CARDIAC DRUGS – Overview of relevant pathophysiology and main classes of drugs

This introduction briefly overviews the topics of three lectures. It is included to briefly review the underlying pathophysiology of heart conditions, and their treatment with drugs.

The notes are a general introduction to drugs that act upon the heart, and that are used in various cardiac diseases including: myocardial ischaemia (and angina pectoris), myocardial infarction; cardiac arrhythmias (dysrhythmias) and heart failure.

The pharmacology of cardiac drugs involves many different classes of drugs. To understand their therapeutic actions it is important to have a basic understanding of the physiology and pathology of the heart.

Myocardial ischaemia and infarction is a common cause of cardiac arrhythmias and heart failure. Myocardial ischaemia is an insufficiency of blood flow in one or more coronary arteries, and results mostly from atherosclerotic narrowing in one or more myocardial arteries. When narrowing is accompanied by thrombosis (as a result of activation of coagulation, and aggregation of platelets) such that blockade of a coronary artery is virtually complete, the resulting ischaemia is sustained and as a result the cardiac tissue that was fed by that artery dies and turns into an infarct (dead tissue). Such changes can disturb cardiac rhythm and/or produce a pathological reduction in cardiac output (heart failure). There are of course other causes of cardiac arrhythmias and heart failure. Angina pectoris (pain from temporary myocardial ischaemia) occurs when the lumen of a large coronary artery is significantly obstructed (by more than 70%) by atherosclerotic plaques. If the work demand on the heart increases such that the blood supply from that artery cannot increase anymore, a region of myocardial ischaemia occurs and pain is generated.

Normal cardiac functioning depends upon the inherent electrophysiological and contractile functions of myocardial cells, with the autonomic nervous system, ionic balance and hormones playing lesser, but important roles. Cardiac myocytes include specialized nodal [sinoatrial (SAN) and atrioventricular (AVN)], atrial (A) and ventricular (V) cells. Further subdivisions of cell types can be made, even in nodal and atrial tissue. In ventricular tissue there are special cellular conduction pathways (His-Purkinje system) while epicardial, sub-epicardial, sub-endocardial and endocardial cells all differ. In terms of the neuronal control of the heart, sympathetic nerves innervate all parts of the heart whereas parasympathetic nerves innervate only atria, SAN and AVN.

The electrophysiological behaviour of cardiac cells varies between different cardiac cells types. However, most electrical activity in heart cells can be explained by the relative ionic balance of Na⁺, K⁺ and Ca²⁺ across the membranes of the different cardiac cells, as well as brief temporary changes in permeability to such ions through voltage and time dependent ion channels. Intra- to extracellular ion balance is dependent upon ionic pumps and exchangers, such as Na/K ATPase and the Na/Ca exchanger.

Normal electrical activity and contractile activity requires a coherent and coordinated activation of the whole heart. It begins with the spontaneous generation of a beat at the SAN node, transmission to, and spread across, the atria, followed by subsequent slowing and collection of a wave of excitation at the AVN. Excitation is slowed in the AVN from where it emerges to excite the His/Purkinje system. The impulse from the His/Purkinje rapidly transmits orderly excitation throughout the ventricles. Normally, only cardiac nodal cells generate spontaneous beating. His Purkinje cells may do so, but atrial and ventricular cells normally do not, unless they are damaged.

Contractile force is generated by contractile (A & V) tissue. Such cells have an internal architecture that contains a defined (more so for V than for A cardiac cells) sarcoplasmic reticulum for storing and releasing calcium ions. Calcium ions activate actin-myosin interaction to generate cardiac contractile force. The atria contract to aid ventricular filling, while subsequent ventricular contraction provides cardiac output through the pulmonary artery and aorta.
Adequate cardiac output requires coordinated rhythmic beating as a result of sequential activation of voltage dependent ion channels in the different types of cardiac cell. The major ion channels responsible for generating action potentials are those for Na+, K+ and Ca++. Subtypes exist, but for simplicity there is one major one for Na+, one major one for Ca++ and various for K+. The sequential and selective activation of these channels generates action potentials that are characteristic for N cells, A cells, His–Purkinje and V cells.

**INOTROPISM & Heart Failure**

Cardiac inotropes change cardiac muscle contractility. Inotropism can be **positive or negative** in terms of the contractile force generated by cardiac muscle at different initial resting tensions (Starling curve). A leftward shift in the Starling curve is positive inotropism - a rightward shift negative inotropism. Within limits, for many mammalian species, an increase in heart rate will increase contractile force.

An increase in the rate of development of contraction can be considered inotropism since it often results in an increase in the maximum contraction.

*Luseotropism* is the rate of relaxation from contraction. Positive means an increase, and negative a decrease.

*Dromotropism* is speed of conduction through the AVN conduction node.

Positive cardio inotropic drugs are sometime used in the treatment of heart failure (insufficient cardiac output) to sustain an adequate cardiac output. Negative inotropism is an adverse effect of some drugs.

**Basic Contractile Physiology** varies with cell type (N, A, V). Cardiac cells have well organized actin/myosin filaments in V cells, less in A cells, and are indistinct in N cells (similar to smooth muscle cells). A well developed sarcoplasmic reticulum is important for contraction since contractile force depends upon external calcium entry via L type channels triggering Ca++ release from sarcoplasmic reticulum (SR) via ryanodine receptors.

Contraction occurs as follows: Phase 0 (sodium currents in A & V cells) initially depolarizes cells and thereby activate the opening of L-type Ca channels to produce an inward Ca++ current (I_{isi}). This, via a ryanodine receptor-linkage, releases Ca++ from the sarcoplasmic reticulum and actin-myosin interactions result. Unlike the case with skeletal muscle, the ability of cardiac muscle sarcoplasmic reticulum (SR) to hold and release Ca++ is limited. It depends upon The SR phosphorylation state, hence cAMP and PK (protein kinase) activity.

Inotropism (contractility) in vivo is modulated by pre- and after-load (Starling) and via sympathetic nerves and β₁ receptor stimulation. Alpha and β₂ receptors play minor roles. β₁ receptor stimulation elevates intracellular cAMP which, via kinases, phosphorylate L type Ca channels, as well as the sarcoplasmic reticulum - processes that lead to more Ca++ for contraction.

Parasympathetics (ACh) mediate negative inotropism by reducing Ca currents, **(but only in atria)** β₁ adrenoceptor agonists, whether endogenous agonists (NE (norepinephrine), or circulating E (epinephrine), act physiologically and pathologically to stimulate adrenoceptors. Beta agonists are both positive inotropes and positive luseotropes (increase rate of development of contraction, maximum contraction, and rate of relaxation. The cardiac inotropic actions of β agonists are oxygen-wasting and reduce cardiac efficiency.
PHARMACOLOGY OF CONGESTIVE HEART FAILURE.

Basic Physiology of the Heart
Cardiac myocytes have:
  - well-organized actin/myosin filaments (midway between the highly organized skeletal and the less well-organized smooth muscles). Varies with cardiac muscle type: nodal, atrial, Purkinje, ventricular (epi- to endocardium).
  - well-organized sarcoplasmic reticulum which varies with cardiac tissue type – most organised in ventricles.
  - contraction requires the entry of calcium through L type channels to trigger release of calcium from sarcoplasmic reticulum and activation of contraction.

  Inotropism (contractility status) depends upon resting tension, modulated by the autonomic nervous system, chiefly via sympathetic nerve activity and subsequent β1 receptor stimulation, as well as by various other hormones and ions. Ionotropism is positive or negative, luseotropism is rate of relaxation - removal of activating Ca++ – again positive or negative.

β1 receptor stimulation results in positive inotropism via elevation of intracellular cAMP leading to phosphorylation of L type Ca channels and the sarcoplasmic reticulum, resulting in more Ca++ available for contraction but also speeds up relaxation.

(parasympathetics mediate negative inotropism, but only in atria)

Inotropism in myocytes depends upon initial (resting) tension of the muscle. This relationship is described by the: Frank-Starling curve, thus contractility depends upon pre- and after-load (in situ “venous and arterial” pressures respectively).

Points of Note:
There are a finite number of myocytes in the adult heart - myocytes do not normally undergo significant mitosis.
  - Myocytes are lost as a result of: maintained ischaemia leading to infarction, cardiotoxins, apoptosis, an excessive workload such as occurs with hypertension, cardiac valve defects, blood volume disturbances.
  - Myocytes respond to a sustained and increased work load with hypertrophy.
  - Excessive sustained work demand on ventricular myocytes leads eventually to failure of their contractility - heart failure
  - The weak link in cardiac myocyte contraction is excitation-contraction coupling (the site of cardiac failure).

Future new drug research directions:  Stem cell research to increase myocyte proliferation, angiogenesis, understanding failure in excitation/contraction coupling, suppressing actions of endogenous cytotoxic substances that exacerbate cardiac injury, and/or are released by ischaemia.

THE PATHOPHYSIOLOGICAL CYCLE OF HEART FAILURE

Heart Failure (insufficient cardiac output) follows:- Irreversible loss of myocytes – as a result of age, myocardial ischaemia & subsequent infarction, infection, cardiotoxins, various classes of drugs. These result in excessive chronic demands on the heart due to:-
  - Excessively high heart rate for too long a period
  - Excessively high ventricular pressures (pre- and after-load) as induced by hypertension, incompetence of cardiac valves.
Excess sympathetic activity (β-agonism) – which is oxygen wasting and can increase intracellular calcium loading

Compensatory responses to inadequate cardiac output (both acute and chronic) include:

Increased sympathetic activity. Activation of β and α receptors produce the expected effects on the heart (tachycardia, positive inotropism) and blood vessels (vasoconstriction of arteries and veins), respectively, but paradoxically this can chronically exacerbate the failure.

Retention of sodium and water as a result of reduced renal blood flow and release of renin - angiotensin II, vasoconstriction and increased sympathetic nerve actions on blood vessels. Angiotensin II – stimulates aldosterone release; it is a direct vasoconstrictor; potentiates sympathetic nervous system, and growth factors. Aldosterone mediates retention of sodium (plus water) and increases blood volume
Other endogenous factors possibly involved in heart failure include atrial naturetic factor, tissue necrosis factor, endothelin, apoptotic factors.

The above are all potential targets for drugs which might ameliorate heart failure. Modulation of the renin/angiotensin/aldosterone, and sympathetic, systems are currently the major therapeutic approaches in the treatment of heart failure.

Pharmacological approaches to treating congestive heart failure

The pharmacological approach depends upon whether the failure is acute or chronic, and whether the cause has been identified.

A. Treatment of acute congestive failure: where the goals of emergency treatment are to prevent death, stabilize the patient, and provide symptomatic relief; it can involve the following:

1. Intravenous furosemide (a high ceiling diuretic to produce marked diuresis (loss of fluid volume) and direct vasodilation
2. Intravenous morphine acting centrally to relieve anxiety: it is also a venodilator.
3. Oxygen (since hypoxia due to pulmonary congestion worsens heart failure)
4. Cardiac inotropes given if considered essential: these include:
**Beta1 agonists** for immediate inotropism BUT for short term acute use only since they are oxygen wasting and exacerbate cardiac myocyte damage.

**Digoxin** (see later)

5. Nitrovasodilators *(nitroglycerin, nitroprusside)*

**B. CHRONIC CONGESTIVE FAILURE:** the treatment goals are to provide symptomatic relief, improve life, reduce mortality) with drugs such as:-

1. **Angiotensin converting enzyme inhibitors** -reduce mortality.  
   *(captopril and other ****prils) - orally*

   **Angiotensin receptor antagonists** - may be equivalent to ACEIs with less side effects  
   *(losartan, candarsatan, ****tans) - orally*

2. **Diuretics**  
   *(furosemide, thiazides, spironolactone) - orally*

3. **Beta blockers.**  
   *(carvedilol, metoprolol, increasingly others) - orally*

   4. Angiotensin receptor antagonists + nepri lysin Inhibitors *(e.g. valsartan/sacubitril),

   5. Selective Bradycardic drugs - **ivabradine**

   6. Cardiac glycosides – **oral digoxin**

*Other drugs that have been, and are used, to treat heart failure include:*:-  
Aldosterone inhibitors, Vasodilators, Calcium channel blockers, Ions (K, Mg).

**Pharmacology of above drugs**

**Are generally of limited value**

**POSITIVE INOTROPES**

**cAMP DEPENDENT INOTROPES**

Which increase cardiac intracellular cAMP leading to phosphorylation of calcium channels, and the sarcoplasmonic reticulum, so making more calcium available for contraction at the level of actin and myosin.

**β1 adrenoceptor agonists:**

Endogenous agonists *(NE and circulating E)* also stimulate other types of adrenoceptors but their value is limited. The important point is that the cardiac inotropic actions of β agonists are oxygen wasting, and reduce cardiac efficiency (measured as the ratio of cardiac output to cardiac oxygen use).

**Dopamine** - also an agonist at dopamine receptors: dilates renal blood vessels to help preserve renal function

**Dobutamine** is a more β1 selective agonist

*If such drugs are used, it is only for ACUTE SUPPORT of the cardiovascular system since they are oxygen wasting, reduce cardiac efficiency, and promote excessive intracellular accumulation of calcium with toxicities and side effects that include tachycardia, arrhythmias, worsening of condition, hypokalaemia*
Phosphodiesterase inhibitors (elevate tissue cAMP levels)

Aminophylline - a chemical complex of the xanthine, theophylline, with ethylenediamine is a phosphodiesterase inhibitor that also acts on adenosine receptors. It can be used in acute situations, and also has bronchodilator actions which helps alleviate any associated cardiac asthma.

Orally active cardiac phosphodiesterase (PDE3) inhibitors have been used in the past, but their unfavourable effect of increasing mortality, despite alleviating the cardiac failure, has resulted in their being discontinued or severely limited. Examples include:- amrinone, and other ....ones.

If the above are used, it is only for acute support.

Toxicities and side effects: tachycardia, arrhythmias, nausea, worsening of the condition.

Cardiac glycosides (for a fuller description see later)
The same molecular mechanism can be assumed to be responsible for their therapeutic and toxic actions of all cardiac glycosides. It is inhibition of Na/K ATPase. This leads to intracellular accumulation of Na and, therefore, Ca as well.

Many different cardiac glycosides occur in nature as naturally occurring sugars with a pharmacologically active steroid group – in plants, and even some animals (e.g. some toads).

Digoxin is used therapeutically in USA & Canada (others in other countries). For the most part they have been replaced by different classes of drugs.

Plant cardiac glycosides can be ingested accidentally by children, and thereby a cause of poisoning.

All cardiac glycosides share the same basic molecular mechanism, but vary in pharmacokinetic characteristics (absorption, metabolism, excretion)

DIGOXIN: i.v. or oral (70% absorbed, renal excretion). Therapeutic ratio close to unity so a particular dose beneficial for all would be toxic to some), onset slow (hours), toxicity common, especially when serum K+ is low, including g.i upset and CNS effects. Digoxin-binding antibodies are available for overdose treatment. Digoxin has also been used in ATRIAL FIBRILLATION to reduce ventricular rate. Toxicities and side effects: Arrhythmias, g.i. upset, CNS disturbance in the elderly, coloured vision, rarely gynaecomastia. Excess toxicity is treated with K+, if necessary, and with digoxin antibody fragments.

ANGIOTENSIN-RELATED DRUGS AND DIURETICS

ANGIOTENSIN- RELATED DRUGS have a common beneficial mechanism related to increasing excretion of oedema fluid (excess sodium and water), plus ancillary actions.

Angiotensin converting enzyme inhibitors, angiotensin receptor antagonists and renin inhibitors are used.

These classes of drug could all be expected to have similar utility in congestive heart failure by reducing the activity of the renin-angiotensin system (RAS activity). However, this may not necessarily be the whole case since renin inhibitors may have lesser utility.

Angiotensin converting enzyme inhibitors (ACEIs): e.g captopril, other..... prils.
Reduce symptoms and importantly reduce morbidity and mortality.
Oedema fluid lost - cardiac output rises
Toxicities and side effects:- Cough (10%), rashes, g.i. upset, angioedema

Angiotensin receptor I antagonists: e.g. losartan, and other atans.
May not have complete identity with ACEIs in their actions. Do not reduce angiotensin II levels.
Reduce symptoms of c.h.f. and reduce morbidity and mortality.
**Toxicities and side effects:** less than with ACEIs, **and no cough**

Sacubitril is a pro-drug that is de-ethylated via esterases to **neprilysin** which blocks the enzymes that de-activating vasoactive peptides thereby increasing their ability to vasodilate and reduce extracellular volume via sodium excretion. When given with an angiotensin receptor antagonist is more effective in chronic heart failure in sustaining life.

**DIURETICS**

Two major types: loop (high ceiling) diuretics (e.g. **furosemide**) and distal tubule diuretics (e.g. **thiazides**). Both types cause salt and water loss, and have vasodilator actions. Loop diuretics are more efficacious (higher maximum effect).

**Toxicities and side effects:** electrolyte imbalance (especially $K^+$ and this is potentially dangerous). With the thiazides, hyperuricaemia, hyperglycaemia, adverse renal effects between furosemide with **NSAIDs**.

**OTHER DRUGS**

**BETA BLOCKERS**

At first glance might be thought to exacerbate heart failure by abolishing acute compensatory reflexes resulting in increased cardiac sympathetic drive. While this sympathetic activation of the heart might provide acute benefit in the short term, long term beta activation exacerbates failure and can even cause myocyte death. Beta blockers are now favoured in chronic and less severe cardiac failure. The expected adverse effects on the heart are **not** seen when therapy begins with small, but increasing, doses. Beneficial effects were first seen with **carvedilol** ($\beta_1$ & $\beta_2$, $\alpha$ blocker and antioxidant), but benefit is seen with all $\beta$ blockers.

**Toxicities and side effects:** bradycardia, a.v. block, asthma, exacerbated intermittent claudication, hypotension

**VASODILATORS**

When used acutely (**nitroglycerin** or **nitroprusside** i.v.) can reduce pre- and after-load which provides benefit. Hydralazine, a directly acting vasodilator can be used in conjunction with nitrates.

**Toxicities and side effects:** excess hypotension, reflex tachycardia, SLE (systemic lupus systemic lupus erythematosus) with hydralazine

**Morphine (used acutely only)**

Has a very useful anxiolytic action and is a venodilator that reduces pre-load venous pressures.

**Toxicities and side effects:** respiratory depression, nausea and vomiting, histamine release

Many of the above drugs have covered elsewhere but not all of them. In particular the cardiac glycosides are not covered in any depth. Cardiac glycosides have been known for years but are still pharmacologically interesting, not so much for their usefulness in the therapy of congestive heart failure, but more for their unique pharmacology, as well as the relationships between their molecular, cellular, tissue and organ actions which give insights into physiology and pathology.

The main aspects of the pharmacology of cardiac glycosides are outlined below:-
CARDBAC GLYCOSIDES

Chemical Structure
Natural occurring steroids with a lactone ring plus attached sugars.

SAR
Some degree of structural variation is possible but this does not really influence the basic molecular action. The effects of molecular changes on SAR is principally upon the pharmacokinetic characteristics in terms of duration of action, bioavailability, metabolism and excretion, etc. Basic pharmacophore is 17-C steroid ring coupled to a lactone ring, both essential for action. The sugars alter pharmacokinetics.

Source
Classically from the ‘foxglove’ plant Digitalis lanata, but also found in many other plants (e.g. squill, oleander) and are a source of poisoning. Found in certain animals, particularly in cane toads (Bufo marinus) which are toxic, if eaten or licked. Pharmaceutical source is still digitalis plants grown specifically for the purpose. Possibly a cardiac glycoside is an endogenous cardiotropic substance present in mammalian hearts. The evidence for this is still considered equivocal.

Molecular Mechanism of action
The accepted mechanism of action is inhibition of Na/K ATPase, and hence alteration of the ratio of Na and K in the cell. However some observations may be inconsistent with this mechanism, particularly with respect to speed of onset of action of at least part of the inotropic response to cardiac glycosides in isolated cardiac cells.

Cardiac glycosides are not cardiac selective in their action on Na/K ATPases, but the particular ionic status and resulting physiology of cardiac muscle probably makes cardiac tissue more sensitive in a therapeutically useful manner. Thus, inhibition of Na/K ATPase occurs in all tissues and probably accounts for their toxicity.

Cellular Mechanisms of action
Inhibition of the Na/K ATPase of appropriate degree and duration and results in loss of intracellular K and increase in intracellular Na. One consequence of this is an increase in calcium available for contraction within the cardiac myocyte. The increased Na, is thought to bring in calcium (via Na, being reverse transported in the Ca/Na exchanger for calcium - “pump reversal”).

Loss of Ki, accumulation of Na, in heart cells also occurs in other tissue and this alters the electrophysiology of all tissues containing Na/K ATPases. While this very apparent in cardiac and nervous tissue such molecular actions may account for toxicity of cardiac glycosides. It is important to recognize that different types of tissues differ in the degree to which they rely on membrane pumps and exchangers such as Na/K ATPase and Na/Ca exchangers; this may account for the apparent selectivity of action of cardiac glycosides for cardiac tissue.

Tissue Mechanisms of action
The heart is the therapeutic target for cardiac glycosides and on isolated cardiac tissue preparations the main effects are: initial inotropism without effects on the speed of contraction, or on luseotropism. (in all cardiac preparations, but most marked in “failing” cardiac tissue). Higher doses, or longer exposure, produce arrhythmias as cells begin to depolarize, and cardiac electrophysiology is disturbed.
Inotropic effects can be seen sometimes in smooth muscle, but not particularly in skeletal muscle. This reflects differences in their cellular ion exchange balance and their excitation-contraction mechanisms.
Neuronal tissues can show increased excitability when exposed to cardiac glycosides. Even erythrocytes will lose K, and gain Na, on exposure to cardiac glycosides.

**Organ Mechanisms of action**

The major therapeutic organ is the heart where, in addition to positive inotropism, both Direct and Indirect actions are seen on the rate and rhythm of the heart. As an approximation Indirect actions occur at lower doses while Direct actions occur at higher ones, but this is a loose approximation.

Indirect actions are vagotonic inasmuch as there is increased vagal activity on the atria - particularly on the AV and SA nodes. The aim of digitalis treatment in atrial fibrillation is therefore to control (slow) ventricular rate. The interaction between Direct and Indirect effects on the atria are fascinating in terms of cardiac pathophysiology since digoxin can produce atrial arrhythmias and cardiac glycosides can convert atrial flutter to atrial fibrillation. This apparent worsening of an arrhythmia actually makes it easier to control ventricular rate since varying the degree of atroventricular block in the presence of atrial flutter (a coherent rapid atrial rate) can paradoxically increase ventricular rate to dangerously high levels.

The major toxicities of cardiac glycosides are fatal ventricular arrhythmias due to direct actions on K and Na distributions in cardiac cells, and resulting disturbed electrophysiology. Such arrhythmias account for the fatal effects of cardiac glycoside poisoning. Other toxicities also can be traced to Na/K ATPase inhibition in:- gastrointestinal tract: nausea, vomiting, diarrhoea.

**CARDIAC ARRHYTHMIAS and drug treatment**

The surface ECG (electrocardiogram) is a summation, in the form of a body surface potential, generated as a result of cardiac tissue action potentials and is dominated by the ventricles with their much larger mass. The P wave reflects the spread of atrial excitation; the dominant QRS is ventricular excitation; the T wave ventricular repolarization; and the PR interval, delay at the AV node. The total signal size is in the 1.0mV range.
Currents underlying the potentials are shown by $i_\text{r}$ and its accompanying ion. Each type of ion channel has a characteristic range of potentials over which it is activated, and each current decays with characteristic decay times. In SAN and AVN and atrial cells, muscarinic receptor stimulation activates a $K^+$ channel to make the resting potential more negative while lowering the slope of pacemaker potentials. Beta receptor activation increases $i_{Ca,L}$ (via a cAMP mechanism) in all cells.

Three functional properties of different cardiac cells generate **orderly normal heart beating** in a way that depends on the basic electrophysiology of cardiac cells. The properties are:

**Pacing:** Initiation of the cardiac cycle at special sites (SAN with the AVN in reserve)

**Conduction:** Appropriate speed of impulse transmission (slowest in AVN, faster in atria, much faster in V and fastest in H-P fibres) through different cardiac cell masses.

**Refractoriness:** That period after a first action potential when a second action potential cannot be initiated (refractoriness is longest in H-P, than in V, than in A)

Normally a ‘balance’ of the above three properties produces rhythmic beating initiated by the SAN (modulated by the cardiac autonomic nervous system) and spread in an orderly manner throughout the heart.

Disturbance of the balance of the above three properties can result in cardiac arrhythmias.

Disturbances that can **CAUSE CARDIAC ARRHYTHMIAS** include:

1) Inappropriate cardiac autonomic nerve activity - sympathetic (excitatory) on all parts of the heart; parasympathetic (inhibitory) on atria and SA/AV nodes only.

2) Ions and chemical disturbances - potassium, hydrogen, sodium, calcium

3) Pre-existing anatomical defects – missing, or extra, cardiac tissue, mutation of ion channels, particularly $K$ channels.

4) Pathological damage - enlarged atria, myocardial ischaemia, myocardial infarction (small and large scars)

All of the above can initiate and sustain the electrophysiological mechanisms that give rise to arrhythmias, e.g. **Ectopic foci** – where normally non-pacing cells in A and V takeover pacing.

**Re-Entry** – where a self-sustaining circuit of excitation is set-up in a part of the heart as a result of pathological changes in conduction and refractoriness at a site within the re-entry circuit.

**After potentials** – where a second action potential occurs near the end of a normal action potential.
Types of Arrhythmias that result include:-

SAN and AVN arrhythmias.
Sinoatrial nodal arrhythmias - bradycardia (slow rate), tachycardia (fast rate), sick sinus.
Atrioventricular nodal arrhythmias – ectopic beats, conduction failure (AV block), or AVN re-entry (nodal tachycardias).

ATRIAL arrhythmias.
Atrial Tachycardia (a.k.a. atrial flutter) – often with AV block so V rate does not follow A on 1:1 basis.
Atrial Fibrillation - chaotic atrial contractions that impair atrial filling resulting in an irregular high ventricular rate

VENTRICULAR arrhythmias
Conduction defects in ventricle
Ventricular Tachycardia (VT) - rapid regular V rate which impairs ventricular filling (reduces cardiac output). VT can be episodic (terminate spontaneously) but can degenerate to ventricular fibrillation. (Torsade de Pointes = a special type of ventricular tachycardia (often drug-induced)).
Ventricular Fibrillation (VF) - irregular chaotic ventricular cell depolarizations and uncoordinated contractions hence no cardiac output is possible and hence death ensues unless a rhythm returns after electrical defibrillation.

Current treatment of arrhythmias include:
- Electrical methods: - via electrical stimulators and electrodes implanted internally, or used externally.
- Ablation of damaged cardiac tissue causing an arrhythmia by surgical electro-cautery, or ultrasound means.
- Drug therapy. Many drugs have been used, but with limited success.

The effectiveness of drug treatment depends on various factors, such as:
1. The site and type of arrhythmia (nodal, atrial, ventricular) - non-cardiac causes (e.g. drugs, thyrotoxicosis, ionic imbalance, etc.); mechanisms of induction and maintenance of arrhythmias, such ectopic foci, re-entry)
2. The pharmacological actions of the available antiarrhythmic drugs (electrophysiological, pharmacological and toxicological mechanisms).
3. Pharmacokinetic properties of the different antiarrhythmic drugs.
4. Toxicity of available antiarrhythmic drugs (whether over-expression of basic mechanism of action, ancillary pharmacological actions, or drug specific toxicities).

Examples:-
Beta blockers limited use for atrial and ventricular arrhythmias by blocking arrhythmia-inducing beta-receptor stimulation.

Adenosine given i.v. terminates atrio-ventricular node re-entry arrhythmias by abolishing arrhythmic re-entry circuits in the atrio-ventricular node. Toxicity, mainly vasodilation is short-lived because of the very short half-life of adenosine in the blood.
Attempts to classify antiarrhythmic drugs can be made on electrophysiological, pharmacological and therapeutic uses. The classification systems can be empirical or functional target directed in nature but any classification is neither fully inclusive, nor exclusive.

Two major systems, each of limited utility, are: 1) Vaughan Williams and 2) the Sicilian Gambit. In the absence of a common agreed classification it is difficult to generalize in terms of best drugs for each type of arrhythmia and expected toxicities.

*The Vaughan Williams/Harrison classification is based upon:*-
- **Experimental** actions at the molecular (ion channel) & cellular electrophysiological (ionic current) levels and/or pharmacological properties, of a drug;
- ** Clinically**, on electrophysiological actions of the drug in man.

This *Classification* is incomplete and of limited utility. Initially it was helpful but its utility was severely undermined by failure of many of the drugs in the different is classes (particularly Class I).

The *Sicilian Gambit* attempts to rationalize the use of antiarrhythmic drugs as formulated at a conference on the island of Sicily. It attempts to both rationalize and aid the use of antiarrhythmic drugs based upon: molecular target, ionic mechanisms and channel state dependency of action, and antiarrhythmic usefulness. This leads to a matrix of targets, mechanisms, and therapeutic uses of great complexity that can be presented in a tabular form that aids understanding.

Neither classification is particularly helpful but general problems with regard to the toxicity and usefulness have led to a reduced interest in all antiarrhythmic drugs. Implanted and external electrodes are increasingly used to both detect and treat arrhythmias. Arrhythmias are detected from the ECG while the site of generation can be found by local electrograms. If particular sites for the genesis of certain arrhythmias are found they can be ablated by surgical, or electro-surgical, techniques while electroconversion can be used to terminate severe, and lethal arrhythmias such as a ventricular fibrillation.

The table follows the V-W classification, despite its limitations.

<table>
<thead>
<tr>
<th>Class</th>
<th>Experimental cardiac actions</th>
<th>Clinical cardiac observations</th>
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<tbody>
<tr>
<td>I</td>
<td>All in Class I are cardiac sodium current blockers – reduce Phase 0 of atrial and ventricular action potentials</td>
<td>Depends upon sub-class type</td>
</tr>
<tr>
<td>Ia</td>
<td>Also blocks potassium currents (thereby slow repolarization) and muscarinic receptors. The sodium channel blockade produced is moderately frequency dependence with degree of block greater at high rates. Potentially arrhythmogenic.</td>
<td>Widen QRS and QT. Slows conduction in ventricles and atria. Causes torsade de pointes. Nowadays rarely used due to lack of effectiveness and excessive toxicity.</td>
</tr>
<tr>
<td>Ib</td>
<td>Only blocks sodium channels at high heart rates-(high frequency dependence) which would seem of value but this has not translated into much greater clinical utility.</td>
<td>ECG effects at high but not at normal heart rates, but CNS effects can occur since such drugs easily penetrate into the brain. Rarely used.</td>
</tr>
<tr>
<td>Ic</td>
<td>Blocks sodium channels regardless of heart rate, arrhythmogenic.</td>
<td>Widen QRS and slows conduction in ventricles and atria. Too arrhythmogenic for general use.</td>
</tr>
<tr>
<td>II</td>
<td>Beta blockers which are only effective when cardiac beta activation is causing the arrhythmia – not a frequent occurrence</td>
<td>Bradycardia and prolongation of PR interval. Limited effectiveness.</td>
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<tr>
<td>III</td>
<td>Prolongs action potential (by blocking repolarizing potassium currents)</td>
<td>Widens QT interval and not very effective. High liability for causing the arrhythmia of T de P and so of limited use.</td>
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<tr>
<td>IV</td>
<td>Blocks calcium currents particularly in AV nodal tissue therefore useful value in nodal arrhythmias</td>
<td>Prolong PR interval and may produce bradycardia. Hypotension</td>
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</table>
Other drugs used to treat arrhythmias which are not in the above classification:-

**Adenosine** acts primarily to depress calcium channels in nodal tissue (electrophysiological actions very similar to acetylcholine). Very short duration of action limits side effects; highly effective in paroxysmal atrial tachycardia.

**Digoxin** - a cardiac glycoside whose actions are mediated indirectly via the vagus nerve, as well as directly on cardiac cells (AVN, atria, ventricles). Limited usefulness

**Autonomic drugs** such as muscarinic antagonists (atropinics) which block the action of the parasympathetic nervous system (acetylcholine) on the heart, β₁ agonists to stimulate the heart via beta receptor activation. Can be very effective in particular situations.

**Ions (K⁺, HCO⁻³)** used to correct the ionic imbalances causing arrhythmias

**Selective ion channel blockers**

Highly selective ion channel blockers with specific actions on particular ion channel subtypes are continually being sought in an attempt to find drugs that are selective for particular arrhythmias (as with the Sicilian gambit). This is an active area of research in particular for K channels, for a slow Na channel, and for channels activated by stretch of cardiac tissue. This approach has not proven particularly successful possibly because a single type of ion channel is not, in most cases, the *sine qua non* for any particular arrhythmia.

**TOXICITY & SIDE EFFECTS OF ANTIARRHYTHMICS.**

Can involve the following serious and even life-threatening problems:-

**Cardiac depression & hypotension with:**

- Class I (due to sodium channel blockade and vasodilation).
- Class II (removal of cardiac sympathetic tone).
- Class IV (block of calcium channels in heart and blood vessels).

**Induction of arrhythmias:**

- Sudden death with Class I (especially Class Ic).
- Torsade de pointes (with Class III and Class Ia).
- AV node block (with Class II and IV)

**Vascular depression** (vasodilation): occurs with Class I and IV drugs and adenosine

**Excess pharmacological actions:** Beta blockers produce asthma, fatigue, etc.; atropine-like actions with Class Ia drugs; constipation with verapamil

**Drug specific toxicity:**

- **Digoxin** various gastrointestinal and nervous system toxicities.
- Cinchonism with **quinidine**.
- Lupus syndrome with **procainamide**.
- Pulmonary fibrosis, skin colouration with **amiodarone**