ANTIARRHYTHMIC DRUGS

Principles of cardiac electrophysiology
- contractility of the heart – sequentially and in synchronicity
- relaxation between contractions
- coordinated sequence of changes in membrane potentials and electrical discharges in various heart tissues
- depolarization and repolarization → cardiac action potentials (about 60-70 times per minute)

Conducting system:
- sinoatrial (SA) node
- atria
- atrioventricular (AV) node
- bundle of His-Purkinje fibres
- ventricles

Local differences in vegetative innervation
- SA and AV nodes – supplied by the sympathetic and parasympathetic systems
- The other elements of the conducting system – supplied by the sympathetic nervous system only

Ionic basis of the cardiac resting membrane potential:
- activity of the electrogenic Na+K + -pump
- permeability of the membrane to various ions (ion-selective channels)

Resting potential:
- a transmembrane electrical gradient is maintained, with the interior of the cell negative with respect to outside the cell
- unequal distribution of ions inside vs. outside cell: o Na+ higher outside than inside cell o Ca+ much higher outside than inside cell o K + higher inside cell than outside
- maintenance by ion selective channels, active pumps and exchangers

Action potential:
- The flow of charged ions across cell membranes results in the ionic current that makes up cardiac action potentials.
- The action potential is a highly integrated entity.
- Changes in one current usually produce secondary changes in other currents.

Phase 0 – Rapid depolarization:
- opening of fast Na+ channels and rapid depolarization
- inward current of Na+ , changing membrane potential
- transient outward current due to movement of $Cl^-$and K+

Phase 1 – Initial rapid repolarization
- inactivation of the inward Na+ current (closure of the fast Na+ channels)
- activation of transient outward current (activation of Cl^- and K+ channels)

Phase 0 and 1 together correspond to the R and S waves of the ECG

Phase 2 – Action potential plateau
- balance between inward movement of Ca2+ and outward movement of K+
- a long duration compared to other nerve and muscle tissue
- normally blocks any premature stimulator signals
- corresponds to ST segment of the ECG

Phase 3 – Finale repolarization:
- K + channels remain open
- increasing K+ outward current, causing the cell to repolarize
- K + channels finally close when membrane potential reaches certain level
- corresponds to T wave on the ECG

Phase 4 – Resting phase:
- return of the membrane potential to the resting potential (relatively stable)
- depends on an increase in the conductance of K + channels,
- phase cardiac cells remain in until stimulated,
- associated with diastole portion of heart cycle.

Arrhythmia:
- any abnormality in the normal rhythmic contraction of the heart
- heart condition where disturbances in:
- impulse formation
- impulse conduction o combination of the two

Arrhythmias arise because of:
- Delayed/early after-depolarization (DAD/EAD)
- Reentry
- Ectopic pacemaker activity
- Heart block

Symptoms:
- palpitations, chest pain, weakness, feeling faint, altered consciousness, light-headedness, dizziness, syncope, shortness of breath, dyspnoea, swelling of ankles

Causes:
- hypoxia, ischemia, myocardial infarction, electrolyte disorders, sympathetic overstimulation, drugs, unknown

Classification of arrhythmias, according to:
- the site of origin of the abnormality:
  - supraventricular
  - ventricular
- the rate changes:
  - tachycardia
  - bradycardia

The goals of antiarrhythmic therapy:
- termination of an ongoing arrhythmia
- reduction of arrhythmia-related symptoms
- prevention of an arrhythmia
- prevention of transformation of well-tolerated arrhythmias into malignant
- adjunct therapy to ICD in malignant ventricular arrhythmias
- prevention of deterioration of cardiac function by arrhythmia
- reduction in long-term mortality in asymptomatic patients

Treatment of arrhythmias – present:
- crucial role of electrotherapy (internal cardioverter defibrillator – ICD)
- limited use of antiarrhythmic drugs – by their ineffectiveness and/or toxicity
- increasing meaning of drugs modifying diseases underlying cardiac arrhythmias (ACEI, ARB, spironololactones, β-blockers)

The ideal antiarrhythmic agent should have:
- minimal side effects
- low level of toxicity
- little effect on normal impulse formation
- both oral and parenteral forms available

Treatment of arrhythmias – problems:
- narrow therapeutic index
- adverse reactions (cardiac, non-cardiac)
- potential interactions
- multitude of factors influencing effectiveness (gender, age, genetics, disease state, remodelling,…)
- multiple electrophysiological and pharmacologic effects
- action depending on the route of administration, plasma levels, active metabolites

Proarrhythmia:
- all ADDs may provoke new arrhythmias or deterioration of existing ones
- frequency of proarrhythmia appearance:
  - ✓ **the highest – Class IC, IA, digoxin**
  - ✓ the lowest – Class II, IV, amiodarone

Types of proarrhythmia:
- polymorphic ventricular tachycardia (*Torsade de pointes – Tdp*) – class III, IA
- monomorphic ventricular tachycardias – IA, IC, digoxin, IV (with WPW)
- AV blocks, sinus bradycardia – IB, IA, IC, II, III, IV, adenosine, digoxin, $MgSO_4$

Cardio-depressive effect:
- negative inotropic and/or chrono-/dromotropic effect
- related to the extension of phase 0 (conduction)
- almost all AADs have such effects (e.g. digoxin only negative chrono-/dromotropic)
- the stronger cardiodepressant effect, the greater risk of HF
- significant cardiodepressant effects: IA, IC, IV, adenosine
- slight and infrequent: amiodarone, digoxin (ino-), beta-blockers

Antiarrhythmic drugs (AAD):
- drugs that change the shape of the action potential
- prevent arrhythmias by blocking ion channels or changing autonomic function

Antiarrhythmic Agents – Vaughan-Williams Classification:
- Class I – Na^+-channel blockers
- Class II – β-blockers (sympatholytic agents)
- Class III – K^+-channel inhibitors (prolong repolarization)
- Class IV – Ca^{2+}-channel blockers
- other drugs (adenosine, digoxin, magnesium)

Antiarrhythmic Agents – Pharmacodynamic effects:
- **sodium or calcium channels blockers** – can reduce automaticity and slow impulse conduction
- **potassium channels blockers** – can prolong repolarization and the action potential duration– thereby increase the refractory period
- **β-blockers** – can reduce the sympathetic stimulation of cardiac automaticity and conduction velocity – thereby prevent the overstimulation that contribute to some arrhythmias

Class I – Na^+ - Channel Blockers:
- **inhibit fast sodium channels**
- affect mostly **Phase 0** of depolarization (the rapid inflow of Na^+ through sodium channels)
- ↓ depolarization, ↓ automaticity, ↓ impulse conduction
  - ✓ **IA: quinidine, procainamide, disopyramide**
  - ✓ **IB: lidocaine, mexiletine**
  - ✓ **IC: propafenone, flecainide**

Class I – indications:
Class IA:
- supraventricular arrhythmias: AF and flutter (to maintain sinus rhythm) (not Disopiramide)
- ventricular arrhythmias: prevention of recurrence of VT and fibrillation
- Disopiramide – used with caution in patients with HF and in elderly

Class IB:
- ventricular arrhythmias – lidocaine (i.v.), mexiletine (p.o.)

Class IC:
- rarely used in the acute setting
- serious arrhythmias that have not responded to safer drugs: supraventricular arrhythmias (AF), ventricular arrhythmias (life-threatening)

Class IA – adverse effects:
Quinidine:
- noncardiac: GI complaints (diarrhea), allergic and immunological reactions (thrombocytopenia), cinchonism (headache, tinnitus, dizziness etc.)
- cardiac: hypotension (I.V.) (α-blocking), TdP, ventricular tachycardia, exacerbation of HF or conduction system disease

Procainamide:
- hypotension (i.v.),
- nausea (dose-related) (p.o.),
- lupus-like syndrome (long-term)
- cardiac – similar to quinidine

Disopiramide:
- anticholinergic effects (dry mouth, urinary retention, constipation, blurred vision, worsening of pre-existing glaucoma;
- cardiac – similar to quinidine

Class IA – pharmacokinetics:
Quinidine:
- good absorbtion (variety of oral preparations; usual oral doses of 200÷600 mg 2-4 times daily, extended-release preparation – every 12 hours)
- 80% bound to plasma proteins
- hepatic metabolism (active metabolite)
- $t_{1/2}$: 6÷8 hours
- elimination by the kidneys (20% unchanged)

Procainamide:

- administration: intravenous, intramuscular, orally (better tolerated than quinidine when given i.v.; long-term oral therapy → adverse effects)
- hepatic metabolism: N-acetylprocainamide (NAPA) – major metabolite with class III activity – *torsade de pointes*
- $t_{1/2}$: 3÷4 hours
- renal elimination

Class IB – adverse effects:
Lidocaine (i.v.), Mexiletine (p.o.)

- CNS: paraesthesia, tremor, light-headedness, hearing disturbances, seizures, dysarthria, altered levels of consciousness, nystagmus, convulsions
- Cardiac: the least cardiotoxic Na^+-channel blockers
- GI complaints (Mexiletine – p.o.)

Class IC – adverse effects:
Propafenone, Flecainide

- many – potentially lethal arrhythmias (but NOT TdP) and heart block (appropriate for use only by experienced providers)

Class IB – clinical pharmacokinetics:
Lidocaine

- extensive first-pass hepatic metabolism after oral administration (not effective by this route)
- administered parenterally
- wide distribution (crosses blood-brain barrier and placenta)

Mexiletine

- modified structure to ↓ first-pass hepatic metabolism
- effective chronic oral therapy

Class II – Beta-blockers:

- work most effectively in areas with rich sympathetic innervation – major effect on nodes
- suppress automatism of the conducting system, ↑ nodal conduction time
- extend Phase 4 of the depolarization
- prevent cardiac remodelling – RAA axis suppression

Indications:

- prevent supraventricular and ventricular tachyarrhythmias – e.g. metoprolol
- used as an emergency in SVT – esmolol

metoprolol

- i.v./p.o.
- selective β_1 - antagonist
- protects against free radicles and ischemia

esmolol

- i.v. - rapidly metabolized by plasma esterase; extremely short half-life (short duration of action)

Contraindications:

- low heart rate or heart conduction disorder
- advanced asthma and COPD – for non-selective beta-blockers
- severe peripheral vascular disease
- vasospastic angina

Adverse effects:

- fatigue
- bradycardia
- heart block
- bronchospasm
- peripheral vasoconstriction
- impotence
- mask hypoglycaemia signs

Class III – K^+ - Channel Blockers

- ✓ **Amiodarone, dronedarone** – multichannel blockers
- ✓ **Dofetilide, Ibutilide** – pure K^+-channel blockers
  - ✓ **Sotalol** – non-selective β-blocker, K^+-channel blocker
- affect Phase 3
- prolong repolarization
- prolong action potential duration

Adverse effect: TdP (Sotalol > Dofetilide > Amiodarone)

- a form of polymorphic VT – the ECG exhibits a continuously changing axis; each QRS complex has a configuration that differs from the preceding one
- caused by: AADs (class III, IA), drug-drug interaction, electrolyte disorders
- The use of QT-prolonging drugs is not necessarily associated with ↑ risk of TdP, unless high dosage or concomitant use of metabolic inhibitors (CYP3A4, 2D6).
- Treatment of TdP: I.V. $MgSO_4$, correction of hypokalaemia

Amiodarone:
Indications:

- supraventricular and ventricular arrhythmias

Pharmacokinetics

- extremely long half-life (26-107 days)
- highly lipophilic, large Vd
- hepatic metabolism (active metabolite)
- extremely slow elimination

Interactions:

- inhibitor of CYP450: 1A2, 2D6, 3A4, 2C9, 2C19 and P-gp

Dronedarone – non-iodinated analoque of amiodarone

Sotalol:

- potassium channel blocker – prolongs action potential duration and QT interval
- non-selective β-adrenoreceptor antagonist
- Uses: ventricular arrhythmia, and atrial fibrillation or flutter
- Adverse effects: *torsade de pointes*!

Class IV - Ca^{2+} channel Blockers

- ✓ **Verapamil**, **Diltiazem**

- depress Phase 4
- exert the main action on both nodes – ↓ AV-conduction, ↑ refraction, suppress automaticity of nodes
- negative inotropic effect
- I.V. significantly ↓ BP due to vascular relaxation

Indication: SVT in people without WPW
Adverse effects: severe sinus bradycardia/heart block hypotension (i.v.>p.o.), constipation (verapamil p.o.), gingival hyperplasia

MISCELLANEOUS ANTIARRHYTHMIC AGENTS
Adenosine:

- inhibits AV node – acting on the A1 receptor opens adenosine-sensitive K^+-channel to hyperpolarize and

inhibit the AV node conduction and also indirectly to inhibit Ca^{2+}-channel opening
- rapidly ↓ BP
- **Indication:** paroxysmal SVT, AF and flutter
- **PK:** metabolized by RBCs and vascular endothelial cells ($t_{1/2}$ < 10 s), efficacy requires a rapid i.v. bolus dose
- **Adverse effects:** sense of chest fullness, dyspnoea, transient asystole, bronchospasm

Digoxin:
- positive inotrope
- causes an increase in vagal nerve tone - inhibiting the inflow of Ca^{2+} in AV node and activating ACh-dependent inflow of K^+ in atria; these indirect actions lead to hyperpolarization, shortening of the AP in atria, and increased refraction in AV node

Pharmacokinetics:
- p.o.– capsules, tablets; i.v. – injections
- 70-80 % oral bioavailability
- tissue reservoir – skeletal muscle, not adipose tissue
- elimination – unchanged form, $t_{0,5}$ = 36-48 h – once a day dosing,

Problems:
- narrow therapeutic index – monitoring
- adverse effects: psychiatric, visual, GI, respiratory, proarrhythmias
- interactions
- PK depended on many factors

$MgSO_4$:
- influence Na+/K+ ATPase, Na channels, certain K channels

Indications: (i.v.)
- prevention of recurrent episodes of *torsade de pointes*
- digitalis-inducted ventricular arrhythmias
- supraventricular arrhythmias associated with Mg deficiency

Ranolazine:
Mode of action:
- **inhibits** the relatively small but persistent **late Na^+ current (I_{NaL})** that follows the principal, rapidly inactivating, I_{Na} and influences AP shape and duration – this increases in proarrhythmic conditions (hypoxia, HF, and LQTS3);
- shortens AP recovery and ↑ refractoriness and repolarization reserve;
- ↑ glucose metabolism at the expense of free fatty acid metabolism, thereby enhancing the efficient use of oxygen.

Indication: I_{NaL}-related arrhythmias

Vernakalant:
- **Mode of action:** novel **atrial-selective** K^+ channel blocker (**I_{kur}**, I_{KACh}, I_{to},), prolongs atrial-effective refractory periods with no significant effect on ventricular repolarization
- **Indication:** termination of AF, prevention of returns;
- **Pharmacokinetics:** rapidly eliminated ($t_{0,5}$~3h); metabolized by CYP2D6 (active metabolites); available in oral (also sustained-release) and parenteral forms
- **Adverse effects:** hypotension (but NO TdP)

Dronedarone:
- **Mode of action: multichannel** oral amiodarone analogue without the iodine; blocks I_{Kr}, I_{Ks}, I_{to}, and fast Na^+ and Ca^{2+} channels; ↑ AP duration in atria and ventricles; ↑ QT; α-, β-, and M-blocker
- **Indications:** AF/flutter recurs (maintenance of sinus rhythm) (slows ventricular response); rate-control
- **Pharmacokinetics:** $t_{0,5}$~30h; metabolized by CYP3A4 (N-debuthyl active metabolite) – interactions!
- **Adverse effects:** less toxic than amiodarone (thyroid, pulmonary, or hepatic toxicity and TdP – NOT reported); diarrhea, nausea, abdominal pain, vomiting, teratogenic
- **Contraindications:** HF (advanced, decompensated), AV-blocks (II-III), sick sinus syndrome (unless pacemaker), bradycardia <50bpm, QTc≥500ms, severe hepatic dysfunction; pregnancy
- **Interactions:** inhibits CYP3A4 – ↑ levels of simvastatin, digoxin; NO dronedarone–warfarin interaction

Tedisamil:
- **Mode of action:** class III; slows sinus rate, antianginal and anti-ischemic action;
  blocks I_{Kr}, I_{to}, I_{Ks}, I_{Kur}, I_{KATP}, and I_{Na};
  ↑ QT interval, AP duration and effective refractory periods in atria and ventricles
- **Indication:** conversion of **AF** (not as effective as ibutilide)
- **Adverse effects: TdP** (risk similar to ibutilide)

Ivabradine:
- **Mode of action:** acts on **SA** automaticity; blocks the hyperpolarization-activated cyclic nucleotide-gated channel current (**If**) in the sinus node – ↓ **sinus rate**
- **Indications: HF** (approved), inappropriate sinus tachycardia (**IST**) (***off-label***)
- **Adverse effects: bradycardia**, conduction disturbances, GI side effects, headache, phosphenes (luminous visual phenomena – effects on retinal photoreceptors), fetal toxicity.
- **Contraindications:** HR<60bpm, SA node dysfunction, SA block, AV block (II°/III°), acute decompensated HF, hypotension, severe hepatic impairment
- **Interactions: CYP3A4** inhibitors and inducers

Rotigaptide:
- **Mode of action: gap junction (connexin) modulator** – restoration of inter-cellular conduction may prevent atrial conduction slowing in certain pathological states [*loss of cell contact is important for the genesis of atrial arrhythmias – conduction slowing and gap junction uncoupling may be substrates for AF; mutations in GJA5 (the gene encoding connexin 40), may predispose impairment of gap junction assembly or uncoupling*]
- **Indications: atrial arrhythmias**