Cardiac arrhythmias

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

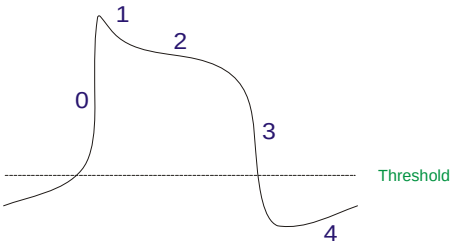
Physiology

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

Tissues with spontaneous pacemaker activity (i_{Si} upstroke)

- SA node ~70 beats per minute
- AV node ~45 beats per minute
- His bundle ~25 beats per minute

Cardiac action potential



• 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
- -vely inotropic via $3Na^+/Ca^{2+}$ exchanger (see digoxin)
- '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, encainide, 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
    - E.g. classes Ia/Ic/III → lengthen QT → 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 $3Na^+/Ca^{2+}$ exchange
    - Hence ↑intracellular $[Ca^{2+}]$
        - +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

- 2^{nd}/intermittent 3^{rd} 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/1^{st} degree heart block indicative of therapy not toxicity
    - More susceptible with ↓K^+, ↓Mg^{2+}, ↑Ca^{2+}
- 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
- $t_{1/2}$ = 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 $t_{1/2}$ 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

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
- **V**ertigo
- **V**isual disturbance
- -**V**ely inotropic
- *P*eripheral neuropathy
- *T*remor
- *H*epatic dysfunction

Interactions
- Largely hepatic P_{450} metabolism + some renal elimination
    - ↑$t_{1/2}$ 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

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 proarryhthmic effects)
  - ↓SA automaticity
  - ↓AVN conduction
  - –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 I_F 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, P_{450} 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
- $t_{1/2}$ = 26-127 days, thus requires loading regime; given IV, antiarrhythmics effects occur within hours – given PO, this takes 1-3 weeks (takes 5x $t_{1/2}$ 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 I_2 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 I_2 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)