Anti-arrhythmic Drugs

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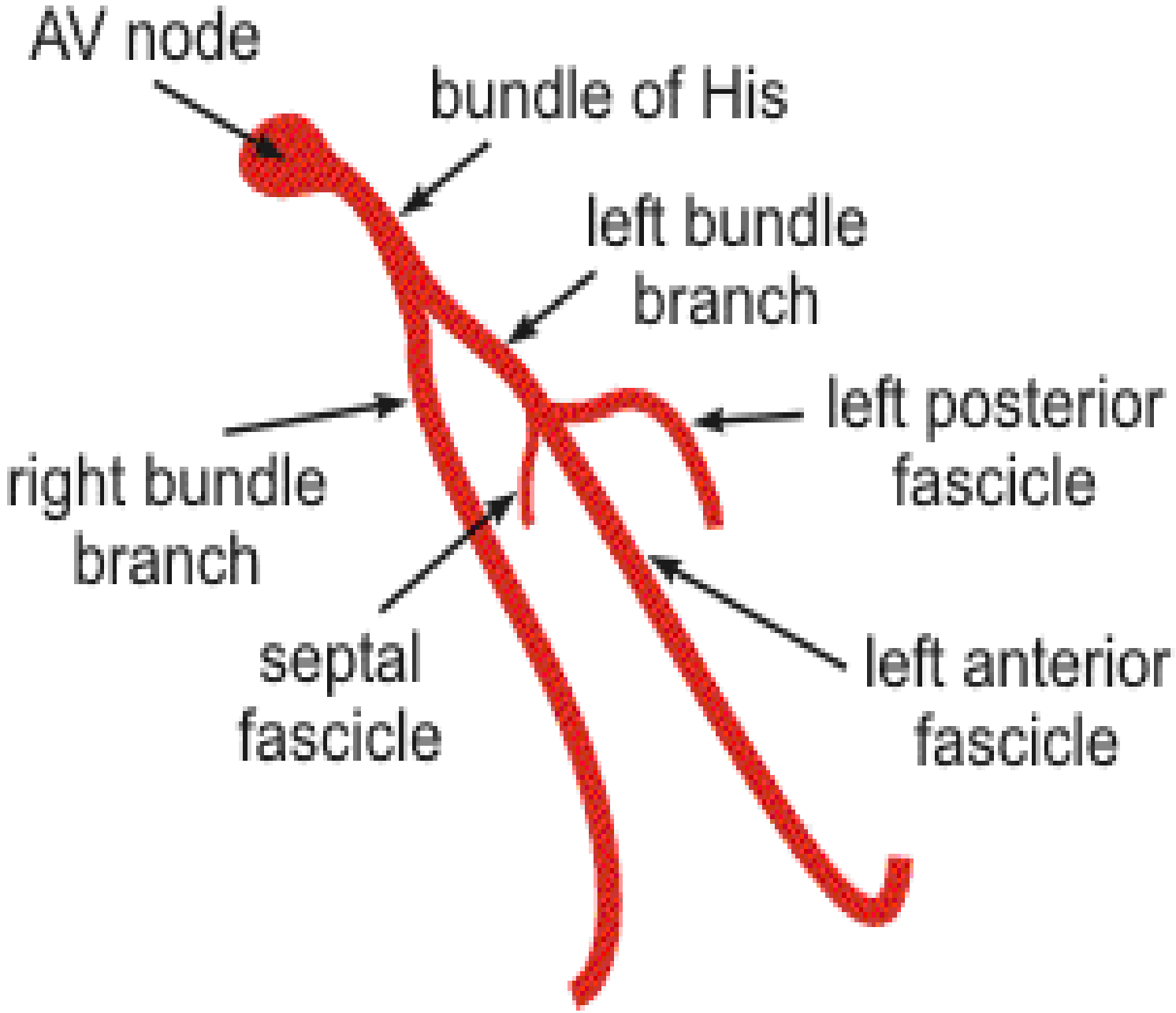
INTRODUCTION

- Arrhythmias are disturbances of the electrical rhythm of the heart.
- Anti-arrhythmic drugs are useful in the treatment and **sometimes** prophylaxis of cardiac arrhythmias.
- However, long term prophylaxis with anti-arrhythmic drugs is not without risks as most anti-arrhythmic agents are themselves pro-arrhythmic agents with –ve inotropic action.
- Generally, treatment of asymptomatic arrhythmias is not recommended.

INTRODUCTION

- Physiologically, the myocardium has muscle cells and conducting tissues (SA node, AV node, Bundle of Hiss and right and left bundles or divisions).
- The heart beat is initiated by an electrical discharge from the SA node followed by depolarization of the atria and ventricles.
- The SA node acts as a pacemaker and its intrinsic rate is regulated by the ANS (sympathetic and parasympathetic systems).
- When the sinus rhythm is slow, a lower centre takes over the role of the pacemaker. This is known as escape rhythm and may arise in the AV node (nodal rhythm) or the ventricle (idioventricular rhythm).


AV node
bundle of His
left bundle branch
left posterior fascicle
right bundle branch
septal fascicle
left anterior fascicle

TYPES OF ARRHYTHMIAS

They are classified according to site of origin of the rhythm into:

1. **Sinus rhythm** disturbances (originates in the SA node):

❖**Sinus arrhythmia**: normal phenomena occurring in young peoples; heart rate increases during inspiration.

❖**Sinus bradycardia** (HR <60) may occur in normal athletes, with AMI, with hypothyroidism or raised intracranial pressure. When symptomatic, it can be treated by atropine injection.

❖**Sinus tachycardia** (HR >100); may occur with chronic anxiety, exercise, anaemia, fever, thyrotoxicosis and with heart failure.

TYPES OF ARRHYTHMIAS

2. Ectopic rhythm disturbances:

❖**Supraventricular** arrhythmias **(atrial or nodal):**

- Ectopic beats: atrial premature contractions (APC)
- Supraventricular Tachycardia (SVT)
- Atrial fibrillation (AF)
- Atrial flutter

❖**Ventricular** arrhythmias**:**

- Ectopic beats: ventricular premature contractions (VPC)
- Ventricular tachycardia (V tach)
- Ventricular fibrillation (VF)
- Asystole

Causes of arrhythmias

➢Arrhythmias are usually manifestations of **structural** heart disease but may also occur in **normal** hearts and many arrhythmias are **idiopathic**. The main causes of arrhythmias are :

1. Ischaemic heart disease

2. Hypertension

3. Cardiomyopathy (Disease of the myocardium)

Factors that precipitate or exacerbate arrhythmias include:

- Ischemia, hypoxia, acidosis or alkalosis
- Electrolyte changes
- Excessive catecholamine exposure, autonomic influences
- Drug toxicity (digitalis or anti-arrhythmic drugs)
- Presence of scarred or diseased cardiac tissue

Mechanisms of arrhythmias

Arrhythmias may result from disturbances in:

- **Impulse formation**
- **Impulse conduction**
- Or **both** factors

Manifestations of arrhythmias

- Palpitation
- Syncope
- Chest pain
- Dyspnoea
- Sometimes may even cause heart failure or sudden death

PHASES OF CARDIAC ACTION POTENTIAL

- **Phase 0** : Rapid depolarization due to Na inflow
- **Phase 1** : Initial repolarization due to K outflow
- **Phase 2** : Influx of Calcium
- **Phase 3** : Rapid repolarization due to K outflow
- **Phase 4** : Complete repolarization with K inflow & Na & Ca outflow

Anti-arrhythmic drugs

- Aim of therapy of arrhythmias is to reduce the ectopic pacemaker activity or to block or disable conduction in the reentry circuits.

- Main mechanisms to achieve these aims are through the use of one of the following:

1. Class I: Sodium channel blockade
2. Class II: Beta-blockers
3. Class III: K channel blockers
4. Class IV: Calcium channel blockade.

Classification of Anti-arrhythmic drugs

1. Class 1 (Na channel blockers):

These act on phase 0 and have membrane stabilizing (Local Anaesthetic effect). They are divided into the following subgroups:

Class 1A: increase action potential duration e.g. quinidine, disopyramide, procainamide
Class 1B: decrease action potential duration e.g. Lignocaine, Mexiletine, Phenytoin
Class 1C: has negligible effects on action potential duration e.g. Flecainide

2. Class II (Beta-blockers):

- These act on phase 4 of action potential
- **Propranolol, Esmolol** are examples

3. Class III (K channel blockers):

- These drugs lengthen refractoriness and prolong action potential duration by acting on phase 1, 2 & 3
- **Amiodarone, Bretylium**

4. Class IV (Ca-channels blockers):

- These act on phase 2 of action potential
- **Verapamil** is an example

TREATMENT OF ARRHYTHMIAS

- **General measures:**
  Avoid smoking, tea, coffee, anxiety

- **Cardioversion** using DC-shock (direct current-shock) which corrects arrhythmias rapidly. It is useful in:
  - Atrial arrhythmias (SVT, AF)
  - Ventricular tachycardia and ventricular fibrillation.

  Cardioversion is risky and contraindicated in patients with digitalis-induced arrhythmias.
- **Pacemaker or surgery**
- **Drugs**

Drugs therapy of arrhythmias

Class 1A:

1. Disopyramide

It is useful orally or IV in:

- **Ventricular arrhythmias (after AMI)**
- SVT of Wolf Parkinson White syndrome

Main adverse effects:

- **Anti-muscarinic** effects
- Decrease blood pressure

2. Quinidine

It is useful in:

- **Atrial fibrillation** or flutter
- Resistant SVT
- Occasionally in ventricular tachycardia

❖It blocks conduction

❖Its use has declined because of its cardiac & extracardiac side effects. Hypotension and heart failure may occur.

3. Procainamide

❖It is useful in **ventricular arrhythmias after AMI**; given initially by IV infusion then orally

❖Main adverse effect is hypotension; prolonged therapy may cause drug-induced SLE

Class 1B

1. Lignocaine (Xylocaine)

- ❖It is useful in **ventricular arrhythmias after AMI**
- ❖It is given only IV (infusion or injection) because it has high 1st pass metabolism and low bioavailability.
- ❖It may cause hypotension, sleepiness, confusion and convulsions with high doses.

2. Phenytoin

- ❖It is useful in **digitalis-induced arrhythmias**

3. Mexiletine

- ❖It is useful orally in ventricular arrhythmias after AMI.
- ❖It may cause tremor, ataxia, dysarthria & hypotension.

Class 1C

1. Flecainide

It is useful in **VPC**, ventricular tachycardia & in SVT when others are ineffective.

Class III

1. Amiodarone

It prolongs phase 1, 2 & 3 of action potential & increases refractory period. It is useful in **SVT**, **AF** and VT when other safer agents are ineffective. It is also useful in WPWS arrhythmias.

It is given once daily orally or by injection

It is highly lipid-soluble & has very large volume of distribution & long t ½ of about 54 days. It causes no myocardial depression.

Main adverse effects are:

Corneal microdeposit (photophobia), photosensitivity

Thyroid disorders

Pneumonitis or pulmonary fibrosis & hepatitis.

2. Bretylium

It is useful IV in resistant **ventricular arrhythmias after AMI** like VF & VT.

Class IV

1. Verapamil

❖It has direct –ve inotropic effects & -ve chronotropic effect (acts on SA node & impairs conduction in AV node). It acts by blocking influx of calcium through L-type channels during phase 2 of action potential.

❖It is useful mainly in **SVT** and **AF.**

Adverse effects :

Headache, constipation, Hypotension, bradycardia.

❖It is not used with: beta-blockers because both have –ve inotropic & chronotropic effects

❖It is contraindicated in heart failure and after AMI

Other Anti-arrhythmic agents

1. Adenosine

- It occurs naturally in the body.
- It is used as **IV** injection in **SVT**
- It slows & inhibits AV nodal conduction.
- Its t½ is 10 seconds & is rapidly metabolized by circulating adenosine deaminase
- **Main adverse effects: bronchospasm** (avoided in asthma), flushing and chest pain

2. Digoxin

- It is obtained from foxglove plant (Digitalis purpurea & Digitalis lanta).
- Its mechanism of action is by inhibiting ATPase (Na-pump) in cardiac cells:
- Leading to increase intracellular Na
- Leading to influx of Ca & increase intracardiac Ca
- Increasing myocardial contractility (+ve inotropic effect)
- Leading to increase cardiac output and decrease sympathetic tone
- It has indirect –ve chronotropic effect through increasing vagus tone
- It is given orally or IV.
- It is excreted unchanged in urine (85 %) with a t ½ of 36 hours

Therapeutic uses of digoxin:

- **Arrhythmias** as **AF & SVT**
- **Heart failure** particularly when associated with arrhythmia like AF.

- **Smaller doses of digoxin are used in:**
- Elderly, renal disease, hypothyroidism, in the presence of hypokalemia

Digoxin toxicity:

Digoxin has a narrow therapeutic index. Manifestations of digoxin toxicity include:

- Cardiac effects: arrhythmias and heart block
- GI effects: nausea and vomiting.
- CNS effects: headache, confusion, nightmares, psychosis, **coloured vision**

Treatment of digoxin toxicity:

- Stop therapy and correct hypokalemia
- Correct arrhythmias using phenytoin or atropine
- Give digoxin antibody infusion

Summary of drug therapy of main types of arrhythmias:

- **APC:** choice: a **beta-blocker** if symptomatic
- **PVC:** choice: **Disopyramide**, Lignocaine, Flecanide
- **Atrial fibrillation:** choice: **Propranolol**, **amiodarone**, **digoxin**
- **SVT:** choice: **Beta-blocker**, **verapami**, adenosine
- **Ventricular tachycardia:** choice: **Lignocaine**, amiodarone