

Cardiac arrhythmias & anti-arrhythmic drugs



The ionic basis of normal cardiac action potential

- Three types of ion channels are responsible for the generation and propagation of cardiac action potential:

(1) The fast Na^+ - channels:

- open very fast and inactivate very fast

- activated at membrane potentials

between -70 and -50 mV

- responsible for the rapid upstroke of AP in the atria, bundle of His, Purkinje fibers & ventricles

(2) Slow Ca^{2+} - Na^{+} channels:

- open slowly and take a long time to inactivate

-responsible for the plateau in the ventricular AP

(3) Slow K^{+} channels: responsible for the repolarisation phase of cardiac action potential

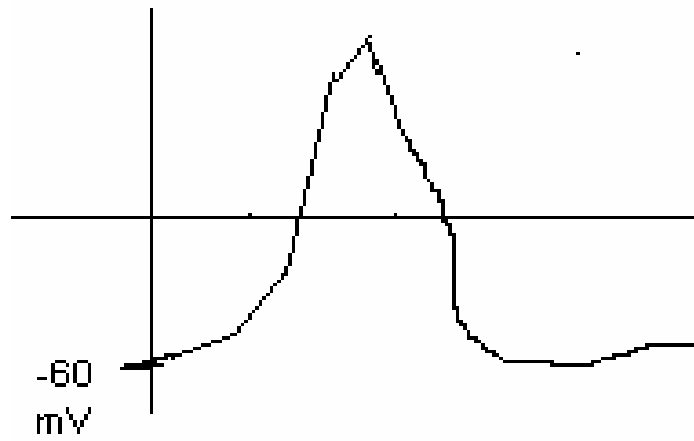
Cardiac muscle can be divided into 3 main types

(1) Tissue with spontaneous pacemaker activity

(a) SA node:

- this is the pacemaker
- generates heart beats (70 – 80 beats /min)
- has no fast Na^+ - channels
- low permeability to K^+
- AP rises slowly & falls slowly

Action Potential on the SA node



(b) The AV node: (40 – 60 beats/min)

-like the SA node AP is due to currents through the Ca^{2+} - Na^+ channels

- AP rises slowly & falls slowly

- In both SA & AV nodes the depolarising phase of AP is carried almost entirely by Ca^{2+}
- Na^{2+} influx plays only a minor role

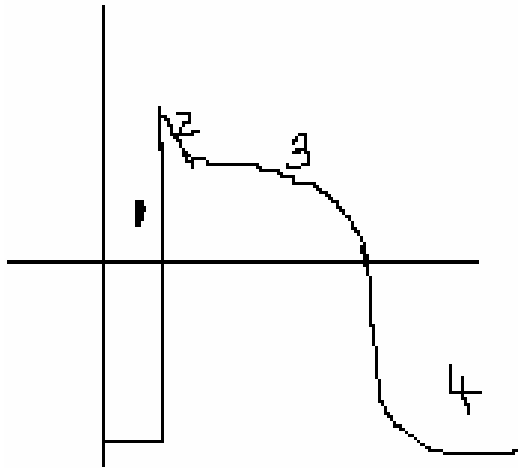
(2) Specialised high velocity conducting tissue.

(a) bundle of His (b) the Purkinje fibres

- AP is due to fast Na^+ currents - upstroke of AP
- The slow Ca^{2+} - Na^+ currents – Plateau of AP
- K^+ channels – repolarising phase

(3) Atrial & Ventricular myocardium

- Fast sodium channels
- Ca^{2+} - Na^{+} channels
- K^{+} channels
- The fast sodium channels make conduction velocity in atria & ventricles faster than that in the AV node
- Allows electric activation of the two to occur in a short period of time
- Permits co-ordinated contraction



Cardiac dysrhythmias (arrhythmias)

- ❑ Disorders of cardiac rhythm
- ❑ Any disorder of cardiac rhythm is an arrhythmia

Cardiac arrhythmias occur due to:

- ❑ Disorders of impulse generation
- ❑ Disorders of impulse conduction
- ❑ Disorders of both generation & conduction

Disorders of impulse generation

- The most common problem is the development of an ectopic focus
- A site of pacemaker activity additional to the SA node

Ectopic foci may be induced by:

- (a) Damage to the cardiac muscle (Myocardial infarction)
- (b) Drugs e.g. general anaesthetics (halogenated anaesthetics can sensitize the myocardium to the actions of catecholamines causing arrhythmias)

(C) Metabolic disturbances e.g.
hyperthyroidism in which there is
increased sympathetic activity &

increased sensitivity to the actions of
catecholamines leading to arrhythmias

(D) Emotion, excitement:

- release catecholamines
- Increase levels of cAMP which is arrhythmogenic

Arrhythmias due to disorders of impulse generation can be classified into 2 groups depending on the location of the ectopic focus

(A) SUPRAVENTRICULAR ARRHYTHMIAS

- Ectopic focus lies in the atria or AV node.
- Supraventricular arrhythmias drive the ventricles at an increased rate which:
 - reduce stroke volume – failure
 - increase work load on the heart

Types:

(1) Atria flutter:

- ❑ Characterized by a regular & very fast atrial rate (150 – 350/min)
- ❑ The ventricular rate becomes abnormally high but regular

Cause of flutter

- ❑ A single ectopic focus in the atria muscle
- ❑ ECG shows several P waves for each QRS complex (in ratios of 2:1, 3:1, or 4:1)
- ❑ P waves are normal

(2) Atrial fibrillation:

- Caused by the presence of multiple ectopic foci in the atrial tissue
- The atria beat at the rate of 200-600/min
- P waves are not normal
- Ventricular rate is higher (much lower than atrial rate) but irregular

(3) Supraventricular paroxysmal tachycardia:

- ❑ Sporadic episodes of increased heart rate
- ❑ Caused by the appearance of an intermittent ectopic focus in the atria
- ❑ Normal sinus rhythm can be induced by reflex vagal stimulation (pressure applied to the eyeballs or to one of the carotid sinus)

(B) VENTRICULAR ARRHYTHMIAS

- Occur when there is an ectopic focus in the ventricles
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Types:

(1) Ventricular fibrillation:

- rapid uncoordinated ventricular contractions
- Severe reduction in cardiac output

NB: -ventricular fibrillations are rapidly lethal

- pharmacological intervention has a limited role

-Patient should be given a DC electric shock to cause reversion to normal rhythm

(2) Ventricular paroxysmal tachycardia

- caused by the intermittent appearance of an ectopic focus in the ventricles

- characterised by:

- (i) sporadic episodes of increased heart rate

- (ii) the QRS complexes outnumber the P waves

DISORDERS OF IMPULSE CONDUCTION

(1) HEART BLOCK

- Most often occur in the AV node and bundle of His
- a block may be caused by a localized damage or depression of AV node or bundle of His

Causes:

- (1) ischaemia of AV node or nodal fibres
- (2) compression of AV node or bundle of His by calcified heart tissue
- (3) inflammation of AV node or bundle of His (different types of myocarditis e.g. diphtheria, rheumatic fever)
- (4) extreme stimulation of the heart by the vagus nerve (carotid sinus syndrome)

Degrees of heart block

- (1) 1st degree heart block: PR interval is prolonged (longer than 0.2 S) but ECG remains normal
- (2) 2nd degree block: Some P waves do not initiate QRS complexes due to failure of AV conduction BUT no additional beats arise from the ventricular pacemaker activity
- (3) 3rd degree block: -AV conduction is blocked
 - Ventricular contractions arise from the ventricular pacemakers

Result:

- slower than normal ventricular rate
- no coordination between P waves and QRS complexes

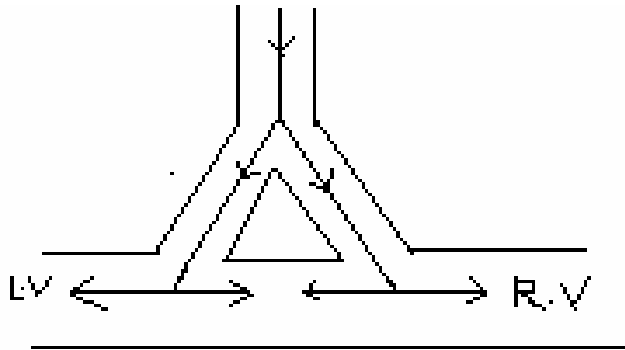
TREATMENT:

- Use of artificial pacemakers
- agonists at β -adrenoceptors may be useful in the short term but in general drug treatment is of limited use for heart block

(2) Re-entry arrhythmias

- occur due to the presence in the cardiac muscle of of abnormal conduction pathways.
- The pathways may be the result of:
 - (a) damage to the heart muscle (myocardial infarction caused by ischaemia)
 - (b) the effect of drugs e.g. β -adrenoceptor agonists, digoxin, quinidine which alter the excitability of the heart muscle

Right bundle branch
left bundle branch



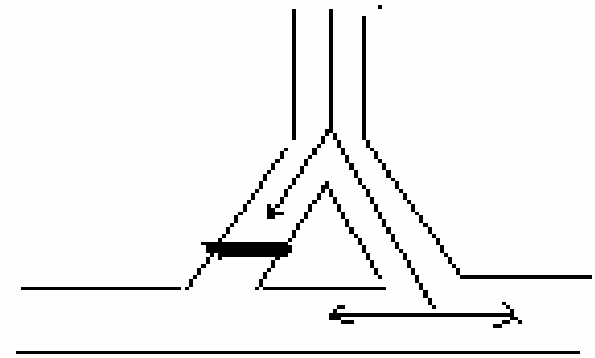
NORMAL HEART

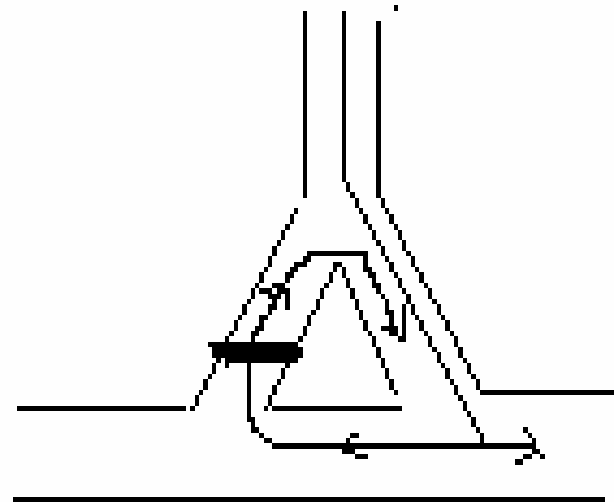
- wave of depolarisation from AV node enters both L & R branches of bundle of His
- waves of depolarisation from either side towards the central portion of V. muscle cancel each other

- only waves travelling upwards to L & R ventricular muscle remain

- these diminish in intensity and die off as they come to the base at the connective tissue btwn ventricles & atria

(B) LEFT BUNDLE DAMAGED





- The right branch is damaged by ischaemia
- ~~anterograde but not retrograde conduction is blocked~~
- the wave of conduction from the normal branch may enter the damaged branch retrogradely and reappear in the normal branch
- this completes a re-entry circuit
- Rare situation: the WOLFF-PARKINSON-WHITE SYNDROME

ANTIARRHYMIC DRUGS

CLASSIFICATION:

GROUP 1: INHIBITORS OF Na⁺ INFLUX

- ❑ Inhibit the fast Na⁺ channels
- ❑ also block the slow Ca²⁺ - Na⁺ channels
- ❑ reduce intracellular Ca²⁺ leading to a -ve inotropic effect
- ❑ must be used with care where heart failure is suspected

- inhibition of Na⁺ channels leads to either:
 - (a) slowing of conduction

- (b) increase in refractory period
- Drugs under this group have local anaesthetic or membrane stabilizing effect

SUBGROUPS:

GP 1A:

- suitable for ventricular & supraventricular arrhythmias
- include: quinidine, procainamide, disopyramide, lorcaïnide

GP 1A:

In the therapeutic concs they:

- raise the shreshold for excitation (lengthen AP duration)
- cause minor slowing of intracardiac conduction
- widen the QRS complex
- they prolong the effcetive refractory period of atrial, venrticular & purkinje fibres

GP 1A:

Quinidine, procainamide & disopyramide
have a low therapeutic index

- aggravate myasthenia gravis (skeletal muscle)
- hypotension (vascular smooth muscle)
- varying degree of atropine-like effect.

GROUP 1 B

— suitable for ventricular arrhythmias —

□ include: lignocaine, phenytoin,
mexiletene & tocainide

Properties:

-they shorten AP duration & effective
refractory period

- have no effect on intracardiac
conduction or QRS complex

GROUP 1B

Lignocaine:

- given I.V. as the 1st line drug in the treatment of ventricular arrhythmias after myocardial infarction & surgery
- inactive orally

Phenytoin:

- used almost exclusively in digitalis-induced ventricular arrhythmias

GROUP 1B

Tocainide:

- analogue of lignocaine
- active orally and I.V
- has similar electrophysiological & haemodynamic properties to lignocaine.
- longer acting

Mexiletene:

- similar electrophysiological properties to lignocaine
- active orally & I.V.

GROUP IC

Drugs in this group have 2 effects:

(a) slow intracardiac conduction

(b) widen the QRS complex

They do not so much affect the threshold of excitation

Included: Flecainide, Encainide,
Propafenone

FLECAINIDE

- ❑ Slows conduction in atria, His-purkinje system, accessory pathways & ventricles

- ❑ in therapeutic concs it causes lengthening of the PR & QRS intervals
- ❑ it is a powerful broad spectrum antiarrhythmic effective VS atrial arrhythmias, tachycardias involving accessory pathways (Wolff-Parkinson-White syndrome) & ventricular arrhythmias

Encainide: similar antiarrhythmic spectrum to flecainide

Propafenone:

- has additional minor β -blocking and calcium channel antagonist properties
- effective against supraventricular and ventricular arrhythmias

GROUP II

β -ADRENOCEPTOR ANTAGONISTS

- effective in arrhythmias associated with sympathetic overactivity or increased circulating catecholamines
- eg. Myocardial infarction, emotion, exercise, anaesthesia
- they reduce automaticity (ectopic pacemaker)

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- increase effective refractory period
 - decrease conduction velocity
 - Propranolol, atenolol, metoprolol, acebutolol & timolol

GROUP II

Bretylium:

- ❑ has adrenergic neurone blocking activity
- ❑ suppresses release of NA
- ❑ It is both GP II & III

GROUP III

DRUGS THAT PROLONG BOTH THE ACTION POTENTIAL AND REFRACTORY PERIOD

- ❑ Also called slow repolarizers
- ❑ they block K^+ -channels
- ❑ prolong the duration of the plateau region of cardiac AP
- ❑ lengthen effective refractory period

Drugs: Amiodarone, bretylium, sotalol

Amiodarone:

- ❑ blocks K^+ & Na^+ - channels
- ❑ it is a non-competitive antagonist at alpha & β -adrenoceptors (Class I and class II effects)
- ❑ effective against many arrhythmias including Wolff-Parkinson-White syndrome)
- ❑ due to side effects it is only used when other drugs can not be used

- ❑ It causes irreversible liver damage, thyroid disorders (its molecule contains iodine)
- ❑ it causes neuropathy & pulmonary alveolitis

Sotalol:

- ❑ it is a non-selective beta-blocker
- ❑ also has class III activity
- ❑ prolongs atrial & ventricular action potential duration
- ❑ prolongs refractory period

GROUP IV

INHIBITORS OF CALCIUM INFLUX

- Inhibit the slow inward Ca^{2+} - current which result in:
 - (1) slowed conduction
 - (2) prolonged refractoriness in the AV node
- useful for supraventricular tachycardia involving the AV node.
- Blocks intranodal re-entry circuits

- effective in some types of re-entry tachycardia in which the AV node is involved
- Not effective in Wolff-Parkinson-White syndrome

Verapamil: effective when the Ca^{2+} channels are either activated or inactivated (occurs when frequency of AP is high) [use-dependent]

Diltiazem: similar antiarrhythmic properties to verapamil

Nifedipine: not anti-arrhythmic. It does not exhibit use-dependence

it also blocks the slow Ca^{2+} channels but it is only effective when the channels are in the activated state

NOT CLASSIFIED

DIGOXIN:

- ❑ slows conduction and prolongs the refractory period in the AV node and bundle of His
- ❑ used in atrial fibrillation which it does not stop but it slows & strengthens the ventricular beat
- ❑ reduces the frequency at which impulses pass along the conducting tissue
- ❑ Principal indication: CHF associated with atrial fibrillation

Adenine nucleotides

□ Adenosine & ATP

- used as substitutes for verapamil in the treatment of supraventricular tachycardias
- they act via purinergic receptors situated in the SA & AV nodes
- stimulation of these receptors hyperpolarises cells resulting in suppression of automaticity and conduction

- Interrupt re-entry circuits in AV nodal tachycardia, and AV tachycardia involving an accessory pathway (Wolff-parkinson-White syndrome).
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ALTERNATIVE TO DRUGS

- (1) use of pacemakers
- (2) DC shock - if atrial size is normal it causes reversion to normal rhythm in most patients with atrial fibrillation (relapse 60% within 1 yr)

(3) surgical ablation of ectopic focus or bundle of His to control supraventricular arrhythmias - pacemaker

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Ed. John L. Reid, Peter C. Rubin & Brian Whiting
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- (5) Textbook of Medical physiology 7th ed. By Arthur C. Guyton

Cardiac glycosides

- ❑ Compounds obtained from plants of the foxglove family
 - *Digitalis lanata* (white fox glove)
 - *Digitalis purpurea* (purple fox glove)
 - other tropical & temperate zone plants
- ❑ Certain toads have skins capable of producing structures similar to the cardiac glycosides (bufadienolides)

- There is evidence of the presence of an endogenous digitalis-like factor closely similar to ouabain
- Its physiological significance still uncertain
- Fox gloves contain several cardiac glycosides with similar actions. Three of these are digoxin, digitoxin and ouabain
- Digoxin is the most important therapeutically

Structure

- ~~The cardiac glycosides have 3 components~~
 - (a) a sugar moiety (1-linked monosaccharides)
 - (b) a steroid
 - (c) a lactone (5-member ring) at C17
- it is essential for activity
- Substituted lactones can retain biological activity even when the steroid moiety is removed
- Bufadienolides have a 6-membered ring

Properties of the cardiac glycosides

	ouabain	digoxin	digitoxin
Lipid solubility	low	medium	high
Oral availability	0	75%	> 90%
T _{1/2}	21	40	168
%PP binding	0	20-40	>90
% metabolized	0	<20	> 80
V distrib (L/kg)	18	6.3	0.6

- Digoxin is the most widely used preparation
- ~~□ Fairly well absorbed after oral administration~~
- About 10% of individuals harbour enteric bacteria that inactivate digoxin in the gut
- This reduces bioavailability requiring higher than average maintenance dosage
- Treatment of such patients with antibiotics can result in a sudden increase in bioavailability and digitalis toxicity

Uses

- Treatment of cardiac failure with rapid atrial fibrillation
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EFFECT ON THE HEART

- Cardiac glycosides increase the force of contraction
- Reduce the rate of conduction through the AV node
- Slow the heart

However they disturb cardiac rhythm through:

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- blockade of AV conduction
 - increasing ectopic pacemaker activity

Mechanism of action

There are two important ion transport mechanisms we need to know:

- (1) The Na^+/K^+ -ATPase
 - An energy dependent transporter
 - Has two α -subunits and two β -subunits
 - It is attached to cell membrane

- Has sites for binding 3 Na⁺ ions and a locus for hydrolyzing ATP facing the inside of the cell membrane
- 2 K⁺ - binding sites facing extracellularly
- Na⁺/K⁺-ATPase hydrolyses one ATP molecule and uses the released energy to remove 3 Na⁺ from the cell in exchange for 2 K⁺ from the extracellular space

(2) $\text{Na}^+/\text{Ca}^{2+}$ exchanger

- Moves 1 Ca^{2+} outward in exchange for 3 Na^+ which move inward into the cell
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Cardiac glycosides:

- Binds to the α -subunit of the Na^+/K^+ - ATPase and inhibit it
- Reduces its affinity for K^+
- Inhibits the exchange of 3 Na^+ for 2 K^+
- The -ve membrane potential is altered
- Excess $[\text{Na}^+]_i$ cause depolarisation

- The increase in intracellular Na^+ decreases the efficiency of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger
- Cause an increase in $[\text{Ca}^{2+}]_i$
- This increases the force with which the heart contracts

The depolarisation that results from the inhibition of the Na^+/K^+ -ATPase has 2 consequences:

The depolarisation that results from the inhibition of the Na^+/K^+ -ATPase has 2 consequences:

- (1) It inhibits action-potential generation and propagation in some cells; leading to transmission block e.g the AV node
 - this is useful in atrial fibrillation
- (2) In other cells e.g in the bundle of His, automaticity is increased
 - Leads to ventricular dysrhythmias

Effects of K^+ depletion

(1) During diuretic therapy

(2) Secondary hyperaldosteronism

- Reduces the availability of K^+ at the K^+ -binding sites of Na^+/K^+ ATPase
- This further limits the $3Na^+/2K^+$ exchange & may lead to the development of fatal ventricular arrhythmias

Indirect actions on cardiac cells

- It augments nerve activity
 - by a central vagal stimulation
 - increases cell sensitivity to Ach
 - these actions slow the heart & summate with the direct AV nodal blocking actions

Digoxin toxicity

- It has a very low therapeutic index
- ~~□ Toxic effects are due to inhibition of the Na⁺/K⁺ ATPase~~
- Stimulate the chemoreceptor trigger zone (CTZ) causing nausea, anorexia & vomiting
- Disturb colour vision
- Impair vision acuity (snowy vision, flickering or flashes of light, dimming of vision)
- May be due to inhibition of Na⁺/K⁺ ATPase necessary for normal cone function

- Cardiac arrhythmias: almost any pathological arrhythmia can be imitated by digoxin toxicity
- Ectopic beats; ventricular tachycardia & fibrillation

The increased automaticity responsible for this arises in the Purkinje fibres

Large $[Ca^{2+}]_i$ cause membrane-potential oscillations

Treatment of digoxin toxicity

- ❑ Terminate digoxin
- ❑ Increase plasma $[K^+]$ to stimulate Na^+/K^+ ATPase and aid Ca^{2+} extrusion via the Na^+/Ca^{2+} exchanger
- ❑ Use phenytoin/propranolol
- ❑ Digoxin-specific antibody fragments are also available for use in life-threatening situations

Position of Digoxin Vs other drugs

- ❑ ACEIs have shown a better performance in prolonging survival in patients with heart failure
- ❑ Recent studies have shown that while digoxin does not reduce mortality it does reduce hospitalisation when added to diuretics & ACEIs in patients with chronic heart failure