Cardiac arrhythmias

This document does not consider management of individual arrhythmias – look elsewhere, e.g. OHCM.

Physiology

**Automaticity** = ability of specialised cardiac conducting tissue to spontaneously initiate a cardiac electrical impulse

Tissues with spontaneous pacemaker activity (i_{dep}, upstroke)
- SA node ~70 beats per minute
- AV node ~45 beats per minute
- His bundle ~25 beats per minute

Cardiac action potential

![Cardiac action potential diagram](image)

- Phase 0: rapid depolarisation due to sodium influx \( i_{Na} \)
- Phase 1: brief rapid depolarisation due to potassium efflux \( i_{Na}, i_{To} \)
- Phase 2: slow repolarisation due to calcium influx \( i_{Si} \)
- Phase 3: rapid repolarisation due to potassium efflux \( i_{K} \)
- Phase 4: slow depolarisation due to potassium influx, sodium and calcium efflux \( i_{F} \)

Aetiology of cardiac arrhythmias
1. Altered rate of spontaneous discharge
2. Formation of re-entry circuits + premature beat

Vaughan-Williams classification

**Class I**
- Block rapid sodium influx in phase 0 of action potential
- ‘Membrane stabilisers’
  - Ia: lengthen refractory period (phase 2) E.g. quinidine, procainamide, disopyramide
  - Ib: shorten refractory period E.g. lignocaine
  - Ic: no effect on refractory period E.g. flecainide, encaïnide, propafenone

**Class II**
- Reduce phase 4 discharge rate by blocking sympathetic tone
- ‘β-blockers’
  - E.g. atenolol, bretylium tosilate, sotalol

**Class III**
- Lengthen refractory period without effect on phase 0 – block \( i_{K} \) during phase 3
- ‘Amiodarone-like’
  - E.g. amiodarone, bretylium tosilate, sotalol

**Class IV**
- Depress phase 2 slow inward calcium current and thus prolong refractory period
• ‘CCBs’ (excluding DHPs)
  E.g. verapamil
• Procorolan

**Others** that do not fit this classification
  E.g. adenosine, digoxin

*Note*
1. Drugs are classified according to their predominant mode of action but often act by several mechanisms, particularly at high doses
2. A physiological classification gives little indication of appropriate drug selection for a given rhythm disturbance
3. All anti-arrhythmic drugs are pro-arrhythmic
  o E.g. classes Ia/Ic/III \(\rightarrow\) lengthen QT \(\rightarrow\) potential for torsades

### Non-pharmacological measures

Choice of therapy depends on state of patient, arrhythmia and availability.

**Acute**
- Vagal manoeuvres
- Electrical DC cardioversion
  - Very effective, hence used when patient is very unwell (e.g. arrest)
- Pacing
  - Internal
  - External

**Chronic**
- Pacing
  - Internal
- AICD
- Radiofrequency ablation
- Surgical, e.g. Maze procedure

### Adenosine

**Mechanism**
- Purine nucleoside
- Acts at specific purine receptor, activating K+ channels
- Temporarily blocks AV conduction
- \(t_{1/2} = 8-10s\)

**Indications**
- *Diagnostic*, to reveal atrial activity
- *Therapeutic*, in termination of AVNRT/AVRT

**Administration**
- Use in monitored area only, with ECG
- Rapid IV bolus injection into a large arm vein, large flush
- 6-12-12-12mg

**Contraindications**
- Sick sinus syndrome, unless pacing wire in situ
- Known 2\(^{nd}/3^{rd}\) degree heart block
- Asthma

**Cautions**
- AF/atrial flutter with accessory pathway
- Heart transplant (use 3mg starting dose)

**Adverse effects**
- Transient chest discomfort, facial flushing, bronchospasm, anxiety
- Patients usually feel awful for a few seconds – warn them

**Interactions**
- Antagonised by theophylline
  - Purinoceptor antagonist
- Potentiated by
  - Dipyridamole (need to halve the dose)
    - Inhibitor of nucleoside metabolism
  - Carbamazepine

**Verapamil**

**Mechanism**
- Class IV agent (non-DHP CCB)

**Indication**
- Termination of SVT (adenosine failed)
- Rate control in atrial fibrillation including prophylaxis of paroxysmal AF

**Contraindications**
- Heart failure
- Sinoatrial disease
- Heart block
- SVT in WPW
- VT (may cause fatal hypotension)

**Adverse effects**
- See CCBs

**Interactions**
- Increases plasma digoxin concentration (interferes with tubular clearance)

**Digoxin**

**Mechanism**
- Is one of the active ingredients of the foxglove; a cardiac glycoside
- Direct action
  - Competes with K⁺ at Na⁺/K⁺-ATPase
  - Decreased passive 3Na⁺/Ca²⁺ exchange
  - Hence ↑intracellular [Ca²⁺]
    - +ve inotropic action
- Indirect action
  - ↓sympathetic/↑ parasympathetic (vagal) tone
    - ↓SA automaticity
    - ↓AVN conduction

**Indications**
- AF/atrial flutter, to slow rate of ventricular response
- Cardiac failure for positive inotropic action

**Administration**
- Oral or IV (response may still take several hours, greater risk of arrhythmias)
- Loading regime, e.g. 500µg – 12h – 500µg – then 62.5-250µg/day (depends on age, size, renal function)
  - ↓dose in elderly, RF, CCF, amiodarone use (halve dose)
  - ↑dose in thyrotoxicosis (double dose)
Contraindications
- 2nd/intermittent 3rd degree heart block
- SVT in WPW
- HOCM (+ve inotropes avoided - can worsen obstruction)

Adverse effects
- *Any* cardiac arrhythmia, but esp. bradycardia and heart block
  - Pulsus bigeminus may herald toxicity
  - ↓ST/1st degree heart block indicative of therapy not toxicity
  - More susceptible with ↓K⁺, ↓Mg²⁺, ↑Ca²⁺
- Anorexia, N, V, D, abdo pain
- Neuropsychiatric
  - Xanthopsia
  - Confusion and restlessness
- Gynaecomastia (steroid-like structure)

Interactions
- Displaced from protein by amiodarone
- Quinidine/quinine and CCBs interfere with tubular clearance
- Neomycin prevents conversion to inactive metabolite in GI tract

Note
- Is renally excreted and toxicity risk increased in renal impairment
- DigIToxin is hepatically metabolised
- t₁/₂ = 36h, so usually loading regime given
- Has narrow therapeutic index; TDM available but correlation between level and degree of toxicity is not tight (toxicity also depends on susceptibility of conducting system), i.e. use clinical judgement
- Overdose managed by
  - Cardiac pacing for bradyarrhythmias
  - Phenytoin useful for tachyarrhythmias
  - Digibind antibody fragments

Lignocaine

Mechanism
- Class Ib agent (shortens refractory period)

Indications
- Largely superseded by amiodarone
- Second line treatment and prophylaxis of ventricular arrhythmias, esp. after MI
  - Selectively active in suppressing ventricular premature beats/VT

Contraindications
- Sino-atrial disorders
- Heart block

Adverse effects
- Bradycardia, hypotension, heart failure
- Convulsions, blurred vision, paraesthesiae

Note
- Very short t₁/₂ and extensive first-pass metabolism restricts to IV use
- Hepatic metabolism
- Mexiletine is a similar agent with kinetics supporting oral administration, but patients don’t usually tolerate it (mostly CNS side-effects)

Procainamide

Mechanism
- Class Ia agent (lengthens refractory period)

**Indications**
- Ventricular arrhythmias, esp. after MI

**Administration**
- IV

**Contraindications**
- Heart failure
- Heart block
- SLE
- Torsades (can exacerbate)

**Adverse effects**
- N, D
- Rashes
- SLE-like syndrome
- Agranulocytosis
- Angioedema

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**Flecainide**

**Mechanism**
- Class Ic agent (no effect on refractory period)

**Indication**
- Paroxysmal AF
- SVT with accessory pathways
- VT where other drugs ineffective

**Administration**
- Oral or IV

**Adverse effects**
- Vertigo
- Visual disturbance
- Vely inotropic
- Peripheral neuropathy
- Tremor
- Hepatic dysfunction

**Interactions**
- Largely hepatic P450 metabolism + some renal elimination
  - $\uparrow T_{1/2}$ in elderly/HF/RF

**Note**
- Flecainide fell into disuse following premature termination of the CAST study
- This study evaluated flecainide in the suppression of ectopic ventricular activity post MI
- Sudden cardiac mortality in the placebo group was significantly lower than in the flecainide group
  - Underlines the arrhythmogenic nature of anti-arrhythmics
  - Would probably have happened with amiodarone etc.?
  - Flecainide unfortunate choice due to its metabolic pathway?
  - Now only used in patients without prior MI, and at low risk of developing MI

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**Propafenone**

**Mechanism**
- Class Ic agent, some class II activity
Adverse effects
• Antimuscarinic

**Beta-blockers (as anti-arrhythmic agents)**

**Mechanism**
• Block dysrhythmogenic effect of catecholamines (no significant own proarrythmic effects)
  o ↓SA automaticity
  o ↓AVN conduction
  o –vely inotropic

**Indications**
• Emergency rate control in AF (act much faster than digoxin – no loading)
• Prophylaxis or rate control in SVT/AF

**Adverse effects**
• See β-blockers

*Note*
**Sotalol** also possesses class III (amiodarone-like) activity, unlike other β-blockers its only indications are arrhythmias
**Esmolol** is an ultra-short acting β-blocker that is given by IV infusion to control rate in SVT (40mg over 1min, then 50μg/kg/min)

**Sotalol**

**Mechanism**
• Class II/III agent

**Indications**
• Paroxysmal SVT
• Maintenance of sinus rhythm after cardioversion of atrial fibrillation/flutter
• Non-sustained VT

**Ivabradine (Procorolan®)**

**Mechanism**
• Selective sinus node If inhibitor

**Indications**
• Angina in patients in sinus rhythm in whom a β-blocker is CI

**Contraindications**
• HR<60
• Other drugs: non-DHP CCBs, QT-prolonging drugs, P450 inhibitors
• AMI

**Adverse effects**
• Usually mild
• E.g. transient visual disturbances (phosphenes) due to similar ion channel in retina

INITIATIVE study: at least as effective as β-blockers, <1% withdrew due to SEs

**Amiodarone**

‘Ami-wonder-one’… but toxicity!
Mechanism
- Class III agent
- β-blocking action at high dose

Indications

Acute
- Refractory VF/VT, after 3 shocks

Chronic
- Atrial and ventricular arrhythmias, incl. paroxysmal ones

Administration
- Check baseline TFT/LFT/CXR, then TFT/LFT every 6m
- t1/2 = 26-127 days, thus requires loading regime; given IV, antiarrhythmics effects occur within hours – given PO, this takes 1-3 weeks (takes 5x t1/2 to reach steady state)
- Irritant – give by central line if possible

Contraindications
- Sinus bradycardia, sinus node disease
- Heart block
- Thyroid dysfunction
- Iodine sensitivity
- Pregnancy and breast-feeding
- Avoid IV use in respiratory failure or shock

Adverse reactions
- Photosensitivity (wear sunscreen)
- Skin discoloration
- Peripheral neuropathy
- Ataxia
- Corneal microdeposits (reversible; rarely cause night glare)
- Optic neuritis (rare)
- Metallic taste
- Thyroid
  - Hypothyroidism (most common)
    - Blocks peroxidase/deiodinase
    - Amiodarone metabolite, desethylamiodarone, is toxic to follicular cells
  - Hyperthyroidism
    - Type 1: due to I2 content (1/3 of molecular weight is iodine) – give carbimazole
    - Type 2: due to thyroiditis – give steroids
- Pulmonary fibrosis (associated with cumulative dose)
- Bronchospasm in respiratory failure
- Bradycardia and heart block
- Induction of ventricular arrhythmias (torsades)
- Hepatitis, ↑liver density on CT (due to I2 content)
- Hypersensitivity incl. anaphylaxis and vasculitis
- Thrombocytopenia, haemolytic anaemia, aplastic anaemia

Interactions
- Digoxin, warfarin (compete for protein binding)
- Hepatic metabolism, biliary and intestinal excretion

Note
- Least negatively inotropic antiarrhythmics with the exception of digoxin

Dronedarone
Amiodarone derivative with less side-effects
Magnesium

Indications
Not truly an antiarrhythmic, but useful in
- Refractory VF (with possible hypomagnesaemia)
- VT (with possible hypomagnesaemia)
- Torsades de pointes

Mechanism
- Physiological CCB (like potassium)