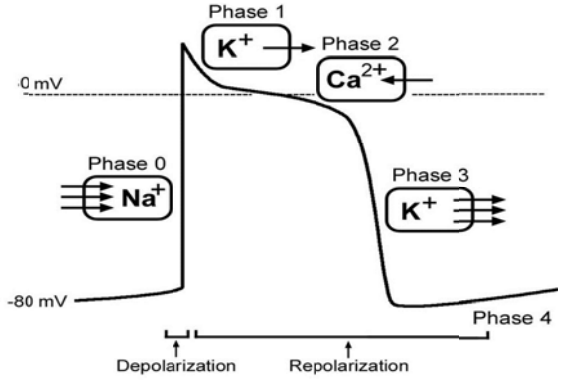
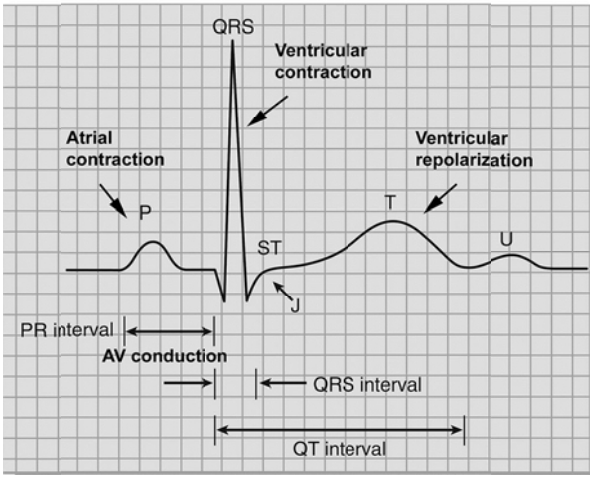
Part 6: Cardiac arrhythmia and antiarrhythmic drugs

Basic information

Cardiac action potential

- In the resting state, K^+ ions is found mainly intracellular, while Na^+ and Ca^{2+} are mainly extracellular making the interior of the cell electrically *negative*.
- Contraction and relaxation occur when rapid redistribution of ions across the cell membrane occurs during 4 phases known as **"action potential".**





Phases of action potential:

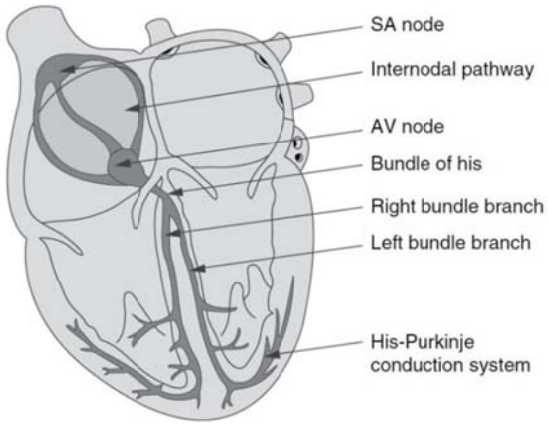
- **Phase 0:** rapid depolarization of the cell due to rapid influx of Na^+.
- **Phase 1:** short period of rapid re-polarization due to outflow of K^+.
- **Phase 2:** "plateau": delay in re-polarization due to slow influx of Ca^{++}.
- **Phase 3:** second period of rapid repolarization due to rapid out-flow of K^+.
- **Phase 4:** the resting state is restored. Na^+ ions are extruded out the cell and K^+ ions returns back by the Na^+/K^+ pump and so on.
- The slope of phase 4 determines when the 2nd action potential starts. When the slope is increased, the distance between 2 cardiac cycles shortens (i.e. tachycardia) and vice versa.

Impulse formation (automaticity)

- Cardiac **automaticity** refers to the ability of certain cells to self-generate electrical impulses that spread throughout the heart.
- Under normal conditions, the **SA node** is the dominant pacemaker (i.e. has the highest automaticity).
- Normal myocardial cells don't have automaticity i.e. cannot generate impulses.
- Under certain pathologic conditions, some myocardial cells may acquire spontaneous repetitive firing, this is called **abnormal automaticity** or **ectopy**. These **ectopic** pacemakers compete with the SA node for control of the heart.

Impulse conduction

- Electrical activity spreads from the **SA node** to the ventricles via the **AV node** and the **bundle of His**, and then down through the right and left **bundles**.
- In the **ECG**, the **P wave** represents the spread of depolarization wave through the atria (atrial contraction). The **QRS complex** represents the spread of depolarization wave through the ventricles (ventricular contraction). The **ST segment** and **T wave** represent ventricular repolarization (relaxation).



Cardiac arrhythmia

Arrhythmia means disturbance in the normal heart rhythm. It results from:

- Abnormal impulse generation;
- Abnormal impulse conduction;
- Both.

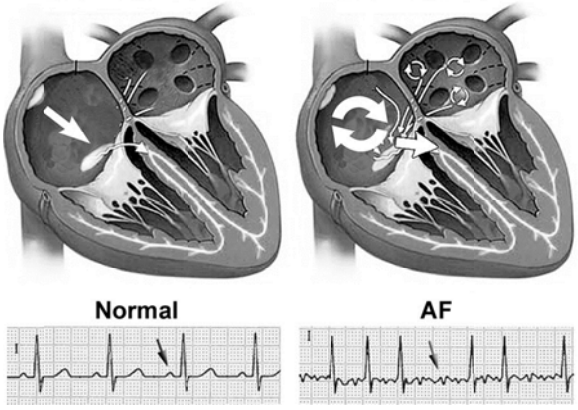
Abnormal impulse formation:

- **Nodal abnormality:** e.g. sinus tachycardia and sinus bradycardia.
- **Extranodal abnormality:** e.g. premature atrial or ventricular contractions (ectopic beats).

Abnormal impulse conduction

- **Re-entry:**

- This is a circus movement of an impulse that circulates around certain area in a unidirectional fashion and excites the conducting system more than once.
- It is the most common cause of **atrial flutter** and **fibrillation** (AF).
- Wolff–Parkinson–White syndrome (WPW) is an example of anatomically defined re-entry. WPW syndrome is an atrioventricular re-entrant tachycardia, secondary to an accessory AV conducting pathway (see before).

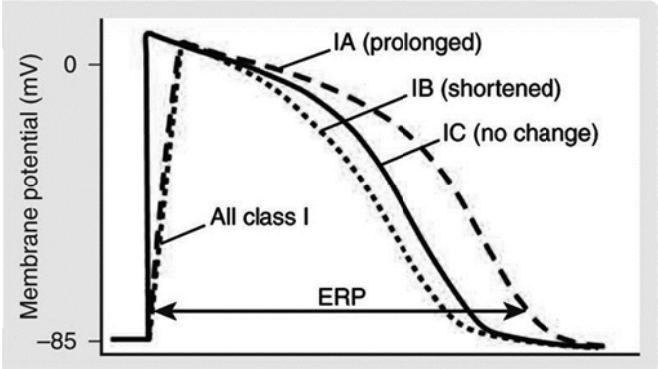


- **Heart block:**
  - AV conduction is **delayed** (first degree), **intermittent** (second degree), or **completely blocked** (third degree).

ANTIARRHYTHMIC DRUGS

- Antiarrhythmic drugs produce effects by altering one or more of the following factors: 1) Automaticity; 2) Conduction velocity; 3) Refractory period; 4) Membrane responsiveness.
- Almost all antiarrhythmic drugs have more than one mechanism of action. The simplified **Vaughan Williams classification system** assumes that each drug has **one main** mechanism of action:

Class I: Na⁺ channel blockers:



- **Class IA: e.g. quinidine, procainamide, disopyramide**: moderately block **Na⁺** channels and ↑ ERP (effective refractory period) and APD (action potential duration)
- **Class IB: e.g. lidocaine, mexiletine:** weakly block **Na⁺** channels and ↓ ERP and APD.
- **Class IC: e.g. flecainide, propafenone:** strongly block **Na⁺** and **K⁺** channels with no effect on ERP or APD.

Class II: Beta-blockers: e.g. propranolol, bisoprolol, metoprolol

They ↓ AV conduction and inhibit phase 4 depolarization.

Class III: K⁺ channel blockers: e.g. amiodarone, dronedarone, ibutilide, sotalol

They inhibit mainly **K⁺** channels and ↑ ERP.

Class IV: Ca⁺ channel blockers: e.g. verapamil and diltiazem

They inhibit mainly **Ca^{2+}** channels and ↑ ERP.

Other unclassified drugs: digoxin, adenosine, Mg sulphate

Quinidine (subclass 1A)

Mechanism and pharmacological effects

- It blocks **activated Na^+** channels leading to decrease the rate of phase-0 depolarization, decrease excitability, and ↑ APD and ERP.
- It blocks **muscarinic** and **α** receptors leading to atropine-like action (vagolytic) and hypotension.
- Quinidine has complex effect on **AV conduction** due to direct and vagolytic actions:
  - At low doses: its vagolytic action predominates → ↑ AV conduction.
  - At therapeutic doses: its direct action predominates → ↓ AV conduction
- It has –ve inotropic effect and antimalarial effect (against *P. falciparum*).

Therapeutic uses

- Quinidine was used for many years to treat **supraventricular** and **ventricular** arrhythmias, and to **maintain** sinus rhythm after conversion from atrial flutter and fibrillation; however, it is **rarely** used today because of availability of more effective and less toxic drugs.

Adverse effects and precautions

- **Cinchonism:** tinnitus (i.e. hearing of ringing or hiss), headache, blurred vision, vomiting, and diarrhea.
- **Hypotension:** after rapid i.v. infusion due to α-receptors blockade.
- **Paradoxical tachycardia:** quinidine has atropine-like action and, it may ↑ AV conduction and cause "*paradoxical tachycardia*". Digitalis or verapamil should be given before quinidine to offer rate control by ↓ AV conduction.
- **Quinidine syncope:** quinidine ↑ QT interval and may predispose the patient to a serious type of arrhythmia *(torsade de pointes).* Quinidine therefore should not be given to patients with long QT syndrome or with other drugs that ↑ QT interval.

Procainamide (subclass 1A)

- This drug is equivalent to quinidine as an antiarrhythmic agent and has similar cardiac and toxic effects. Like quinidine, its use now is very **limited.**
- **Additional adverse effect:** procainamide is metabolized by hepatic acetylation; 30% of patients (slow acetylators) develop drug-induced systemic lupus erythematosus (SLE) after long term therapy.

Drug-induced SLE like syndrome

Hydralazine (+++)
Procainamide (++)
Isoniazid (+)
Quinidine (+)
Phenytoin (+)

Lidocaine (subclass 1B)

- Lidocaine (lignocaine) is exclusively **Na^+ channel blocker**; it is highly selective for damaged tissues.
- It undergoes extensive first-pass metabolism so, it is **not given orally**.
- It is given only **i.v.** for acute suppression of ventricular arrhythmia associated with **acute MI** (not for long-term treatment). The usual dose is 50-100 mg i.v. half of this dose may be repeated after 5-10 min if necessary.
- It has **no effect** on AV conduction, so it is **not used** for supraventricular arrhythmia.
- Most adverse effects are **neurologic**.

N.B.

- **Mexiletine** is very similar to lidocaine but can be given **orally**. It is used primarily for long-term treatment of ventricular arrhythmias associated with **previous MI**.
- **Phenytoin** is antiepileptic drug with class 1B activity. It is used primarily in the treatment of **digitalis-induced tachyarrhythmia**. It has a limited role in the treatment of other ventricular arrhythmias. The IV loading dose is 250 mg given over 10 minutes.

Flecainide (subclass 1C)

- It blocks both **Na^+** and **K^+** channels leading to decrease the rate of phase-0 depolarization and **slows AV conduction**. Due to its complex effects on cardiac tissue, the APD is **not altered**.
- It is used for atrial and ventricular arrhythmia and for maintenance sinus rhythm after conversion from atrial flutter and fibrillation.
- Flecainide increases the incidence of ventricular fibrillation and sudden death after MI (proarrhythmic effect), so it is **contraindicated** for patients with ischemic heart disease or structural heart disease (e.g. LV hypertrophy).

Class II: Beta blockers

Mechanism of action

They ↓ sympathetic stimulation, inhibit phase 4 depolarization, depress automaticity, prolong AV conduction, ↑ heart rate and ↓ contractility.

Therapeutic uses

- All arrhythmia induced by sympathetic overactivity.
- Arrhythmia due to thyrotoxicosis.

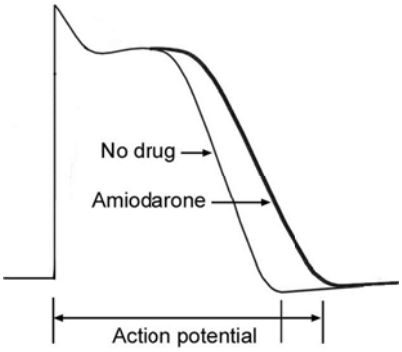
- Arrhythmia associated with HOCM.
- Supraventricular arrhythmia (AF).
- Arrhythmia due to mitral valve prolapse.

Class III: Amiodarone

- It is structurally related to thyroxine. It contains ~ 40% iodine. **Dronedarone** is chemically similar to amiodarone but does not contain iodine.
- Amiodarone has **long t½** and **large Vd** so, it can accumulate in many tissues leading to wide range of adverse effects.

Mechanism of action

- Blocks mainly **K^+** channels → slowing of phase 3 → ↑ ERP.
- Blocks **Na^+** channels → ↓ excitability.
- Blocks **Ca^{2+}** channels → – ve inotropic and chronotropic effects.

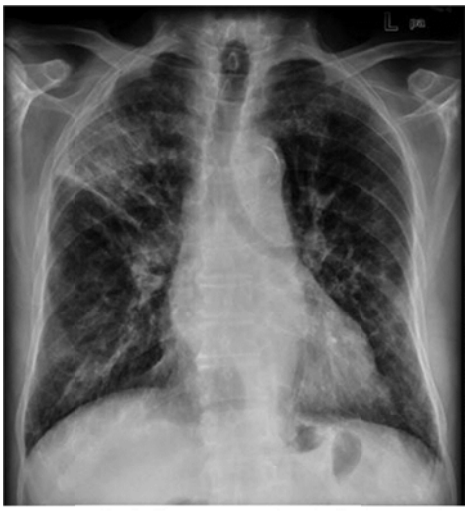


Therapeutic uses: (most types of arrhythmia)

- Supraventricular and ventricular arrhythmia.
- WPW syndrome.
- Arrhythmia resistant to other drugs.

Adverse effects

- Dose-related **pulmonary toxicity** (fibrosis) is the most important adverse effect.
- **Hepatic** toxicity.
- **Thyroid dysfunction**: hypo- or hyperthyroidism because of its iodine content.
- **Corneal microdeposits:** reversible, does not affect vision.
- **Bradycardia** and heart block.
- **Photosensitivity** leading to gray-blue skin discoloration in sun-exposed areas.



Chest x-ray in an elderly patient on amiodarone demonstrates numerous reticular opacities most marked in the right upper zone

Class IV: CCBs (verapamil and diltiazem)

Mechanism of action: They ↓ SAN activity and AV conduction

Therapeutic uses

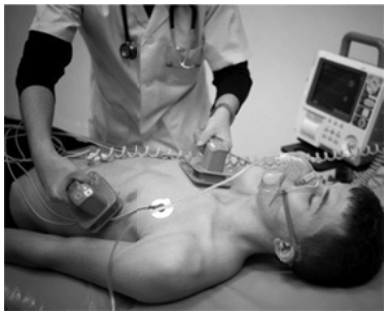
- Non-dihydropyridines (verapamil and diltiazem) are primarily used to reduce HR in **supraventricular tachycardia** (SVT) and arrhythmia associated with HOCM.
- CCBs have **no role** in the chronic management of **ventricular tachycardia** (VT). IV verapamil should **never be used** in the acute management of VT, as it may cause hemodynamic collapse.

Other antiarrhythmic agents: Adenosine

- It is a purinergic **A1 receptor agonist**; this leads to opening of K^+ channels and inhibition of Ca^{2+} channels (i.e. hyperpolarization) in the AV conducting system and directly **inhibits AV nodal conduction**.
- It has very short half-life of 8-10 seconds.
- It is the drug of choice for immediate termination of paroxysmal supraventricular tachycardia (including WPW syndrome). It is given as a bolus dose of 6 mg i.v. followed, if necessary, by a dose of 12 mg.
- The drug is less effective in the presence of adenosine receptor blockers such as **theophylline** or caffeine.
- It is contraindicated in patients with **asthma** because it can cause **bronchospasm**.

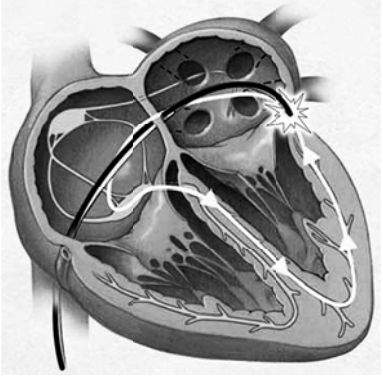
Non-pharmacological methods

DC cardioversion



- It is application of direct current (electric shock) to the chest wall for **emergency** control of any type of arrhythmia especially **rapid AF** in an unstable patient (i.e. hypotensive).
- The patient should be **heparinized** before the procedure.
- Following electrical cardioversion, patients should be anticoagulated for at least 4 weeks.

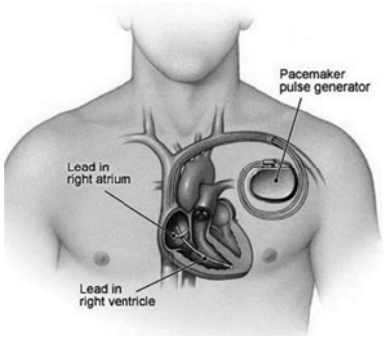
Laser ablation



- It is used for many types of arrhythmias.
- A catheter is inserted into a specific area of the heart. A special machine directs energy through the catheter to small areas of the heart muscle that causes the abnormal heart rhythm. This energy "disconnects" the pathway of the abnormal rhythm.
- Laser radiofrequency ablation is the definite treatment of **WPW syndrome**.

Artificial pacemakers and implantable cardioverter defibrillators

- They are battery-powered electronic devices that are implanted under the skin or in the chest cavity to monitor and pace the heart.



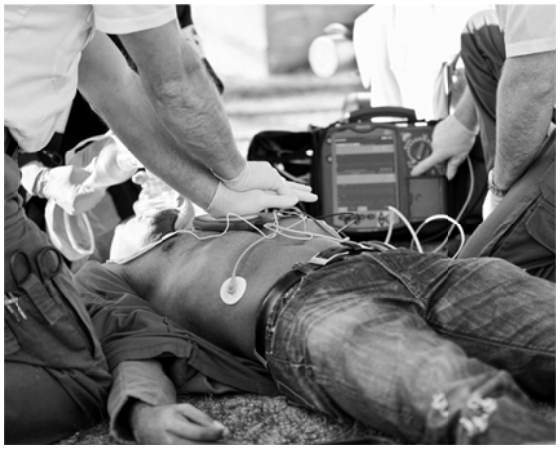
Management of cardiac arrest

Cardiac arrest involves cessation of cardiac **mechanical** activity as confirmed by absence of signs of circulation (absent pulse and apnea).

Causes

- Coronary heart disease (~80%).
- Cardiac disease: e.g. HOCM, Brugada syndrome.
- Cardiac arrhythmia especially ventricular.
- Others: trauma, electrolyte imbalance, electrical shock, drugs, etc.

Patterns of arrest



- Complete asystole: the ECG is flat line.
- Ventricular fibrillation: ECG shows fibrillation waves.
- Pulseless electrical activity (PEA): There is some electrical activity (other than VF) without detectable pulse.

Management

- The ultimate goal of treatment is to preserve life by early CPR 30:2 i.e. cycles of 30 chest compressions followed by 2 rescue breaths.
- Administer electrical defibrillation at 360J then repeat CPR for 2 min.
  → No response → **Epinephrine** 1 mg i.v. /3-5 min with CPR.
  → No response → DC shock with CPR for 2 min.
  → No response → **Amiodarone** 300 mg i.v. with CPR.
  → No response → DC shock with CPR.

Shock – Drug **– Shock –** Drug **– Shock**