THERAPY OF CARDIAC ARREST, ISCHAEMIA AND FAILURE
(a) To describe the international cardiopulmonary resuscitation guidelines.

(b) To describe the role of defibrillation and its potential benefits and risks during cardiac arrest.

(c) To describe the pharmacology of adrenaline, vasopressin, amiodarone and lignocaine with reference to cardiopulmonary resuscitation.

(I) International Cardiopulmonary Resuscitation Guidelines:

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Commence CPR
30 compressions (at 100/min) : 2 breaths
Minimise interruptions to CPR

Attach Defibrillator/Monitor

Assess rhythm

Shockable rhythm
(VF or pulseless VT)

Shock
Monophasic (360 J)
Biphasic (200 J)

Commence CPR
30 compressions (at 100/min) : 2 breaths
5 sets of 30:2 → lasts 2 mins
Minimise interruptions to CPR

Non-shockable rhythm
(Asystole or PEA/EMD)

Commence CPR
30 compressions (at 100/min) : 2 breaths
5 sets of 30:2 → lasts 2 mins
Minimise interruptions to CPR

Return of spontaneous circulation?

Post-resuscitation care
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(II) Role of defibrillation during cardiac arrest:

- Indications for defibrillation – VF and pulseless VT
- Single shock is given:
  - Biphasic defibrillator → 200 J for all shocks
  - Monophasic defibrillator → 360 J (max energy) for all shocks
- Mechanism of action – Defibrillation shock applied through chest produces simultaneous depolarisation of a mass of myocardial cells (esp SA node) → enable resumption of organised electrical activity (as normal sinus rhythm)
- Note – ↑ success of defibrillation is a/w (i) Good CPR and (ii) Early defibrillation

(III) Drugs used during cardiac arrest:

Note – Route of drug administration:
- (1) IV → preferred route
  - Peripheral IVC → quick and easy to establish (but slower drug delivery and risk of tissue extravasation)
  - CVC → preferred due to more rapid drug delivery (but insertion takes time and has risks)
- (2) I/O → alternate to IV → produces similar plasma [drug]
- (3) ETT
  - Absorption is variable → plasma [drug] is ↓ cf. IV/I0 (need 3-10x ↑ dose)
  - Useful for certain drugs only (adrenaline, lignocaine, atropine) → other drugs cause mucosal/alveolar damage

(1) Adrenaline:
- Class – Naturally-occurring catecholamine
- Indications:
  - (i) VF/pulseless VT (during CPR after failed 2nd shock attempt, then during CPR every 2nd loop)
  - (ii) Asystole and PEA (immediately, then during CPR every 2nd loop)
- Mechanism of action:
Direct-acting sympathomimetic agent with equal agonist effects on \( \alpha \) and \( \beta \) receptors.

During cardiac arrest it causes \( \alpha \)-mediated peripheral vasoconstriction that redirects available C.O. to myocardium and brain. Also facilitates defibrillation by improving myocardial blood flow during CPR.

**Dosage:**
- 1 mg (1 mL of 1:1,000 or 10 mL of 1:10,000) every 2\(^{nd}\) loop during CPR
- Repeated smaller doses or IVI (1-20 mcg/min) to produce adequate BP after ROSC

**Issues:**
- (i) Tachyarrhythmias and severe HTN post-resuscitation
- (ii) Tissue necrosis if extravasation occurs → thus, requires CVC insertion

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**(2) Amiodarone:**
- Class – Class III anti-arrhythmic agent (as a iodinated benzofurane derivative)
- **Indications:**
  - (i) VF/pulseless VT (during CPR when arrest refractory to 3\(^{rd}\) shock attempt and vasopressor)
  - (ii) Prophylaxis against recurrent VF/VT
- **Mechanism of action:**
  - (i) Mainly a class III anti-arrhythmic effect → blocks K\(^+\) channel
  - (ii) Also has class I (Na\(^+\) blockade), class II (\( \beta \)-blockade) and class IV (CCB) effect
  - (iii) Antiadrenergic effect → non-competitive inhibition of \( \alpha \) and \( \beta \) receptors
- **Dosage** – 300 mg bolus (+/- 150 mg bolus +/- 15 mg/kg infusion over 24 hrs)
- **Issues:**
  - (i) Hypotension
  - (ii) Bradycardia, heart block and even sinus arrest
  - (iii) Prolong QTc → Torsades de Pointes

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**(3) Lignocaine:**
- Class – Class IB agent (as an amide LA agent)
- **Indications** – Used in situations where amiodarone cannot be used
- **Mechanism of action** – Inhibit fast Na\(^+\) channels (mild potency)
- **Dosage** – 1 mg/kg bolus (+/- 0.5 mg/kg bolus). Infusion not recommended until ROSC
- **Issues:**
  - CNS toxicity
    - Excitatory symptoms initially → circumoral tingling, dizziness, tinnitus, paraesthesia, irritation/agitation, then seizures
    - Depressive symptoms later → CNS depression, confusion, apnoea, coma
  - CVS toxicity
    - Bradycardia, AV heart block and even asystole
    - Unresponsive hypotension

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**(4) Vasopressin:**
- Class – ADH (peptide hormone)
- **Indications** – Alternative vasopressor to adrenaline
- **Mechanism of action** – At high doses → (i) V1R-mediated (Gq) peripheral vasoconstriction that redirects available C.O. to myocardium and brain, and (ii) acts synergistically with catecholamines
- **Dosage** – 40 units bolus
- **Issues** – Severe HTN post-resuscitation

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**(5) NaHCO\(_3\):**
- Class – Alkalinising solution
- Indications – Routine use for cardiac arrest not recommended (esp if early and efficient CPR and adequate ventilation instituted) → consider use with ↑ K⁺, metabolic acidosis, TCA OD, protracted cardiac arrest (> 15 mins)
- Mechanism of action – HCO₃⁻ combines with H⁺ to form H₂CO₃ → dissociates into CO₂ and H₂O
- Dosage – 1 mmol/kg (over 2-3 mins), guided as per ABG
- Issues:
  - Metabolic alkalosis (and IC acidosis due to CO₂ liberated from HCO₃⁻)
  - Electrolyte imbalance – ↓ K⁺ and ↑ Na⁺
  - ↑ osmolality
  - Blocks IV lines → precipitates with adrenaline and Ca²⁺

(6) Magnesium:
- Mechanism of action – Not entirely clear. It is an electrolyte vital for membrane stability (Ie. ↓ Mg²⁺ → hyperexcitable membrane causing arrhythmias)
- Indications:
  - (i) Torsades de pointes
  - (ii) Cardiac arrest a/w digoxin toxicity
  - (iii) VF/ pulseless VT (refractory to defibrillator shocks and vasopressor)
  - (iv) ↓ K⁺ and/or ↓ Mg²⁺
- Dosage – 5 mmol bolus, repeated once and then infuse 20 mmol over 4 hrs
- Issues:
  - Muscle weakness (and respiratory failure)
  - Hypotension
  - Somnolence and CNS depression
To describe the pharmacology of drugs used to manage myocardial ischaemia/infarction with particular reference to nitrates, beta blockers, calcium antagonists, anti-platelet agents, anti-coagulants and fibrinolytic agents.

Myocardial ischaemia → occurs when there is inadequate myocardial O₂ supply to meet myocardial O₂ demand → thus, the aim of treatment is to:
- (i) ↑ O₂ myocardial supply by ↑ coronary blood flow (as heart already has ↑ extraction ratio) → either (i) ↑ coronary perfusion pressure (∝ ↑ aortic diastolic pressure) and/or (ii) ↑ diastolic perfusion time of coronary arteries (Ie. ↓ HR)
- (ii) ↓ O₂ myocardial demand → either (i) ↓ HR and/or (ii) ↓ myocardial contractility

Drugs used to treat myocardial ischaemia/infarction:

(1) Nitrates
- Class: Organic nitrate
- Mechanism of action:
  o NO liberated from GTN via a thiol-dependent pathway (nitrate reductase – 1⁰ly in liver, but also in vascular SM cells)
  o NO → activates guanylyl cyclase in VSMC 1⁰ly in veins (> arterioles) → ↑ IC [cGMP] → cGMP activates protein kinases → cause ↓ IC [Ca²⁺] (by ↓ Ca²⁺ influx and ↑ Ca²⁺ sequestration in SER) → relaxes venous VSMC (> arteriolar VSMC) → 1⁰ly veno-dilation (> arteriolar vasodilation)
- Effect on myocardial O₂ supply/demand:
  o ↑ O₂ supply – ↑ blood flow to subendocardial tissue (2⁰ to large coronary artery vasodilation), without a coronary steal effect
  o ↓ O₂ demand – ↓ wall tension due to (i) ↓ preload/LVEDP (2⁰ to venodilation) and (ii) ↓ afterload (2⁰ to arteriolar vasodilation)
- Issues:
  o Headaches
  o Facial flushing
  o Hypotension with reflex tachycardia
  o Tolerance (esp with > 24 hrs of continuous treatment)

(2) Beta-blockers
- Class: β₁ selective agents (Eg. metoprolol, atenolol, esmolol)
- Mechanism of action:
  o Bind selectively and competitively to cardiac β₁-adrenergic receptors (GPCR – Gs) → inhibit catecholamines or other sympathomimetics from provoking a response → thus, ↓ activation of adenylyl cyclase → ↓ cAMP and PKA activation
  o Causes – (i) ↓ myocardial contractility, and (ii) ↓ SAN/AVN activity
- Effect on myocardial O₂ supply/demand:
  o ↑ O₂ supply – ↑ diastolic perfusion time of coronary arteries due to ↓ HR
  o ↓ O₂ demand – ↓ HR and ↓ myocardial contractility
- Issues:
  o Acute HF/cardiogenic shock
  o Severe bradycardia and bradyarrhythmias
  o Hypotension
  o CNS effects (depression, nightmare, lethargy)
  o Masks symptoms of ↓ BGL
  o Loss of β₁ selectivity at high doses → unwanted β₂ effects (↓ BGL, bronchospasms, peripheral vasoconstriction, GI effects)
  o Withdrawal syndrome if ceased abruptly with chronic use (rebound HTN, tachycardia, arrhythmias, myocardial ischaemia)

(3) Calcium antagonists
- Class: Verapamil (class I – phenylalkylamine) or Diltiazem (class III – benzothiazepine)
- **Mechanism of action:**
  - Inhibit L-type Ca\(^{2+}\) channels (binds to cytoplasmic aspect of channel (esp when in opened state during depolarisation) and maintains it in a close/inactivated state)
    - \( \rightarrow \downarrow \text{Ca}^{2+} \text{ influx} \rightarrow \downarrow \text{IC [Ca}^{2+}] \)
  - Causes – (i) \( \downarrow \) myocardial contractility, (ii) relaxation of arteriolar SM cells, and (iii) \( \downarrow \) SAN/AVN activity

- **Effect on myocardial O₂ supply/demand:**
  - \( \uparrow \) O₂ supply – (i) \( \uparrow \) diastolic filling time due to \( \downarrow \) HR, and (ii) Coronary artery vasodilation
  - \( \downarrow \) O₂ demand – (i) \( \downarrow \) contractility, (ii) \( \downarrow \) HR, and (iii) \( \downarrow \) afterload (2° to arteriolar vasodilation)

- **Issues:**
  - Headaches
  - Flushing
  - Peripheral oedema
  - Hypotension
  - Bradycardia and bradyarrhythmias
  - N/V

**Note:**
- Clinical effects and potential for adverse effects are SYNERGISTIC with each of these agents listed above
- Above agents can worsen myocardial ischaemia due to either (i) hypotension (\( \downarrow \) coronary perfusion pressure \( \rightarrow \downarrow \) O₂ supply), and/or (ii) tachycardia (\( \downarrow \) diastolic perfusion time \( \rightarrow \downarrow \) O₂ supply; also \( \uparrow \) O₂ demand)

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(4) Anti-platelet agents (See “Drugs and coagulation”)

(5) Anti-coagulants (See “Drugs and coagulation”)

(6) Fibrinolytic agents (See “Drugs and coagulation”)
To describe the pharmacology of drugs used to manage acute or chronic cardiac failure with particular reference to sympathomimetics, phosphodiesterase inhibitors, digoxin, diuretics, ACE inhibitors, nitrates and beta blockers.

(1) Inotropes:

Inotrope → drug that alters the force of contraction of cardiac muscle without changing the preload or afterload

Nb. +ve inotrope ↑ cardiac contractility; -ve inotrope ↓ cardiac contractility

(1) Sympathomimetics (see “Pharmacology of autonomic nervous system”):

- Includes:
  - (i) Catecholamines (natural – Adr, NAd, DA; synthetic – Isoprenaline, dobutamine, dopexamine)
  - (ii) Synthetic noncatecholamines (Ephedrine, metaraminol)

- Mechanism of action – Directly and/or indirect exert agonist activity at cardiac β1 receptor → via Gs mechanism (↑ IC cAMP) → ↑ IC [Ca2+] → +ve inotropy

(2) Phosphodiesterase inhibitors (PDEi):

- (a) Selective PDEi
  - Types:
    - (i) Bipyridine derivatives (Amrinone, Milrinone)
    - (ii) Imidazole derivatives (Enoximone)
  - Clinical uses – Short-term management of acute LVF (esp those who are refractory to catecholamines or β-blocked):
    - ↑ C.O. due to “inodilator” effect → +ve inotropy (↑ myocardial contractility) and vasodilation (↓ afterload)
    - Acts synergistically with catecholamines independently of β-adrenoceptor effect (as these agents also ↑ IC [cAMP])
  - Mechanism of action – Competitive inhibition of PDE III → ↓ hydrolysis of cAMP and cGMP → ↑ IC [ ] cAMP and cGMP → activates protein kinases
    - Within myocardium → PDE III inhibition results in ↑ slow-inward Ca2+ current → ↑ Ca2+ for contractile element activation AND ↑ diastolic relaxation (enhance Ca2+ removal from myoplasm) → +ve inotropy
    - Within vascular SM → PDE III inhibition results in ↓ slow-inward Ca2+ current → vasodilation

- Pharmacokinetics:

<table>
<thead>
<tr>
<th></th>
<th>Amrinone</th>
<th>Milrinone</th>
<th>Enoximone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>IV (bolus, then infusion) or PO</td>
<td>IV (bolus, then infusion) or PO</td>
<td>IV only (due to significant hepatic first-pass metabolism)</td>
</tr>
<tr>
<td>Metabolism and elimination</td>
<td>Renal excretion (40%) → elimination t ½ 6 hrs</td>
<td>Renal excretion (80%) → elimination t ½ 3 hrs</td>
<td>Hepatic metabolism to an active metabolite (10% activity but longer t ½ of 8 hrs → renally excreted) Elimination t ½ 5 hrs</td>
</tr>
</tbody>
</table>

- CVS effects – All agents have the following effects:
  - ↑ C.O. due to ↑ SV (↑ contractility) → ↓ LV EDP
  - ↑ HR
  - ↓ SBP (due to vasodilator effect)
  - Lack anti- or pro-arrhythmic effects
  - Cardiac MRO2 extraction ratio unchanged (due to ↓ ventricular wall tension and ↑ coronary perfusion 2º to coronary vasodilation)
- Issues:
  - All have ↑ therapeutic indices cf. cardiac glycosides (100:1 vs 1.2:1) → side-effects include hypotension (due to vasodilation), thrombocytopenia (with chronic therapy) and hepatic dysfunction (with chronic therapy)
  - Chronic oral milrinone for severe CHF is a/w ↑ morbidity/mortality
  - Severe renal dysfunction warrants dose reduction (due to renal clearance)

- (b) Non-selective PDEi (Eg. Aminophylline)
  - A methylxanthine derivative → comprises of a complex of 80% theophylline and 20% ethylenediamine (used to ↑ solubility of theophylline)
  - Clinical uses:
    - (i) Treat bronchospasm a/w acute asthma exacerbation refractory to β2-agonists and steroids (Nb. acts synergistically with β2 agonists)
    - (ii) Treat LVF (rarely)
  - Mechanism of action:
    - (i) Non-selective inhibition of all PDE isoenzymes (I-V) → ↓ hydrolysis of cAMP and cGMP → ↑ IC [ ] of cAMP and cGMP → this causes:
      - ↑ Ca²⁺ entry into myocardium → +ve inotropy
      - ↓ Ca²⁺ entry into smooth muscle → vasodilation and bronchodilation
    - (ii) Directly releases NAd from SNS neurons to act on adrenoceptors (of which it acts synergistically with as they both ↑ IC [cAMP])
    - (iii) Competitive inhibition of adenosine receptors
  - Pharmacokinetics:
    | Absorption | PO (good GIT absorption with > 90% bioavailability) and IV |
    | Metabolism and elimination | - Hepatic CYP450 metabolism (90%) and renal excretion (10%) → Elimination t ½ 9 hrs |
    | | - Clearance ↑ with smoking and CYP450 induction (phenytoin, carbamazepine, rifampicin, barbiturates) |
    | | - Clearance ↓ with CYP450 inhibition (cimetidine, erythromycin, OCP) |
  - Pharmacodynamic effects:
    | CVS | - Mild +ve ino- and chronotropy |
    | | - Coronary and peripheral vasodilation |
    | Respiratory | - Bronchodilation |
    | | - ↑ respiratory centre sensitivity to CO₂ |
    | CNS | CNS stimulant |
    | Renal | Weak diuretic due to natriuretic effect (inhibits tubular Na⁺ reabsorption) |
  - Issues and side-effects
    - Narrow therapeutic index → therapeutic plasma [ ] ~ 10-20 ug/mL, while toxic plasma [ ] > 35 ug/mL (as CYP450 is saturated and metabolism transforms from 1st to zero-order kinetics)
    - Toxicity:
      - CVS toxicity – Tachyarrhythmias, such as VF (esp with halothane)
      - CNS toxicity – Tremor, insomnia and seizures
      - Rhabdomyolysis
      - N/V
      - Gastro-oesophageal reflux (relaxes LOS)
      - Can cross placenta to cause toxicity
    - Thus requires frequent plasma [ ] monitoring due to variations in its clearance (see above)

(3) Digoxin (see “Anti-arrhythmic drugs”)
  - Cardiac glycoside extracted from the leaves of foxglove plant → steroid cyclopentenophenanthrene nucleus with a:
- Glycone portion (pharmacologically inactive) → a sugar (often glucose) that fixes drug to cardiac muscle
- Aglycone portion (pharmacologically active) → exerts drug activity

Clinical uses:
- Treat chronic low-output HF → weak +ve inotrope that improves symptoms and LV performance (↑ C.O.)
- Treat acute ↓ LVF → rarely used b/c ↑ death from sudden cardiac death due to arrhythmias (despite ↓ mortality from HF), and other more potent and less toxic agents available
- Ideal rate control agent for AF in pts with HF → ↓ HR 2° to slowed AVN conduction improves diastolic coronary perfusion and ventricular filling

Mechanism of action:
- Direct effects on heart
  - Reversible inhibition of Na⁺/K⁺ ATPase in sarcolemma of cardiac cell membrane → binds extracellular α-subunit → induces conformational change that interferes with outward Na⁺ and inward K⁺ transport → results in ↑ [Na⁺]IC and ↓ [K⁺]IC
  - ↑ [Na⁺]IC causes ↓ Ca²⁺ extrusion across a Na⁺/Ca²⁺ exchanger → ↑ [Ca²⁺]IC → results in +ve inotropy and ↑ force of contraction
  - ↓ [K⁺]IC causes – (i) ↑ effective refractory period of AVN → slowed conduction rate through AVN → ↓ HR, and (ii) ↑ automaticity (excitability)
- Alters ANS activity
  - Digoxin activates vagal nuclei centrally and sensitises arterial baroreceptor → ↑ PNS activity (↑ ACh effect on cardiac mAChR)
  - Causes – (i) ↓ SAN activity, and (ii) prolongs effective refractory period of AVN and slow conduction through it → both causes ↓ HR

Pharmacodynamics:
- CVS effects:
  - Dose-dependent ↑ myocardial contractility → ↑ SV → ↑ C.O.
  - Blunts excess SNS a/w compensatory response to HF → ↓ SVR → ↓ afterload → ↑ C.O.
  - Vagotonic effect, ↓ SAN discharge, ↓ AVN conduction → ↓ HR
- Renal effects
  - ↑ RBF/GFR due to ↑ C.O. → ↑ diuresis

Important to note → ECG features of digoxin:
- Prolonged PR interval (delayed conduction through AVN)
- Shortened QTc interval (more rapid ventricular repolarisation)
- Scaphoid ST segment depression (decreased slope of phase 3)
- Flattening or inversion of T-waves

Nb. They do NOT suggest toxicity → they disappear 3 weeks after digoxin is ceased

- Digoxin toxicity → digoxin has a very narrow therapeutic index → toxicity occurs in 20% of patients:
  - GI symptoms – Anorexia, N/V, diarrhoea, abdominal pain
  - CNS symptoms – Visual disturbances (deranged red-green colour perception), headaches, confusion, drowsiness, muscle weakness
  - CVS symptoms – Any arrhythmia can occur, although atrial tachycardia with block is more common, while death is usually a/w VF
    - ↑ automaticity – PVBs, atrial and ventricular tachycardias, bigemini, Etc.
    - Delayed AVN conduction – Junctional rhythm and AV heart block
    - Sinus arrest (at high doses) due to SAN block by vagal tone
(4) Myofilament calcium sensitizers (Eg. levosimendan):
- Mechanism of +ve inotropy – ↑ myocardial contractility due to enhanced myofilament contractile response (ie. prolonged actin-myosin interaction) to Ca\(^{2+}\), INDEPENDENT of IC [ ] of Ca\(^{2+}\) or cAMP

(5) Glucagon:
- Overview – Polypeptide hormone secreted from pancreatic \(\alpha\)-cells
- Clinical use – Limited role in treating LVF. Mainly used to ↑ HR/contractility in setting of \(\beta\)-blocker overdose. Only given IV (as it is a peptide)
- Mechanism of action:
  o (i) Acts on glucagon receptors (GPCR; Gs) → ↑ AC and IC cAMP → ↑ Ca\(^{2+}\)
  o (ii) Also evokes release of catecholamines
- CVS effect:
  o ↑ C.O. (due to ↑ SV and HR)
  o ↑ MAP (due to ↑ C.O.)
  o SVR unchanged or ↓
  o ↑ automaticity of SAN/AVN
- Side-effects – ↑ BGL, ↓ K\(^+\), systemic HT (due to catecholamine release), N/V

(6) Calcium (as 10% CaCl or Ca gluconate)
- Clinical use – Treat circulatory collapse due to CCB overdose, ↑ K\(^+\) or ↓ Ca\(^{2+}\)
- Mechanism of action – ↑ IC [Ca\(^{2+}\)]
- IV Ca\(^{2+}\) produces intense +ve inotropy and ↑ BP for short period of time (10-20 mins):
  o ↑ C.O. (due to ↑ SV a/w ↑ contractility) → ↓ LV EDP
  o ↑ BP (due to ↑ C.O.)
  o ↓ HR and SVR
- Issues – Cardiac arrhythmias (esp in those on digoxin and ↓ K\(^{+}\))

(7) T3/T4:
- +ve ino- and chrono-tropic effects due to IC mechanisms

(II) Other drugs used to treat heart failure:

(1) Diuretics (see “Diuretics”):

<table>
<thead>
<tr>
<th>Class</th>
<th>MOA</th>
<th>Use in heart failure</th>
<th>Issues and notable points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide (HCT,</td>
<td>Inhibits Na(^+)/Cl(^-) cotransporter in early</td>
<td>- Requires good renal function</td>
<td></td>
</tr>
<tr>
<td>indapamide)</td>
<td>DCT and cortical portion of TAL of LoH</td>
<td>- Metabolic alkalosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ ↓ Na(^+) (and H(_2)O) reabsorption</td>
<td>- ↑ BGL, TAG, cholesterol and urate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ↓ BP 2° hypovolaemia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- ↓ Na(^+), Cl(^-), K(^+), Mg(^{2+}), Ca(^{2+}) → arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Inhibit NKCCT cotransporter in medullary portion of TAL of LOH</td>
<td>All diuretics cause ↓ ECFV (and intravascular</td>
<td></td>
</tr>
<tr>
<td>(Furosemide)</td>
<td>→ ↓ Na(^+), K(^{+}) and Cl(^-) reabsorption → ↓ medullary hypertonicity</td>
<td>- Potent diuretic ideal to treat APO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Similar side-effects as thiazides → but also nephro- and oto-toxicity</td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonists (Spironolactone)</td>
<td>Binds to cytoplasmic mineralocorticoid receptor at principal cell of CD/DCT → competitive antagonist to aldosterone → ↓ Na⁺ (and H₂O) reabsorption</td>
<td>↓ preload</td>
<td>- Used in severe LVF → improves LV remodelling (esp post-MI) → ↓ mortality - Issue with ↑ K⁺</td>
</tr>
</tbody>
</table>

(2) ACE inhibitors (see “Anti-hypertensive drugs”):
- Types:
  - Group 1 (Captopril) – Active drug that is metabolised into active metabolites
  - Group 2 (Enalopril, Ramipril) – Prodrug that increases oral bioavailability prior to activation by hepatic metabolism to a diacid moiety
  - Group 3 (Lisinopril) – Active drug that is not metabolised and excreted unchanged in urine
- Mechanism of action:
  - Competitive inhibitor of ACE in pulmonary endothelium causes ↓ conversion of AI to AII → ↓ activation of AII receptor (AT₁ subtype – Gq mechanism)
  - Results in ↓ vasoconstriction, ↓ aldosterone release (from adrenal cortex), ↓ Na⁺/H₂O retention, ↓ SNS activation, and ↓ thirst
- Use in heart failure:
  - (i) ↓ afterload (due to ↓ SVR)
  - (ii) ↓ preload (due to ↓ intravascular volume)
  - (iii) Remodelling myocardium in LVF (esp a/w MI) → causes LVH to regress → improves LV function and survival
- Issues – Angiooedema and dry cough (due to bradykinin), ARF, ↑ K⁺, and hypotension

(3) Nitrates (see “Anti-hypertensive drugs”):
- Mechanism of action:
  - NO is liberated from GTN via a thiol-dependent pathway involving nitrate reductase → occurs 1ºly in the liver, but also in vascular SM cells
  - NO then activates guanylyl cyclase in VSMC 1ºly in veins (> arterioles) → ↑ IC [cGMP] by converting GTP to cGMP → cGMP activates various protein kinases that cause ↓ IC [Ca²⁺] by ↓ Ca²⁺ influx into VSMC and ↑ sequestration of Ca²⁺ in SER → results in relaxation of VSMC → 1ºly veno-dilation (> arteriolar vasodilation)
- Use in heart failure – ↓ preload (due to venodilation)
- Issues:
  - (i) Tolerance if used > 24-48 hrs (due to depletion of thiol/sulphhydryl groups within vascular SM cells)
  - (ii) Side-effects – Headache, facial flushing, postural hypotension (a/w reflex tachycardia and syncope), and rarely methaemoglobinaemia

(4) Beta blockers (see “Adrenoceptor blocking agents”):
- Type – Cardioslective (β₁-selective) β-blockers (Eg. metoprolol, carvedilol, atenolol)
- Mechanism of action – Bind selectively to β₁-adrenergic receptors → competitively inhibit catecholamines or other sympathomimetics from provoking a β₁ response → thus, inhibits Gs response (↓ AC activation → ↓ IC cAMP)
- Use in heart failure
  - (i) Favours myocardial O₂ supply > demand → ↑ O₂ supply (due to ↑ diastolic perfusion time of coronary arteries due to ↓ HR) and ↓ O₂ demand (due to ↓ -ve ino- and chronotropic effects) → ↓ myocardial ischaemia/infarction
  - (ii) ↓ renin release from JGA → ↓ AII and aldosterone production → ↓ myocardial remodelling → ↑ LVEF and survival
- Issues:
  o (iii) ↓ catecholamine-induced arrhythmias a/w sudden cardiac death
  o (i) Dose-dependent loss of $\beta_1$ selectivity $\rightarrow$ unwanted $\beta_2$ antagonist effects
  o (ii) –ve inotropy (can ppt LVF) and –ve chronotropy (severe bradycardia)
  o (iii) CNS symptoms (depression, lethargy, nightmares)
  o (iv) Abrupt cessation of chronic therapy $\rightarrow$ rebound HTN, myocardial ischaemia and arrhythmias