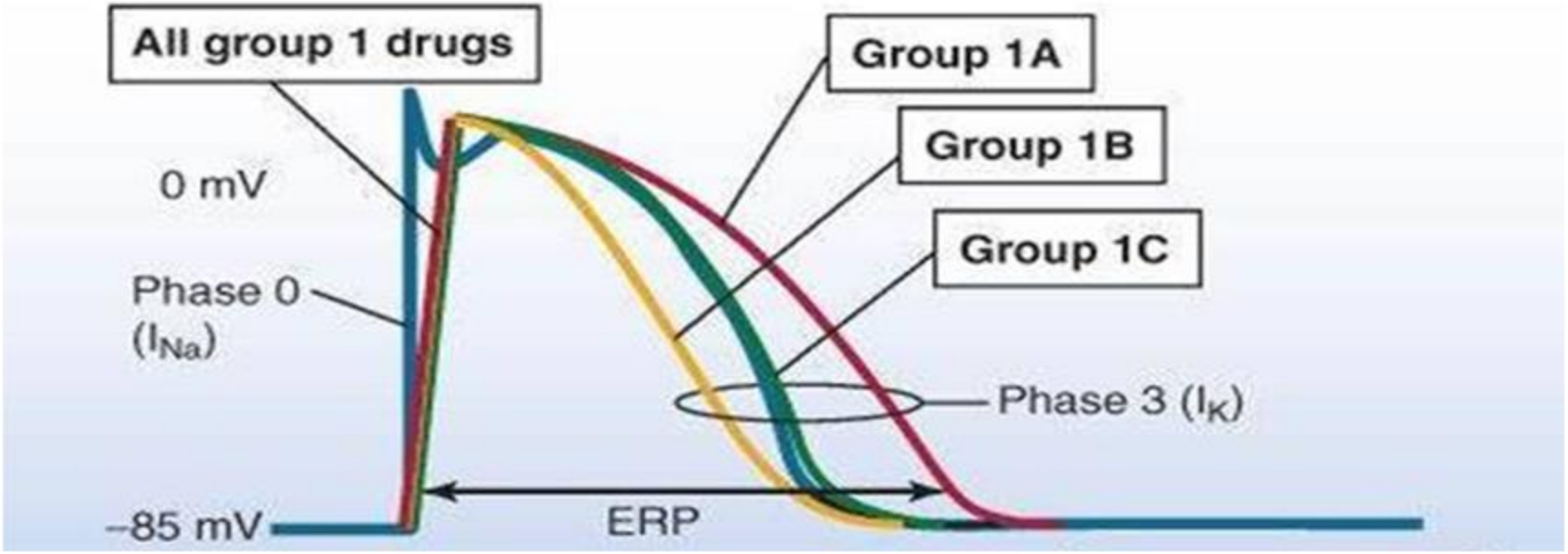
Type IC
- Flecainide
- Propafenone

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

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

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

Group 1 anti-arrhythmic drugs



Class I Antiarrhythmic Drug Effects

On the Ventricular Action Potential:

On the ECG:

↑QRS & ↑QT

↓QT

↑↑QRS

SUBGROUP 1A

1-quinidine

Mechanisms and actions

1. **Blocking Na+ channels:**
    1. Suppresses ectopic activity and terminating abnormal automaticity.
    2. Depresses conduction velocity and terminate abnormal reentry.
2. **Blocking K+ channels:**
    1. 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

a) Supraventricular arrhythmias:

1. Treatment of paroxysmal Supraventricular tachycardia.
2. 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.

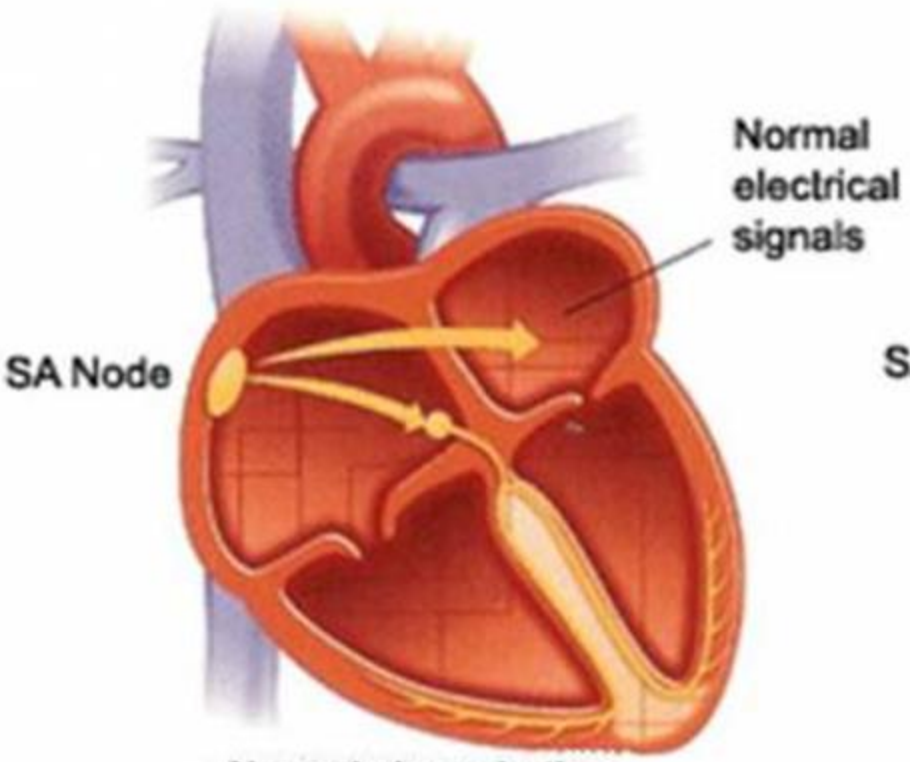
➢ **Co-medications** with quinidine in case of AF (**Anti-coagulants** + **verapamil** or **Beta blockers**).

b) Ventricular arrhythmias:

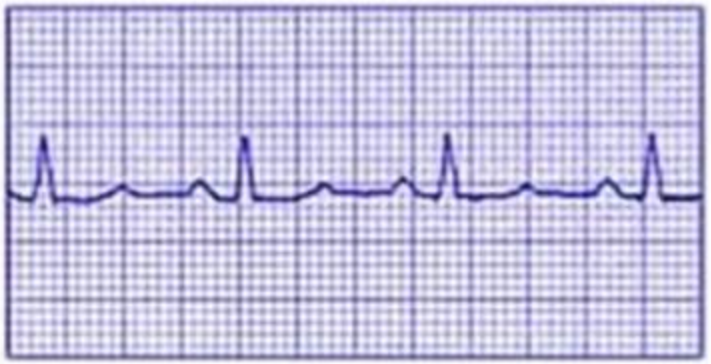
1. Treatment of ventricular extrasystole.
2. Prevention of recurrence of paroxysmal ventricular tachycardia after cardioversion.

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

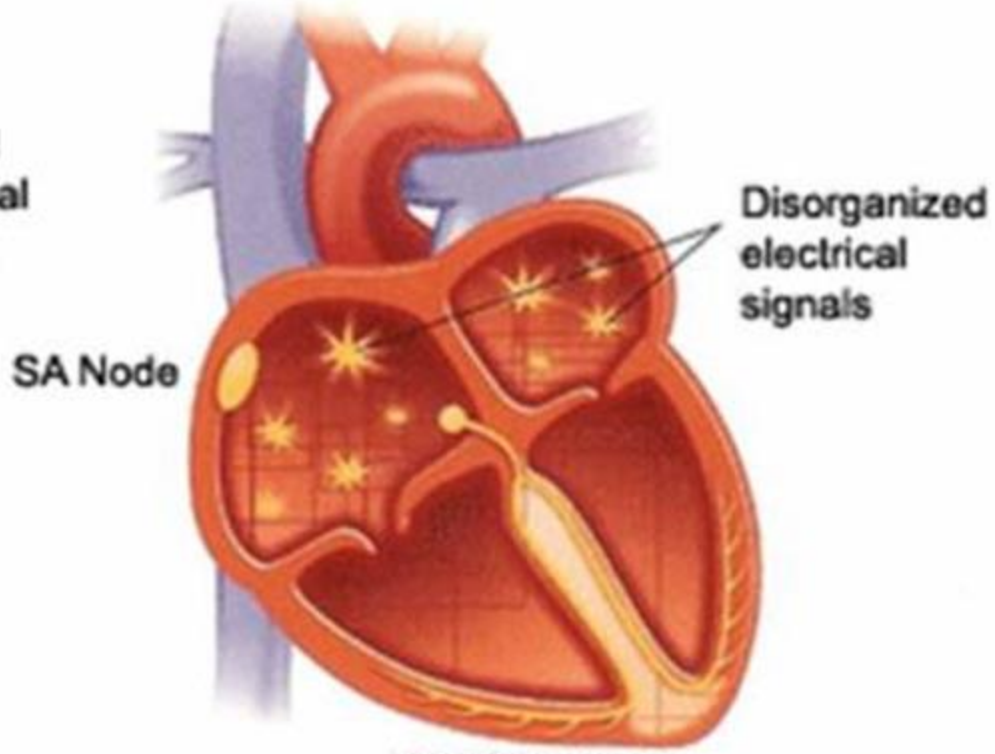
Normal conduction



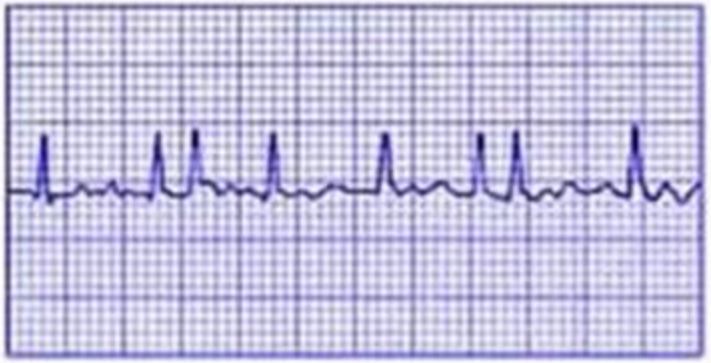
Normal sinus rhythm



Atrial fibrillation



Atrial fibrillation



N.B. Treatment of atrial fibrillation:

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

1. Block of A-V nodal conduction by β-blockers (as esmolol), or Ca^{++} channel blockers (as verapamil) or digoxin to decrease the A-V nodal conduction, so protect the ventricles from receiving rapid atrial impulses.
2. The use of anticoagulant 3 weeks before and 4 weeks after the use of these drugs as atrial fibrillation 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* (Torsade de pointes) *and can leads to sudden death.*
- Torsade de pointes is due to blocking of K^+ channels.

2- Embolism with old standing AF: because of AF, blood stagnation occurs leading to 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.

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

DON'T GIVE QUINIDINE AFTER DIGOXIN

ii- Atropine- like actions

In some individuals, quinidine may increase AV conduction and ventricular rate in producing ***paradoxical ventricular tachycardia***.

iii- Extracardiac toxicity

1. ***GIT toxicity***: nausea, vomiting and **diarrhea** (diarrhea is common & 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.

2-Procainamide

Like quinidine in pharmacological effects and uses but differ in:

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

3-Disopyramide

It resembles quinidine in its pharmacological effects and uses 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).

SUBGROUP 1 B

Lidocaine

-It is local anesthetic and anti-arrhythmic.

Mechanism of antiarrhythmic action: It acts by **blocking of activated and inactivated Na+ -channels**.

- ✓ Na+ channel blockade decrease 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.**
- ✓ **Lidocaine** does not affect atrial electrophysiology.
- ✓ Group 1 B causes **shortening of ERP and action potential duration**.

- ➢ Therapeutic doses **do not affect contraction** or vascular resistance (Lidocaine is the least cardiotoxic & least hypotensive anti-arrhythmic drug).

Pharmacokinetics:

1) If used orally there is 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 dysrhythmia.

Therapeutic uses in arrythmia:

Lidocaine (I.V.) is used in ventricular arrhythmias caused by:

1. Myocardial infarction.
2. Open heart surgery.
3. Digitalis intoxication.

- Effective, rapid onset & short duration.

Adverse effects of lidocaine

1. ***CNS stimulation:*** disorientation, confusion, tremors, convulsion & then finally CNS depression.
2. **Hypersensitivity reactions**.
3. **Hypotension** in high 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 if the activity of these centers is enhanced as in cases of **digitalis toxicity.**

SUBGROUP 1C

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

- They act by blocking of Na -channels.
- They are the most potent antiarrhythmic drugs that decrease in the conduction in all cardiac cells including anomalous in A-V pathway which causes Wolff Parkinson White Syndrome (WPWS).
- They cause minimum changes in ERP.

Therapeutic uses:

Effective in both atrial and ventricular arrhythmia but used mainly in:

a. Severe life-threatening ventricular tachyarrhythmia.
b. 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)

Members:

1. Amiodarone (the most widely used antiarrhythmic drug), and dronedarone.
2. Sotalol (non-selective Beta-blocker)
3. Bretylium (adrenergic neuron blocker)
4. Dofetilide (pure potassium channel blocker).

General characters:

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

1- Amiodarone

Pharmacological effects:

- It **blocks K^+-channels** causing marked prolongation of cardiac action potential duration. **It increases the ERP of atrium, ventricle and A-V node**
- It also **blocks Na+-channels**, **Ca++ channels**, **beta and α-adrenergic receptors.**
- It **reduces normal automaticity** (of S-A node) and abnormal automaticity
- It **decreases the conduction** of A-V node.
- Peripheral **vascular dilation** due to Ca^{++} channel blocking and α-blocking activity.
- **Structural analog to thyroid hormone** and binds to its receptors.

Pharmacokinetics:

- used orally, has delayed onset and longer duration of action.
- It has the longest **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. Treatment of ventricular fibrillation if it is resisted to lidocaine and 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** and can be administered twice daily at a fixed dose of 400 mg.
- 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,** resulting in prolongation of action potential.
- It is 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** and **diltiazem**) exhibit antiarrhythmic effects predominately at the **AV-node** via blocking of slow inward Calcium current, with minimal effects on atrial and ventricular myocytes or the His–Purkinje system.

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.

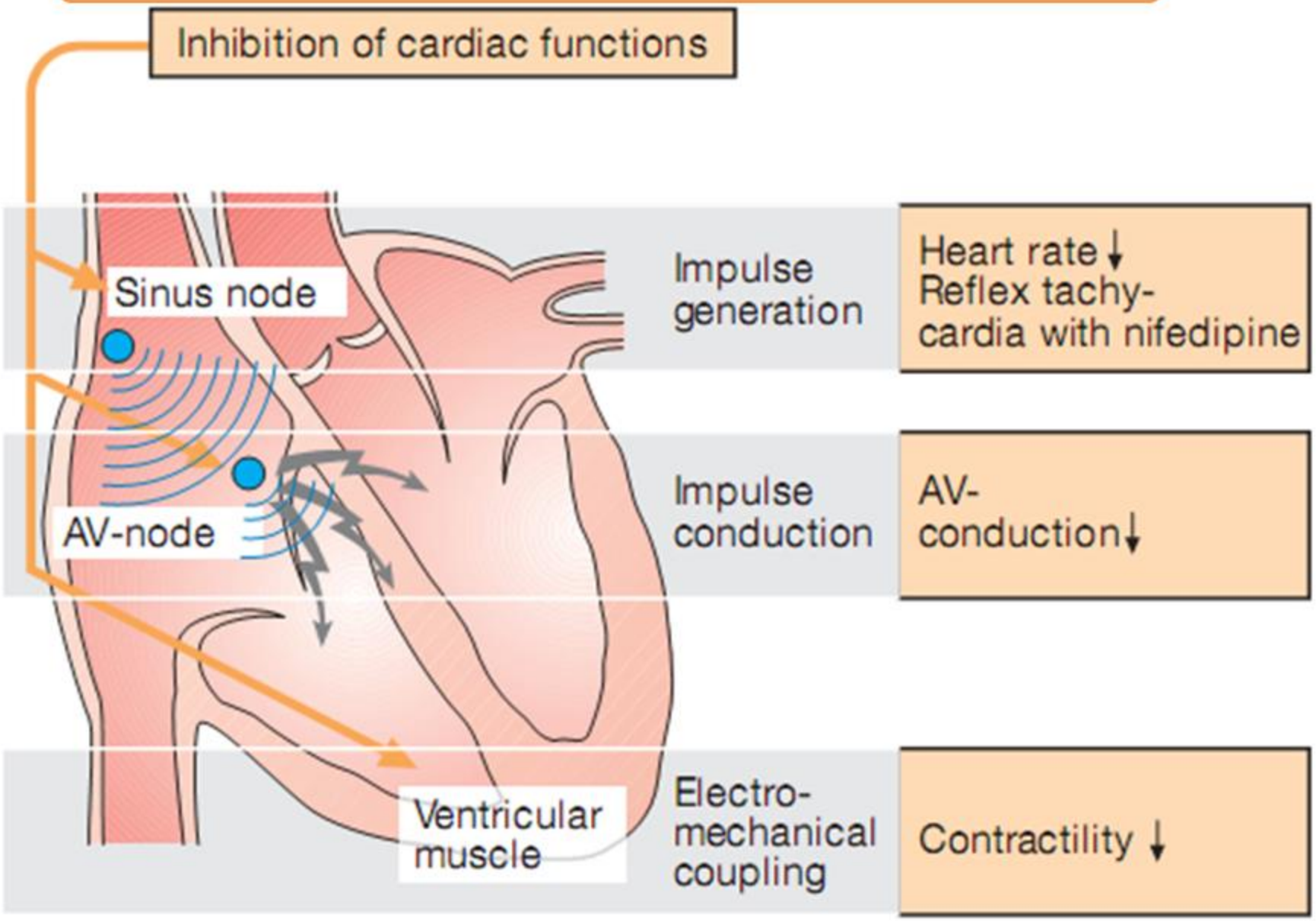
2- AV block.

3- Cardiac failure.

4- Constipation with verapamil.

N.B. Avoid combining verapamil with beta blockers to avoid severe cardiac depression

Cardiac effects of 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:
- Digitalis induced arrhythmias if hypomagnesemia is present.
- Some cases of torsades de pointes and acute myocardial infarction even if serum Mg^{++} is normal.

3- Digoxin

- Mechanism: **inhibition of Na+/K+ ATPase.**
- It causes decrease in both SA and AV nodal functions (partially through increased vagal activity). It increases cardiac contractility.
- Used to protect ventricles from supraventricular arrythmias like atrial fibrillations.

4- Ranolazine

- like amiodarone, blocking sodium, potassium, and calcium channels.
- The net effect is a concentration-dependent prolongation of action potential duration and an early decrease after depolarizations.
- It is a a new agent in the control of atrial fibrillation

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.**


merci
thank you
gracias
obrigado
danke
go raibh maith agat
grazie
спасибо
mochchakkeram
dakujem
sukriya
bedankt
arigato
ngiyabonga
terima kasih
sagolun
chokrane
dziekuje
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