# SNS COLLEGE OF ALLIED HEALTH SCIENCE

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## DEPARTMENT OF OPERATION THEATRE AND ANAESTHESIA TECHNOLOGY II YEAR

## COURSE NAME: PHARMACOLOGY

## TOPIC INOTROPES

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# INOTROPES

**Definition:**

Inotropes are pharmacological agents that alter the force or strength of myocardial contraction (cardiac contractility).

**Classes of Inotropes:**

1. Positive Inotropes: Enhance myocardial contractility (e.g., catecholamines, phosphodiesterase inhibitors, cardiac glycosides).
2. Negative Inotropes: Reduce myocardial contractility (e.g., betablockers, calcium channel blockers).

# CLASSIFICATION OF POSITIVE INOTROPES

1. Catecholamines:
   Epinephrine (Adrenaline)
   Norepinephrine (Noradrenaline)
   Dopamine
   Dobutamine
   Isoprenaline (Isoproterenol)

2. Phosphodiesterase Inhibitors:
   Milrinone
   Amrinone (Inamrinone)

# CLASSIFICATION OF NEGATIVE INOTROPES:

1. BetaBlockers:
   Atenolol
   Propranolol
   Metoprolol

2. Calcium Channel Blockers:
   Verapamil
   Diltiazem

3. Antiarrhythmics (e.g., Class I and III agents like amiodarone, though primarily used for rhythm control).

# PHARMACODYNAMICS

**POSITIVE INOTROPES:**

**Catecholamines**: Stimulate β1adrenergic receptors, leading to increased contractility and heart rate. Epinephrine and norepinephrine also act on αreceptors, causing vasoconstriction.

**Phosphodiesterase** Inhibitors: Inhibit PDE3, increasing cyclic AMP,

**Cardiac Glycosides**: Inhibit Na+/K+ATPase, increasing intracellular sodium, which reduces calcium extrusion via the Na+/Ca2+ exchanger, enhancing contractility.

**Levosimendan**: Sensitizes troponin C to calcium, improving contractility without increasing oxygen demand; also opens ATP sensitive potassium channels, causing vasodilation.

## NEGATIVE INOTROPES

**BetaBlockers**: Block β1adrenergic receptors, reducing cyclic AMP and calcium influx, decreasing contractility and heart rate.

**Calcium Channel Blockers**: Inhibit calcium entry into cardiac and smooth muscle cells, reducing contractility and causing vasodilation.

# ADRENALINE (EPINEPHRINE)

**Class**: Sympathomimetic (catecholamine)
**Pharmacodynamics**: Acts on alpha-1, alpha-2, beta-1, and beta-2 adrenergic receptors, increasing heart rate, contractility, blood pressure, and causing bronchodilation and vasoconstriction.
**Pharmacokinetics**:
**Metabolism**: Hepatic
**Excretion**: Renal
**Dilution**: IV: 1 mg (1 mL of 1:1000) in 10 mL normal saline (NS) to make 1:10,000.
Endotracheal: 2–2.5 mg diluted in 5–10 mL NS.
**Dosage**:Cardiac arrest: 1 mg IV every 3–5 minutes.
Anaphylaxis: 0.3–0.5 mg IM (1:1000) every 5–15 minutes.
Infusion: 0.01–0.1 mcg/kg/min for hypotension.
**Mechanism of Action**: Binds to adrenergic receptors, activating G-protein-coupled pathways, increasing cyclic AMP (beta receptors) or intracellular calcium (alpha receptors).
**Adverse Effects**: Tachycardia, hypertension, arrhythmias, anxiety, tremors, headache, pulmonary edema.
**Uses**: Cardiac arrest, anaphylaxis, severe hypotension, bronchospasm (e.g., asthma).
**Mode of Administration**: IV, IM, SC, endotracheal, intracardiac (emergency).

# ISOPRENALINE (ISOPROTERENOL)

**Class**: Sympathomimetic (synthetic catecholamine)
**Definition**: A synthetic beta-adrenergic agonist, primarily stimulating beta-1 and beta-2 receptors.
**Pharmacodynamics**: Increases heart rate and contractility (beta-1), causes bronchodilation and vasodilation (beta-2).
**Pharmacokinetics**:
**Metabolism**: Hepatic
**Excretion**: Renal
**Mechanism of Action**: Stimulates beta receptors, increasing cyclic AMP, leading to cardiac stimulation and smooth muscle relaxation.
**Adverse Effects**: Tachycardia, palpitations, hypotension, arrhythmias, angina.
**Uses**: Bradycardia refractory to atropine, torsades de pointes, bronchospasm (rarely used).
**Mode of Administration**: IV infusion.
**Dilution**: 1 mg in 500 mL D5W or NS (2 mcg/mL).
**Dosage**: 0.01–0.2 mcg/kg/min.

# EPHEDRINE

**Class**: Sympathomimetic (indirect-acting)
**Definition**: Stimulates release of norepinephrine from nerve endings.
**Pharmacodynamics**: Increases heart rate, blood pressure, bronchodilation.
**Pharmacokinetics**:
**Metabolism**: Hepatic.
**Excretion**: Renal
**Mechanism of Action**: Releases norepinephrine, stimulating adrenergic receptors.
**Adverse Effects**: Tachycardia, hypertension, anxiety, insomnia, urinary retention.
**Uses**: Hypotension, nasal decongestion, asthma (historical).
**Mode of Administration**: IV, IM, oral.
**Dilution**: 5 mg/mL, may dilute in 5–10 mL NS for IV.
**Dosage**: 5–25 mg IV or IM, 25–50 mg oral.

# DOPAMINE

**Class**: Sympathomimetic (catecholamine)
**Definition**: Precursor to norepinephrine, used as an inotrope and vasopressor.
**Pharmacodynamics**: Stimulates beta-1, alpha-1, and dopamine receptors; dose-dependent effects (low: renal vasodilation; high: vasoconstriction).
**Pharmacokinetics**:

**Absorption**: IV only.
**Metabolism**: MAO and COMT.
**Excretion**: Renal, half-life ~2 minutes.

**Mechanism of Action**: Activates adrenergic and dopaminergic receptors, increasing cyclic AMP.
**Adverse Effects**: Tachycardia, arrhythmias, hypertension, angina, gangrene (extravasation).
**Uses**: Hypotension, shock, heart failure.
**Mode of Administration**: IV infusion.
**Dilution**: 400 mg in 250 mL D5W or NS (1600 mcg/mL).
**Dosage**: 2–20 mcg/kg/min, titrated to effect.

# DOBUTAMINE

**Class**: Sympathomimetic (synthetic catecholamine)
**Definition**: Selective beta-1 adrenergic agonist.
**Pharmacodynamics**: Increases cardiac contractility and heart rate, minimal vascular effects.
**Pharmacokinetics**:
**Absorption**: IV only.
**Distribution**: Wide.
**Metabolism**: Hepatic.
**Excretion**: Renal
**Mechanism of Action**: Stimulates beta-1 receptors, increasing cyclic AMP.
**Adverse Effects**: Tachycardia, arrhythmias, hypertension, angina.
**Uses**: Heart failure, cardiogenic shock.
**Mode of Administration**: IV infusion.
**Dilution**: 250 mg in 250 mL D5W or NS (1000 mcg/mL).
**Dosage**: 0.5–20 mcg/kg/min, commonly 2.5–5 mcg/kg/min.

# NORepinephrine (NORADRENALINE)

**Class**: Sympathomimetic (catecholamine)
**Definition**: Endogenous catecholamine used as a vasopressor with inotropic effects
**Pharmacokinetic**s: Metabolism: Hepatic  Excretion: Renal.
**Mechanism of Action**: Binds to adrenergic receptors, activating G-protein-coupled pathways; beta-1 stimulation increases cyclic AMP, enhancing calcium influx for inotropy; alpha-1 increases intracellular calcium for vasoconstriction.
**Adverse Effects**: Tachycardia, hypertension, arrhythmias, peripheral ischemia, tissue necrosis (from extravasation), anxiety, headache, pulmonary edema.
**Uses**: Septic shock, cardiogenic shock, hypotension unresponsive to fluids, adjunct in cardiac arrest.
**Mode of Administration**: IV infusion (preferably via central line to avoid extravasation).
**Dilution**: 4-16 mg in 250 mL D5W or NS (16-64 mcg/mL concentration).
**Dosage**: Initial: 0.01-0.1 mcg/kg/min IV infusion; titrate up to 0.5-1 mcg/kg/min for severe hypotension.

# MILRINONE

**Class**: Phosphodiesterase inhibitor (PDE3 inhibitor)
**Definition**: Bipyridine derivative used as an inodilator for short-term management of heart failure.
**Pharmacodynamics**: Increases myocardial contractility (inotropy), improves relaxation (lusitropy), and causes peripheral and pulmonary vasodilation, reducing preload and afterload.
**Pharmacokinetics**: Metabolism: Hepatic). Excretion: Renal
**Mechanism of Action**: Inhibits PDE3 enzyme, preventing breakdown of cyclic AMP, leading to increased intracellular cAMP, enhanced calcium handling, and smooth muscle relaxation.
**Adverse Effects**: Hypotension, arrhythmias (ventricular tachycardia), headache, nausea, thrombocytopenia (less common than amrinone), hypokalemia.
**Uses**: Acute decompensated heart failure, cardiogenic shock, post-cardiac surgery support.
**Mode of Administration**: IV bolus followed by infusion.
**Dilution**: Dilute in 0.45% or 0.9% NS or D5W; typical concentration 200 mcg/mL.
**Dosage**: Loading: 50 mcg/kg IV over 10 minutes; maintenance: 0.375-0.75 mcg/kg/min (adjust for renal function; max 1.13 mg/kg/day)

# LEVOSIMENDAN

**Class**: Calcium sensitizer (with PDE3 inhibitory and K+ channel opening effects)
**Definition**: Inodilator that enhances myocardial contractility without increasing oxygen demand, used for acute heart failure.
**Pharmacodynamics**: Increases contractility, causes arterial and venous vasodilation, improves lusitropy; minimal increase in heart rate.
**Pharmacokinetics**: Metabolism: Hepatic Excretion: Fecal (majority), renal (minor
**Mechanism of Action**: Binds to troponin C, sensitizing it to calcium for inotropy; mild PDE3 inhibition increases cAMP; opens ATP-sensitive K+ channels for vasodilation.
**Adverse Effects**: Hypotension, headache, atrial fibrillation, tachycardia, nausea, hypokalemia.
**Uses**: Acutely decompensated chronic heart failure, cardiogenic shock, post-cardiac surgery low-output syndrome.
**Mode of Administration**: IV infusion (over 24 hours; optional loading dose).
**Dilution**: Dilute in D5W to 0.025-0.05 mg/mL.
**Dosage**: Loading (optional): 6-24 mcg/kg over 10 minutes; maintenance: 0.05-0.2 mcg/kg/min for 24 hours.

# GLUCAGON

**Class**: Hormone (pancreatic alpha-cell derived)
**Definition**: Polypeptide hormone primarily for hypoglycemia, with secondary inotropic effects in overdose scenarios.
**Pharmacodynamics**: Positive inotropic and chronotropic effects on the heart
**Pharmacokinetics**:
Absorption: IV, IM, SC, intranasal. Metabolism: Hepatic, renal, plasma. Excretion: Renal
**Mechanism of Action**: Binds to glucagon receptors (G-protein-coupled), increasing cyclic AMP independently of beta-adrenergic pathways, enhancing contractility and rate.
**Adverse Effects:**
Nausea, vomiting, hyperglycemia, hypokalemia, tachycardia, hypertension, abdominal pain.
**Uses:** Beta-blocker or calcium channel blocker overdose (for inotropy), severe hypoglycemia, adjunct in anaphylaxis or shock.
**Mode of Administration**: IV bolus or infusion, IM, SC.
**Dilution:** Reconstitute 1 mg vial with sterile water; for infusion, dilute in D5W or NS (e.g., 10 mg in 100 mL).
**Dosage**: Inotropy (overdose): 2-5 mg IV bolus (repeat if needed), then 1-10 mg/hour infusion; hypoglycemia: 1 mg IV/IM/SC

# DIGOXIN

- **Definition**: Cardiac glycoside for rate control.
- **Mechanism of Action**: Inhibits Na+/K+ ATPase, increases vagal tone, slows AV conduction.
- **Pharmacodynamics**: Slows heart rate in atrial fibrillation, no QT effect.
- **Pharmacokinetics**:
  - **Absorption**: Oral.
  - **Metabolism**: Minimal hepatic.
  - **Excretion**: Renal
  - **Dosage**: 0.5-1 mg (loading), 0.125-0.25 mg/day.
- **Onset/Duration**: 1-2 hours (oral), 5-30 min (IV)/2-3 days.
- **Interactions**: Amiodarone, verapamil increase levels.
- **Side Effects**: Nausea, arrhythmias, visual disturbances

# Comparison Table of Positive Inotropes

| Drug | Class | Mechanism | Dosage | Adverse Effects | Uses | Administration | Dilution |
|---|---|---|---|---|---|---|---|
| **Epinephrine** | Catecholamine | α1, α2, β1, β2 agonist; ↑ cAMP (β), ↑ Ca2+ (α) | Cardiac arrest: 1 mg IV q3-5 min; Anaphylaxis: 0.3-0.5 mg IM; Infusion: 0.01-0.1 mcg/kg/min | Tachycardia, hypertension, arrhythmias, pulmonary edema | Cardiac arrest, anaphylaxis, hypotension, bronchospasm | IV, IM, SC endotracheal | IV: 1 mg in 10 mL NS (1:10,000); ET: 2-2.5 mg in 5-10 mL NS |
| **Norepinephrine** | Catecholamine | α1, β1 agonist; ↑ cAMP (β), ↑ Ca2+ (α) | 0.01-0.1 mcg/kg/min IV, titrate to 0.5-1 mcg/kg/min | Tachycardia, hypertension, arrhythmias, ischemia | Septic/cardiogenic shock, hypotension | IV infusion (central line) | 4-16 mg in 250 mL D5W/NS (16-64 mcg/mL) |
| **Dopamine** | Catecholamine | β1, α1, dopamine receptors; ↑ cAMP | 2-20 mcg/kg/min IV | Tachycardia, arrhythmias, hypertension, gangrene | Hypotension, shock, heart failure | IV infusion | 400 mg in 250 mL D5W/NS (1600 mcg/mL) |
| **Dobutamine** | Synthetic Catecholamine | β1 agonist; ↑ cAMP | 0.5-20 mcg/kg/min IV | Tachycardia, arrhythmias, hypertension | Heart failure, cardiogenic shock | IV infusion | 250 mg in 250 mL D5W/NS (1000 mcg/mL) |
| **Isoprenaline** | Synthetic Catecholamine | β1, β2 agonist; ↑ cAMP | 0.01-0.2 mcg/kg/min IV | Tachycardia, hypotension, arrhythmias | Bradycardia, torsades, bronchospasm | IV infusion | 1 mg in 500 mL D5W/NS (2 mcg/mL) |

| Drug | Class | Mechanism | Dosage | Adverse Effects | Uses | Administration | Dilution |
|---|---|---|---|---|---|---|---|
| **Milrinone** | PDE3 Inhibitor | Inhibits PDE3; ↑ cAMP, ↑ Ca2+ handling | Loading: 50 mcg/kg IV; Maintenance: 0.375-0.75 mcg/kg/min | Hypotension, arrhythmias, thrombocytopenia | Acute heart failure, cardiogenic shock | IV bolus + infusion | 200 mcg/mL in NS/D5W |
| **Amrinone** | PDE3 Inhibitor | Inhibits PDE3; ↑ cAMP | Loading: 0.75 mg/kg IV; Maintenance: 5-10 mcg/kg/min | Thrombocytopenia, hypotension, hepatotoxicity | Congestive heart failure | IV bolus + infusion | 1-3 mg/mL in NS/D5W |
| **Digoxin** | Cardiac Glycoside | Inhibits Na+/K+ ATPase; ↑ Ca2+ | Loading: 0.5-1 mg; Maintenance: 0.125-0.25 mg/day | Nausea, arrhythmias, visual disturbances | Heart failure, atrial fibrillation | Oral, IV | IV: undiluted |
| **Levo simendan** | Calcium Sensitizer | Sensitizes troponin C, PDE3 inhibition, K+ channel opening | Loading: 6-24 mcg/kg; Maintenance: 0.05-0.2 mcg/kg/min | Hypotension, tachycardia, atrial fibrillation | Acute heart failure, cardiogenic shock | IV infusion | 0.025-0.05 mg/mL in D5W |
| **Glucagon** | Hormone | Glucagon receptor; ↑ cAMP (non-adrenergic) | Inotropy: 2-5 mg IV bolus, 1-10 mg/hr; Hypoglycemia: 1 mg | Hyperglycemia, nausea, tachycardia | Beta-blocker overdose, hypoglycemia | IV, IM, SC | 10 mg in 100 mL D5W/NS |

# THANK YOU