Pharmacology of inotropes and vasopressors
3.3 Recognises and manages the patient with circulatory failure
4.4 Uses fluids and vasoactive / inotropic drugs to support the circulation

**PR_BK_41** Drugs and the sympathetic nervous system: adrenergic receptors and molecular mechanisms of action: Indications for pharmacological use of naturally occurring catecholamines and synthetic analogues.

**PR_BK_43** Cardiovascular system: general: drug effects on the heart [inotropy and chronotropy] and on the circulation: arterial and venous effects; systemic and pulmonary effects

**PR_BK_44** Inotropes and pressors: Classification; site of action. Synthetic inotropes compared with adrenaline

**PB_BK_38** Cardiac muscle contraction
Definitions

- **Inotrope**: increases cardiac output by increasing velocity and force of myocardial contraction

- **Vasopressor**: causes contraction of arteriolar and venous smooth muscle

- **Inodilator**: increases cardiac output by a combination of inotropic and vasodilator effects
Mechanisms of drug action

- **Sympathomimetics**
  - α-agonists
  - β-agonists
  - Dopamine agonists (D₁-like, D₂-like)
  - Phosphodiesterase inhibitors (PDE 3)

- **Others**
  - Vasopressin (V₁)
  - Levosimendan
  - Cardiac glycosides
α-agonists

α₁ receptors: vascular smooth muscle contraction

Diagram:
- **α agonist** → **α₁ receptor** (cell membrane)
- **Gq**
- **phospholipase C**
- **PiP₂** → **IP₃** → ↑cytosolic Ca²⁺ → **protein kinase C** → **protein kinase** (calmodulin-dependent)
- **DAG**
- **VASOCONSTRICION**
**β-agonists**

- \( \beta_1 \) (\( \beta_2 \))
  - Inotropy (force)
  - Chronotropy (rate)
  - Dromotropy (conduction)

- \( \beta_2 \)
  - Vasodilatation
Phosphodiesterase 3 inhibitors

- Heart and vascular smooth muscle
- Inodilators
- Lusitropic (improved diastolic relaxation)
Vasopressin (AVP, ADH)

- Hypothalamic nonapeptide hormone, released from posterior pituitary
- $V_1$ receptor agonist - potent arterial vasoconstrictor
- $V_2$ receptors in renal collecting duct – water reabsorption
Levosimendan

- Calcium sensitiser - ↑ sensitivity of contractile proteins to Ca\(^{2+}\) without ↑ intracellular Ca\(^{2+}\)

- Inotropic and chronotropic effects

- Independent of adrenoceptors and cAMP

- Vasodilator: opens ATP-sensitive K\(^+\) channels on vascular smooth muscle
Cardiac glycosides: digoxin

Inhibits Na\(^+\)/K\(^+\) pump in myocardial cell membrane

→ intracellular Na\(^+\)
→ intracellular Ca\(^{2+}\) (Na\(^+\):Ca\(^{2+}\) exchanger)
→ force of contraction
Drugs: Catecholamines

Aromatic ring + two adjacent OH groups (*catechol*) + ethylamine group

Substitutions on ethylamine group → sympathomimetic activity

Dopamine, adrenaline, noradrenaline are naturally occurring
Synthetic Catecholamines

Isoprenaline

Dobutamine

Dopexamine
<table>
<thead>
<tr>
<th>Agent</th>
<th>$\beta_1$ effects</th>
<th>$\beta_2$ effects</th>
<th>$\alpha$ effects</th>
<th>DA effects</th>
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<tbody>
<tr>
<td></td>
<td>Inotropy</td>
<td>Vasodilatation</td>
<td>Vasoconstriction</td>
<td>Renal/ mesenteric vasodilatation Natriuresis</td>
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<tr>
<td></td>
<td>Chronotropy</td>
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<td>Dromotropy</td>
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<tr>
<td>Noradrenaline</td>
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<tr>
<td>Adrenaline</td>
<td>$\beta$ effects predominate at low dose, $\alpha$ at high dose</td>
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<tr>
<td>Dopamine</td>
<td>DA effects at low dose, $\beta$ at moderate dose and $\alpha$ at high dose</td>
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<tr>
<td>Dobutamine</td>
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<tr>
<td>Isoprenaline</td>
<td>++++</td>
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</table>
Pharmakokinetics of catecholamines

- $t_{1/2}$ 1-2 minutes

- Re-uptake into tissues $\rightarrow$ Metabolism by MAO and COMT

- Steady-state plasma concentration in 5-10 min

- Short half-life allows rapid titration
Benefits and side-effects

**β1**  
Increased cardiac output

- Tachycardia, arrhythmia, ↑ myocardial O₂ consumption, myocardial ischaemia

**β2**  
Vasodilatation, ↑ cardiac output, ↓ myocardial O₂ consumption

- Hypotension

**α**  
↑ systolic and diastolic blood pressure

- May decrease renal, mesenteric and skin blood flow.  
  ↑ cardiac afterload and myocardial oxygen demand.
Adrenaline (epinephrine)

- Potent $\beta$-agonist $< 0.1 \mu g/kg/min$

- Potent $\alpha_1$-agonist $> 0.1 \mu g/kg/min \rightarrow$ vasoconstriction

- Renal and mesenteric vasoconstriction $\rightarrow$ ischaemia and renal failure

- Metabolic - hyperglycaemia and hyperlactaemia

- Cardiac toxicity with prolonged, high dosage
Adrenaline

Anaphylaxis
- blocks mediator release
- reverses bronchospasm and vasodilatation
- 50-100 µg (0.5-1ml of 1:10,000) IV
- 0.5 to 1mg (0.5-1ml of 1:1,000) IM

Cardiac arrest
- vasoconstriction → diversion of blood to essential organs
- diastolic pressure and coronary flow increased
- 1mg IV, every 3-5 minutes of resuscitation
Adrenaline

**Cardiogenic shock**
- increased cardiac output
- Arrhythmogenic
- $\uparrow$ afterload & myocardial $O_2$ demand
- second-line treatment

**Septic shock**
- restores MAP and cardiac output
- ischaemia of intestinal mucosa, lactic acidosis, hyperglycaemia
- $\uparrow$ renal vascular resistance $\rightarrow$ reduced RBF
- $2^{nd}$-line agent
Noradrenaline (norepinephrine)

- $a_1 > \beta$ above 0.05µg/kg/min
- arterial constriction $\rightarrow$ ↑ SBP and DBP
- venous constriction $\rightarrow$ ↑ venous return
- reflex bradycardia
- effect on cardiac output variable/ minimal
- renal and mesenteric vasoconstriction (?)
- high doses $\rightarrow$ digital gangrene
- myocyte apoptosis in prolonged infusion
Noradrenaline

**Septic shock**
- first line vasopressor (Surviving Sepsis Campaign)
- ensure adequate fluid resuscitation first
- ↑ gastric mucosal and renal perfusion in vasodilated, normovolaemic cases

**Anaphylaxis**
- Second line agent, for resistant hypotension
Dopamine

- Direct: α, β, DA agonist
- Indirect: releases NA from sympathetic nerve terminals

- 2-5µg/kg/min (DA) → ↑ RBF, diuresis, natriuresis
- 5-10 µg/kg/min (β) → ↑ cardiac output
- 10-20 µg/kg/min (α) → vasoconstriction

- Arrhythmogenic, ↓ hypoxic drive, delirium, vomiting, immunosuppression
- Vasopressor in septic shock
- No evidence for renal protection
Dobutamine

- Synthetic derivative of isoprenaline
- \( \beta \)-agonist (weak \( \alpha_1 \)). \( \beta_1 > \beta_2 \).
- 2-20 \( \mu \)g/kg/min \( \rightarrow \) inotropic + moderate ↑ HR
- SVR unchanged or slightly reduced
- Myocardial \( O_2 \) demand increased (stress testing)
Dobutamine

Cardiogenic shock/ acute heart failure
- first-line inotrope
- ↑ cardiac output + reduced ventricular afterload
- may cause hypotension

Septic shock (with ↓ CO)
- noradrenaline + dobutamine as effective as adrenaline, with fewer side-effects
Dopexamine

- Synthetic analogue of dopamine
- 60x potency of dopamine at $\beta_2$ receptors, 1/3 potency at DA receptors
- No $\alpha$ activity
- Inodilator
- Dose-dependent tachycardia
- ? Beneficial effects on inflammation, splanchnic circulation and renal function
Isoprenaline

- Synthetic
- Potent, non-selective β-agonist
- Historical role in treatment of bradycardia and heart block
- Superseded by more effective agents with fewer side effects (tachycardia, arrhythmia)
Non-catecholamine sympathomimetic amines

- Metaraminol, ephedrine, phenylephrine
- Lack 2\textsuperscript{nd} hydroxyl group on 1\textsuperscript{o} aromatic ring.
Metaraminol

- **α and β agonist, mainly vasoconstrictor**
- **↑ SBP and DBP**
- Reverses hypotension caused by GA/ spinal anaesthesia
- Vasoconstriction may → transient bradycardia
- Indirect β-effects → tachyphylaxis
- 0.5-1mg IV, repeated as necessary
Ephedrine and phenylephrine

**Ephedrine**
- α and β
- Vasopressor and inotrope in anaesthetic-induced hypotension
- Useful for bradycardic, hypotensive patient
- Uterine blood flow maintained - drug of choice in pregnancy
- 3-6mg IV, repeated as necessary. 25-50mg IM
- Action partly indirect → tachyphylaxis

**Phenylephrine**
- Selective α-agonist
- Rapid onset of action, duration 5-10 minutes
- Vasoconstrictor - IV bolus (0.1-0.5mg) or infusion.
Vasopressin

- $V_1$ agonist (and $V_2$ receptors in renal collecting duct)
- Potent vasoconstrictor
- CPR: not shown to produce better results than adrenaline
- Rescue therapy in septic shock resistant to NA. No mortality benefit of low-dose AVP over NA (VASST trial)
- GI ischaemia, ischaemic skin lesions, reduced CO
Phosphodiesterase inhibitors

- Amrinone, milrinone, enoximone
- $\uparrow$ CO, $\downarrow$ afterload, minimal effect on myocardial $O_2$ demand
- Lusitropic – improved diastolic relaxation
- Adrenoceptors not involved - no tachyphylaxis
- Treatment of AHF with reduced cardiac output: little evidence of long-term survival benefit
- Low CO states following cardiomyotommy
- Long $t_{1/2}$ (milrinone 2 hours)
- May cause hypotension
Levosimendan

- Inodilator
- Diastolic relaxation maintained
- Beneficial effects on myocardial energy balance
- Effective in acute and chronic heart failure
Management of shock

Inotropes and vasopressors are used for the treatment of circulatory failure unresponsive to fluid therapy alone.
Management of shock

**ABC**

Aim - adequate perfusion and oxygen delivery to tissues

\[
\text{DO}_2 = \text{arterial oxygen content} \times \text{cardiac output}
\]

\[
\text{DO}_2 = [\text{SpO2} \times \text{Hb} \times 1.34] \times \text{CO}
\]
Management of shock

Optimise LV preload

Blood pressure = CO x SVR

CO = SV x HR

SV: Preload
    Afterload
    Contractility
Management of shock

Optimise LV preload

Fluid challenge

Monitor: Clinical signs
CVP
PAOP (Swan-Ganz)
Stroke volume variation (LiDCO)
Global end-diastolic volume (PiCCO)
Corrected flow time (ODM)
Management of shock

Optimise CO and BP

- Low CO $\rightarrow$ inotrope

- Low SVR $\rightarrow$ vasopressor

- Mixed pathology $\rightarrow$ combination
Management of shock

What are optimal cardiac output and BP?

Adequacy of tissue perfusion indicated by:

- Urine output
- Conscious state
- Skin temperature
- Serum lactate
- Acid-base status
Cardiogenic shock

- Optimise preload
- Pump failure
- Pure inotrope or inodilator
- Avoid ↑ afterload/ myocardial O\textsubscript{2} consumption
- Avoid arrhythmia

- In MI, inotropes may cause infarct expansion, ↑ cytosolic Ca\textsuperscript{2+} and apoptosis
Cardiogenic shock/ AHF

**Dobutamine**
- American College of Cardiology/ AHA recommendation for acute MI with moderate hypotension
- May cause hypotension and tachycardia - caution in profound shock
- Combination with dopamine may limit side effects

**Adrenaline**
- Low-dose infusion in profound shock
- High dose → ↑ afterload and myocardial O₂ demand
- Arrhythmia, promotes coronary thrombosis

**Noradrenaline**
- Has been recommended for severe, refractory cardiogenic shock
- Improves coronary perfusion (↑ DBP)
- Antithrombotic effect
- ↑ afterload and myocardial oxygen demand
Acute Heart Failure

- Aim to ↑ CO, ↓ end-diastolic pressure, improve perfusion and diuresis, allowing re-introduction of ACEIs, diuretics, β-blockers

- Dobutamine – but CHF associated with uncoupling of adrenoceptors from intracellular transduction → resistance to treatment

- Positive inotropes increase mortality in CHF (↑ intracellular Ca^{2+})
Acute Heart Failure

PDE3 inhibitors

- CCF with ↓ cardiac output
- Minimal effect on myocardial O$_2$ demand
- Hypotension and long t$_{1/2}$
- Similar outcomes to dobutamine

Levosimendan

- CCF with ↓ cardiac output
- No ↑ myocardial O$_2$ demand
- ? Survival benefit compared with dobutamine
Septic shock

Vasopressor

- Surviving Sepsis Campaign: 1st line noradrenaline or vasopressin (alternative or in addition)

- Adrenaline may → intestinal ischaemia, lactic acidosis, hyperglycaemia, reduced RBF

- Dopamine in selected cases (no risk of arrhythmia, low cardiac output)
Septic shock

**Inotrope (↓ CO)**

- Dobutamine

- Noradrenaline + dobutamine effective as adrenaline in restoring CO and BP, but less effect on lactate and GI perfusion
Septic shock

Other

- Corticosteroids (SSC)
- Dopexamine?
Dopamine:

a) may produce ventricular arrhythmias
b) increases mesenteric blood flow at high doses
c) crosses the blood-brain barrier
d) is synthesised from L-dopa
e) is inactivated in alkaline solution
The following are precursors of adrenaline:

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>a) Tyrosine</td>
<td>T</td>
</tr>
<tr>
<td>b) Phenylalanine</td>
<td>T</td>
</tr>
<tr>
<td>c) Dopamine</td>
<td>T</td>
</tr>
<tr>
<td>d) Isoprenaline</td>
<td>F</td>
</tr>
<tr>
<td>e) Noradrenaline</td>
<td>T</td>
</tr>
</tbody>
</table>
Dopexamine:

a) causes arterial vasoconstriction  F
b) is an agonist at dopaminergic D1 and D2 receptors  T
c) increases the force of myocardial contraction  T
d) increases renal blood flow  T
e) causes arrhythmias  T
Dobutamine:

<p>| | |</p>
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<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>is structurally similar to isoprenaline</td>
</tr>
<tr>
<td>b)</td>
<td>activates adenyl cyclase</td>
</tr>
<tr>
<td>c)</td>
<td>has a selective action on beta-1 adrenoreceptors</td>
</tr>
<tr>
<td>d)</td>
<td>has a half-life of 2 minutes</td>
</tr>
<tr>
<td>e)</td>
<td>increases the left ventricular end-diastolic pressure</td>
</tr>
</tbody>
</table>


Trials


