Basic Cardiovascular Pharmacology

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Ahmed S. Awad, Megan Linehan, Danielle Evans, Lauren A. Igneri, and Muhammed Muntazar

Medicine heals doubts as well as diseases.

—Karl Marx

Abbreviations

BP	Blood pressure
cAMP	Cyclic adenosine monophosphate
CPB	Cardiopulmonary bypass
cGMP	Cyclic guanosine monophosphate
HIT	Heparin-induced thrombocytopenia
LV	Left ventricle or left ventricular
MAO	Monoamine oxidase
MAP	Mean arterial pressure
PCC	Prothromobin complex concentrate
PDA	Phosphodiesterase
SVR	Systemic vascular resistance

A. S. Awad (✉) · M. Linehan
Department of Anesthesiology and Perioperative Medicine, Cooper University Hospital, Camden, NJ, USA
e-mail: ahwad1900@gmail.com

D. Evans · L. A. Igneri
Department of Pharmacy, Cooper University Hospital, Camden, NJ, USA

M. Muntazar
Department of Anesthesiology and Perioperative Medicine, Cooper University Hospital, Camde, Browns Mills, NJ, USA

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Overview

The pharmacologic agents commonly used in the treatment of cardiothoracic surgery patients are agents that (1) have a direct or indirect effect on the heart and circulatory system (e.g., vasopressors, inotropes, vasodilators, antiarrhythmic medications, and medications used to treat myocardial ischemia) and (2) those that do not have a direct effect on the heart and circulation (e.g., hematologic agents, diuretics, anesthetic agents, and antihyperglycemic agents). This chapter will describe briefly the pharmacology of the most commonly used medications in the perioperative management of cardiac surgery patients used including (1) the pharmacodynamics, i.e., the effect of the drug on the body, such as the cardiovascular and central nervous systems; (2) the pharmacokinetics, i.e., the effect of the body on the drug, such as absorption and distribution; and (3) the side effects of the pharmaceutical agents used.

Vasopressors

Vasopressors are a class of short-acting drugs that constrict blood vessels, leading to an increase in systemic vascular resistance (SVR) and consequent increase in mean arterial pressure (MAP). Through this hemodynamic effect, vasopressors help maintain organ perfusion when the vascular resistance is inadequate. The drugs are given intravenously, preferably through a central line, thus having an immediate effect. Vasopressors are different from inotropes, which only increase myocardial contractility; some vasopressors increase both SVR and myocardial contractility. The mechanism of action of vasopressors is mediated by alpha receptors, beta receptors, or vasopressin-1 receptors on the smooth muscle of vessels; some vasopressors affect multiple receptors. Activation of these receptors increases cytosolic calcium, with consequent vasoconstriction.

Phenylephrine HCl (Neosynephrine)

Mechanism of action:	Powerful direct-acting alpha$_1$-adrenergic agonist. A vasoconstrictor without a direct cardiac effect
Dose:	Bolus: 50–100 μg every 1–2 min as needed Infusion dose: 25–200 μg/min or 0.3–2 μg/kg/min
Onset of action:	Immediate onset
Dilution:	Dilute 10 mg of phenylephrine (1 mL) with 100 mL of the chosen diluent to get 100 μg/mL concentration.
Half-life:	2–3 h. Metabolized by monoamine oxidase (MAO). Clinical effect of bolus administration is brief, with need to re-administer after several minutes.
Hemodynamic effects:	Increases SVR and blood pressure (BP); decreases heart rate (reflex bradycardia)
Clinical usage:	Hypotension, nasal decongestion, mydriasis
Side effects:	Reflex bradycardia, severe hypertension if injected in patients using MAO inhibitors (e.g., tricyclic antidepressants); tissue and skin necrosis with extravasation at the site of injection

Ephedrine Sulfate

Mechanism of action:	Adrenergic agonist agent with mixed effects. Mainly at alpha and $beta_1$ receptors. Acts indirectly through the release of catecholamines. Longer acting and less potent than epinephrine
Dose:	Bolus: 5–10 mg IV every 5–10 min
Dilution:	Dilute 50 mg of ephedrine sulfate (1 mL) with 9 mL of the chosen diluent to get 5 mg/mL concentration.
Onset of action:	1 min
Duration of action:	1 h
Half-life:	3–6 h. Eliminated by liver and kidney
Hemodynamic effects:	Increases systolic, diastolic, and MAP. Increases myocardial contractility, heart rate, and cardiac output
Clinical usage:	Treatment of hypotension, bradycardia, bronchospasm, and urinary incontinence
Side effects:	Repeated doses can result in tachyphylaxis from depletion of catecholamine stores.

Clinical Pearls

1. Crosses the blood-brain barrier, resulting in dose-dependent side effects of anxiety, restlessness, nervousness, and tachycardia.
2. Severe hypertension if injected in patients who are using drugs or medications that inhibit reuptake of norepinephrine (e.g., cocaine) or affect the degradation of norepinephrine (e.g., MAO inhibitors). Chronic cocaine users may be catecholamine depleted and therefore not respond to ephedrine.

Norepinephrine (Levophed)

Mechanism of action:	Sympathomimetic, with direct $alpha_1$ and $beta_1$ agonist properties
Dose:	Bolus: 4–16 μg IV push Infusion dose: 4–10 μg/min or 0.05–0.15 μg/kg/min
Onset of action:	30 s
Dilution:	Dilute 4 mg with 250 mL of 5% dextrose to achieve a concentration of 16 μg/mL.
Half-life:	2 min. Primarily metabolized by MAO and catechol-O-methyltransferase at the synaptic cleft
Hemodynamic effects:	Increases SVR, heart rate, and contractility, thereby raising BP. Has more inotropic effects than chronotropic effects. Causes pulmonary artery vasoconstriction. Sometimes infused through a left atrial line in hypotensive patients who have pulmonary hypertension (minimizes the vasoconstrictor effect in the pulmonary vasculature)
Clinical usage:	Low BP caused by low SVR, as in septic shock. Used when less potent drugs are inadequate
Side effects:	Tachyarrhythmias and ischemia (myocardial, mesenteric, renal, extremities); tissue and skin necrosis, with extravasation at the site of injection

Vasopressin (Pitressin)

Mechanism of action:	A hormone synthesized in the hypothalamus and released from the pituitary into the circulation. Two primary functions: antidiuretic action via activation of the vasopressin-2 receptors and vasoconstriction via activation of smooth muscle vasopressin-1 receptors
Dose:	Bolus: 0.1–0.2 units Infusion dose: 0.01–0.06 units/min (vasodilatory shock)
Onset of action:	Peak effect within 15 min
Dilution:	Dilute 50 units with 250 mL of 0.9% normal saline to get 0.2 units/mL concentration or dilute 100 units with 100 mL of 0.9% normal saline to get 1 unit/mL.
Half-life:	10–20 min; eliminated by liver and kidney
Hemodynamic effects:	Increases SVR
Clinical usage:	Vasodilatory catecholamine-resistant shock; vasoplegia syndrome in patients who are hypotensive after weaning from cardiopulmonary bypass; diabetes insipidus; upper gastrointestinal bleed
Side effects:	Angina pectoris, atrial fibrillation, bradycardia

Clinical Pearls

1. There are no vasopressin receptors in the brain or lung vasculature. Therefore, vasopressin is a good option in patients with pulmonary hypertension who are catecholamine depleted and do not respond to ephedrine. Vasopressin does not increase pulmonary vascular resistance.
2. Effective in hypotensive patients on ACE inhibitors.
3. High risk for intestinal ischemia complications.
4. May decrease urine output.

Angiotensin II (Giapreza)

Angiotensin II is a naturally occurring protein hormone.

Mechanism of action:	Raises blood pressure by two mechanisms: direct action on the adrenal cortex, increasing aldosterone secretion; and activation of angiotensin II type 1 receptor on vascular smooth muscle
Dose:	Bolus: no bolus Infusion dose: initial – 20 ng/kg/min IV. Titrate every 5 min by increments of up to 15 ng/kg/min to achieve target blood pressure; limit the dose to 80 ng/kg/min in the first 3 h of treatment.
Dilution:	Dilute 2.5 mg vial with 250 mL of 0.9% normal saline to achieve a concentration of 10,000 ng/mL
Duration of action:	Short duration of action, metabolized by aminopeptidase A and angiotensin-converting enzyme in plasma and erythrocytes
Half-life:	< 1 min
Hemodynamic effects:	Increases SVR and aldosterone release, thus raising BP
Clinical usage:	Septic or distributive shock
Side effects:	Thromboembolic events, hyperglycemia, peripheral ischemia

Clinical Pearls
Angiotensinogen is a precursor protein produced in the liver and cleaved by renin to form angiotensin I. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE) present in the renal endothelium, lungs, and capillary endothelium (see Fig. 2.8).

Inotropic Support Therapies

Inotropes are medications that increase myocardial contractility. In this section, we discuss the inotropic pharmacologic agents that are used in the management of patients with acute heart failure during cardiac surgery and/or low cardiac output syndrome after cardiac surgery. Low cardiac output syndrome has an incidence of about 10% for isolated coronary artery bypass graft or valve surgery to 27% for combined coronary artery bypass graft and mitral valve surgery. Inotropic support in cardiac surgery may begin before terminating bypass in cases of long cross-clamp periods, preexisting left ventricular (LV) dysfunction, LV hypertrophy, recent infarction, or incomplete revascularization. Support should be maintained for at least 6–8 h or until cardiac contractility and cardiac output improve. Inotropes are also used to maintain hemodynamics in off-pump surgery.

Mechanisms of Action

There are four classes of inotropes with different mechanisms of action:

1. Calcium and calcium-releasing agents. These agents lead to an increase in cytosolic calcium, which improves calcium-dependent myocardial contractility.
   (a) Adrenergic agents: activation of $beta_1$-adrenergic receptors leads to the formation of cyclic adenosine monophosphate (cAMP), which increases intracellular calcium.
   (b) Phosphodiesterase (PDE) inhibition agents: cAMP is metabolized in the cell by the PDE enzyme. Agents that inhibit this enzyme indirectly increase the availability of intracellular calcium (e.g., PDE III inhibitors, such as milrinone).
   (c) Sodium-potassium ATPase inhibition: Agents that inhibit this pump cause an increase in intracellular sodium, which leads to an increase in intracellular calcium (e.g., digoxin).
2. Calcium sensitizers. These agents increase the responsiveness of receptors to calcium (e.g., levosimendan, a calcium synthesizer/K^+-ATP activator that is not yet approved for use in the United States).
3. Cardiac myosin activators. These agents enhance the actin-myosin cross-bridge formation, thus increasing the force generated by cross bridges. The agents also

lengthen the duration of the contraction (e.g., omecamtiv mecarbil, which is not approved in the United States).
4. Lusitropic drugs. These drugs promote diastolic cardiac relaxation through activation of the intracellular calcium uptake system or sarco/endoplasmic reticulum Ca^{2+}-ATPase SERCA2a (e.g., istaroxime, which is not approved in the United States).

Positive inotropic agents commonly used in the cardiac operating room:

1. Calcium
2. Catecholamines
   (a) Dopamine
   (b) Dobutamine
   (c) Dopexamine
   (d) Epinephrine
   (e) Isoproterenol
   (f) Norepinephrine
3. Calcium sensitizers: Levosimendan
4. Cardiac myosin activators: Omecamtiv
5. Cardiac glycosides: Digoxin
6. PDE III inhibitors:
   (a) Enoximone
   (b) Piroximone
   (c) Milrinone
   (d) Amrinone
7. Glucagon

Calcium Chloride ($CaCl_2$); Calcium Gluconate(Kalcinate)

Two forms of intravenous calcium are available: 10% calcium chloride and 10% calcium gluconate.

Mechanism of action:	The electrolyte calcium increases the extracellular and intracellular ionized calcium concentrations. Calcium is the final common pathway necessary to trigger muscle contraction; thus, it may increase periphral vascular resistance (PVR) and cardiac contractility and enhance the effect of inotropic agents.
Dose:	0.5–1 g (5–10 mL of a 10% solution) given IV over a few minutes. IV bolus can cause profound hypertension.
Onset of action:	Immediate onset, peaking at 5 min; eliminated by the gastrointestinal tract and kidney
Duration of action:	10–20 min
Hemodynamic effects:	Increases SVR, MAP, and cardiac output
Clinical usage:	Hypocalcemia associated with hemodilution from priming the cardiopulmonary bypass (CPB) circuit; hyperkalemia, which is a common problem during CPB (secondary to impaired urinary potassium excretion and the use of hyperkalemic cardioplegia solutions); hypomagnesemia; and calcium channel blocker toxicity
Side effects:	Potentiates ischemia-reperfusion injury

Clinical Pearls

1. Calcium chloride is irritating and can cause tissue and skin necrosis with extravasation at the site of injection; thus, administration through a central line is preferred. Calcium gluconate does not cause skin irritation and can be given in a peripheral IV.
2. Calcium chloride has three times more elemental calcium than does calcium gluconate.

Catecholamines

Dopamine, norepinephrine, and epinephrine are endogenous catecholamines, produced by the adrenal medulla. The sequence of synthesis is tyrosine to L-dopa ➔ dopamine ➔ norepinephrine ➔ epinephrine.

Types of Adrenergic Receptors

Alpha-Adrenergic Receptors

(a) $Alpha_1$-adrenergic effects
  (i) Vascular smooth muscle contraction
(b) $Alpha_2$-adrenergic effects
  (i) Vascular smooth muscle relaxation

Beta-Adrenergic Receptors

(a) $Beta_1$-adrenergic effects
  (i) Inotropy (improved cardiac contractility)
  (ii) Chronotropy (increased heart rate)
(b) $Beta_2$-adrenergic effects
  (i) Vasodilation
  (ii) Bronchodilation
(c) $Beta_3$-adrenergic effects
  (i) Enhancement of lipolysis in adipose tissue
  (ii) Thermogenesis in skeletal muscle
  (iii) Urinary bladder relaxation

Dopaminergic Receptors

(a) DA_1 – Mediates vasodilation in kidney, intestine, and heart
(b) DA_2 – Located presynaptically. Inhibits the release of norepinephrine and dopamine. Associated with the antiemetic action of droperidol

Epinephrine HCl (Adrenaline)

Epinephrine is a naturally occurring sympathomimetic catecholamine produced in the adrenal medulla.

Mechanism of action:	At lower doses, beta effects predominate, leading to increased heart rate. As the dose increases, alpha receptor effects dominate, resulting in vasoconstriction.
Dose:	Bolus: 4–10 μg Infusion dose: 1–8 μg/min (0.01–0.05 μg/kg/min) Cardiac arrest: 1 mg every 3–5 min
Onset of action:	Immediate onset
Duration of action:	Short duration, peak at 5 min
Half-life:	2 min; rapid metabolism and neuronal uptake, as it is metabolized by catechol-O-methyltransferase and MAO
Hemodynamic effects:	Increases cardiac output and heart rate at low doses (0.01–0.03 μg/kg/min); increases SVR, with higher doses potentially leading to decreased cardiac output because of increased myocardial afterload
Clinical usage:	Bradyarrhythmia: improving atrial responsiveness to pacing at the conclusion of bypass (stimulation of the sinus node) Bronchospasm: Epinephrine has a robust bronchodilator action and can be used after weaning from CPB to treat bronchospasm. Anaphylactic shock: can be used to treat protamine-induced hypotension Cardiogenic shock: In cardiac surgery, epinephrine can be used to support and improve cardiac output. Administration can begin before terminating bypass in cases of long cross-clamp time, preexisting LV dysfunction, LV hypertrophy, recent infarction, and incomplete revascularization. Drug of choice in heart transplant patients with denervated heart. Works directly on $beta_1$ receptors of the denervated heart, increasing the BP and heart rate
Side effects:	Tachycardia and tachyarrhythmia Increases myocardial work and oxygen consumption; can induce myocardial ischemia Associated with metabolic acidosis, hyperglycemia, hypokalemia, and increased lactate level Severe vasoconstriction with high dose can cause bowel ischemia, pulmonary hypertension, and acute kidney injury.

Clinical Pearls

1. Correction of acidosis is vital, as acidosis decreases epinephrine's effectiveness.
2. Combination of low-dose epinephrine and low-dose milrinone is synergistic, while decreasing the side effects of both drugs.

Dopamine (Intropin)

Dopamine is an endogenous sympathomimetic catecholamine and immediate precursor to norepinephrine.

Mechanism of action:	Dopamine is a positive inotropic and chronotropic agent. It stimulates the adrenergic receptors directly and indirectly. At low doses, dopamine stimulates DA_1 in the central nervous system and renal vascular beds. With moderate doses, it shifts to stimulate $beta_1$-adrenergic receptors in the heart, and then alpha1-adrenergic receptors at high doses.
Dose:	1–20 μg/kg/min continuous infusion
Onset of action:	5 min after initiating IV infusion
Duration of action:	Short, less than 10 min
Half-life:	2 min; through rapid metabolism and neuronal uptake; metabolized by catechol-O-methyltransferase and MAO
Hemodynamic effects:	Dose-dependent Low dose: 1–4 μg/kg/min – increased renal blood flow and urine output Moderate dose: 4–10 μg/kg/min – beta-adrenergic effects with positive inotropic and chronotropic effects, where heart rate, cardiac contractility, cardiac output, and blood pressure increase High dose: >10 μg/kg/min – considered a vasopressor, where alpha-adrenergic effects begin to predominate, with vasoconstriction and increased BP
Clinical usage:	Hemodynamic instability in shock, especially septic shock Cardiogenic shock and low cardiac output syndrome after cardiac surgery Bradycardia
Side effects:	Tachycardia and tachyarrhythmia Increases myocardial work and oxygen consumption; can induce myocardial ischemia Severe vasoconstriction with high-dose dopamine infusion can cause limb ischemia. Symmetrical peripheral gangrene is known as purpura fulminans.

Clinical Pearls

1. Contraindications include pheochromocytoma, uncorrected tachyarrhythmias, or ventricular fibrillation.
2. Extravasation of dopamine during peripheral IV administration can lead to tissue necrosis and should be treated with local injection of diluted phentolamine 5 to 10 mg.

Dobutamine (Dobutrex)

Dobutamine is a synthetic derivative of isoproterenol.

Mechanism of action:	Dobutamine is a positive inotropic and chronotropic medication. It stimulates $beta_1$ in the heart and $beta_2$ in the vascular smooth muscle adrenergic receptors. Unlike dopamine, it matches higher myocardial oxygen demand by increasing coronary blood flow.
Dose:	1–20 μg/kg/min (initial dose is usually 2–5 μg/kg/min)
Onset of action:	Within 5 min after intravenous infusion
Duration of action:	Short duration, 3–5 min
Half-life:	2 min; metabolized in the liver by catechol-O-methyltransferase
Hemodynamic effects:	Decreases SVR and reduces LV afterload, decreases mean arterial pressure, increases cardiac output and heart rate, exerts a moderate pulmonary vasodilator effect, reduces LV wall stress
Clinical usage:	Hemodynamic instability (shock and low cardiac output heart failure) with a mild elevation in SVR; dobutamine stress echocardiography for the detection of functional coronary artery stenosis
Side effects:	Dose-dependent tachycardia and tachyarrhythmia; theoretically, it can cause coronary steal; decreases mean arterial pressure if the increase in cardiac output does not offset the decrease in SVR; tachyphylaxis if used after several days of a continuous infusion

Clinical Pearls

1. Dobutamine is contraindicated in patients with hypertrophic cardiomyopathy and diastolic dysfunction.
2. Alkalinization inactivates catecholamines, including dobutamine, so avoid injecting sodium bicarbonate or any alkaline solutions in the same intravenous line.
3. Dobutamine has little vasoconstrictor activity, so the risk of extravasation and skin necrosis is low. Thus, it can be infused in a peripheral IV.
4. Synergistic effect in improving cardiac output with the use of milrinone.

Isoproterenol (Isuprel)

Isoproterenol is a synthetic sympathomimetic.

Mechanism of action:	Isoproterenol is a positive inotropic and chronotropic agent through nonselective beta-adrenoceptor agonism.
Dose:	Bolus: 1–4 μg Infusion: 1–10 μg/min (0.01–0.06 μg/kg/min) titrated to heart rate and BP goals
Onset of action:	1–5 min after IV infusion
Duration of action:	10–15 min

Half-life:	2.5–5 min; drug is conjugated in hepatic and pulmonary tissue.
Hemodynamic effects:	Isoproterenol decreases SVR, increases cardiac output and heart rate, and decreases pulmonary vascular resistance.
Clinical usage:	Refractory torsades de pointes (a type of polymorphic ventricular tachycardia that can be fatal); refractory symptomatic bradycardia (heart block) or beta-blocker overdose; refractory electrical storm (3 or more sustained episodes of ventricular tachycardia or ventricular fibrillation); post-heart transplantation for heart rate optimization; Brugada syndrome (ST-segment elevation in the right precordial leads of ECG associated with an increased chance of sudden cardiac death due to ventricular fibrillation without apparent structural heart disease); bronchospasm during anesthesia; right ventricular dysfunction
Side effects:	Dose-dependent arrhythmia; coronary steal; hypoxia, by increasing ventilation-perfusion mismatch; reduced MAP

Calcium Sensitizers

Levosimendan (Simdax)

Levosimendan is a positive inotropic agent with ATP-dependent potassium-channel-opening and calcium-sensitizing effects. It improves myocardial contraction and improves relaxation during diastole, which aids ventricular filling. Levosimendan has not been approved by the Food and Drug Administration for use in the United States.

Cardiac Myosin Activators

Omecamtiv mecarbil

Omecamtiv mecarbil is a first-in-class cardiac myosin activator that increases the proportion of myosin heads that are tightly bound to actin and creates a force-producing state that is not related to cytosolic calcium accumulation. Phase I and II trials have been completed in patients with ischemic cardiomyopathy and acutely decompensated heart failure. Phase III studies are underway.

Cardiac Glycosides

Digoxin (Lanoxin)

Digoxin inhibits Na-K-ATPase, which results in increased intracellular calcium concentrations. It is indicated for supraventricular arrhythmias and exhibits positive inotropic effects, but it is rarely used due to its slow onset of action (4–6 h), narrow therapeutic index, and unpredictable dose-response dynamics.

Phosphodiesterase (PDE III) Inhibitors

Enoximone (Perfan)

Enoximone is a specific inhibitor of PDE III in cardiac and smooth muscle. Enoximone was recently evaluated in on-pump cardiac surgery (MOSEC study) and improved 30-day post-surgery renal function. Further studies are needed to validate these findings and delineate therapeutic utility.

Piroximone

Piroximone is a specific inhibitor of PDE III in cardiac and smooth muscle that was studied in animal models in the mid-1980s. This drug is not available in the United States.

Milrinone (Primacor)

Mechanism of action:	Non-catecholamine inodilator that inhibits PDE III and prevents cAMP breakdown, leading to increased intracellular calcium
Dose:	Bolus: 25–75 μg/kg Infusion: 0.375–0.75 μg/kg/min
Onset of action:	5–15 min after intravenous infusion
Duration of action:	2.7 h
Half-life:	2.3 h; 83% is unchanged in urine; 12% is metabolized in the liver by glucuronidation. Active tubular secretion is a major elimination pathway. Half-life is prolonged in renal failure.
Hemodynamic effects:	Decreases SVR, reduces myocardial oxygen demand, increases cardiac output and heart rate, decreases pulmonary vascular resistance, reduces LV end-diastolic pressure
Clinical usage:	Low cardiac output syndrome post-cardiac surgery, right ventricular dysfunction associated with high pulmonary vascular resistance
Side effects:	Decreased MAP; bronchospasm; torsades de pointes; cardiac arrhythmias; increased concentrations in renal dysfunction

Clinical Pearls

1. It has additive effects with epinephrine, dopamine, and dobutamine.
2. The patient's myocardial function should be monitored for a few hours after the drug is administered because of its long half-life.

Glucagon (GlucaGen)

Mechanism of action:	Glucagon has positive chronotropic and positive inotropic effects in low cardiac output failure after cardiac surgery.
Dose:	Bolus: 2–5 mg IV every 30–60 min Infusion: 1–10 mg/h
Onset of action:	5–10 min after IV bolus
Duration of action:	20–30 min for bolus
Half-life:	3–6 min; eliminated by liver and kidney
Hemodynamic effects:	Increases cardiac output, decreases pulmonary vascular resistance
Clinical usage:	Low cardiac output syndrome after cardiac surgery; severe hypoglycemia; gastrointestinal smooth muscle relaxation for endoscopy; treatment of beta-adrenergic blocker toxicity
Side effects:	Severe hyperglycemia; hypokalemic syndrome; contraindicated in pheochromocytoma, glucagonoma, diabetes mellitus, and insulinoma

Methylene Blue (Methylthionine Chloride, Urolene Blue)

Mechanism of action:	It inhibits nitric oxide synthase and guanylate cyclase, thus decreasing vascular smooth muscle relaxation.
Dose:	Bolus: 1–2 mg/kg IV injection slowly over 5 min; may repeat in 1 h
Onset of action:	Almost immediate
Duration of action:	30 min
Half-life:	5–6 h
Hemodynamic effects:	Increases MAP, SVR Increases pulmonary vascular resistance
Clinical usage:	Vasoplegia syndrome post CPB refractory to catecholamines
Side effects:	Methemoglobinemia at higher doses; hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency

Vasodilator Drugs

Vasodilator drugs treat hypertension by decreasing systemic vascular resistance through many mechanisms. Arterial vasodilators reduce afterload, which results in increased cardiac output. Additionally, they improve myocardial oxygen demand dynamics. Venous dilators reduce preload; they are used to treat systemic hypertension if cardiac output is satisfactory. If the cardiac index is 2.0–2.2 L/min/m^2, accompanying inotropic support should be administered to improve myocardial function.

Nitroprusside (Nipride, Nitropress)

Mechanism of action:	Relaxes smooth vascular muscles by converting to nitric oxide, which increases cyclic guanosine methyl phosphatase (cGMP)
Dose:	Infusion: 0.5–10 μg/kg/min
Onset of action:	0.5–1 min
Duration of action:	1–10 min
Half-life:	3–6 min. Sodium nitroprusside is broken down in red blood cells to cyanide and nitric oxide. Cyanide is changed to thiocyanate in the liver by rhodanese.
Hemodynamic effects:	Reduced preload and afterload; decreased cardiac output; dose-dependent decrease in systemic vascular resistance and pulmonary vascular resistance; reflex tachycardia
Clinical usage:	Hypertensive emergencies
Side effects:	Prolonged administration leads to accumulation of thiocyanate and cyanide and resultant metabolic acidosis and methemoglobinemia; negative inotropes and inhaled anesthetics potentiate its hypotensive effects; severe renal or hepatic dysfunction increases the risk of thiocyanate and cyanide toxicity.

Clinical Pearls

1. Appropriate antidote therapy should be administered if thiocyanate and cyanide toxicities develop (hydroxocobalamin and methylene blue, respectively).
2. Dose reduction is indicated in patients with renal or hepatic disease.
3. Do not use in cases of compensatory hypertension (aortic coarctation, AV shunting), surgery in moribund patients, those with inadequate cerebral circulation, or defective or absent rhodanese.

Nitroglycerin (Tridil)

Mechanism of action:	Acts as a nitric oxide donor and exerts its vasodilator effects primarily in the venous system by increasing cGMP
Dose:	Bolus: dilute to 40 μg/mL; give 40–80 μg (1–2 mL) at a time. Infusion: 0.5–10 μg/kg/min Sublingual: 400–500 μg; may be used in the holding area if patient develops chest pain
Onset of action:	1 min
Duration of action:	1–10 min
Half-life:	1–3 min; eliminated in urine as inactive metabolites
Hemodynamic effects:	Coronary vasodilator, as it increases collateral coronary flow; venodilator that reduces preload and decreases cardiac output; improves diastolic function; improves subendocardial perfusion; decreases pulmonary vascular resistance
Clinical usage:	Perioperative hypertension; hypertension with myocardial ischemia or high filling pressures; angina and coronary spasm; prevention of radial artery spasm; pulmonary hypertension
Side effects:	Excessive or prolonged administration may result in tolerance or methemoglobinemia; increased pulmonary V/Q mismatch.

Clinical Pearls

1. Antidote therapy with methylene blue should be administered if methemoglobinemia develops.
2. Contraindicated in pericardial tamponade, constrictive pericarditis, restrictive cardiomyopathy, and in the presence of phosphodiesterase inhibitors.

Hydralazine (Apresoline)

Mechanism of action:	Direct arterial vasodilation
Dose:	Bolus: 10–40 mg IV every 4–6 h (perioperative); 5 mg every 15 min (intraoperative) Infusion: 1.5 μg/kg/min (intraoperative)
Onset of action:	10–80 min; peak effect: 20 min
Duration of action:	Up to 12 h depending on acetylator status; metabolites eliminated in the urine
Half-life:	3–7 h
Hemodynamic effects:	Acts as a direct arteriolar vasodilator, resulting in afterload reduction
Clinical usage:	For hemodynamically stable postoperative patients with hypertension when oral administration of an antihypertensive is not possible or when there is an urgent need to lower the BP
Side effects:	Rarely, hydralazine causes a systemic lupus erythematosus with glomerulonephritis syndrome, especially in slow acetylators. It can lead to coronary steal in patients with suspected coronary artery disease, and it can lead to angina attack and myocardial ischemia.

Phentolamine (Regitine, OraVerse)

Phentolamine is an alpha-blocker used in hypertension associated with pheochromocytoma and for the management of alpha agonist vasopressor extravasation. After stopping the vasopressor infusion, the catheter tip should be left in place so that aspiration of fluid from the extravasated area may be attempted. Ten milligrams of phentolamine is mixed in a 10-mL syringe, and 1 mL is injected into the catheter before removal.

Fenoldopam (Corlopam)

Mechanism of action:	DA_1 receptor agonist without adrenergic receptor agonist
Dose:	0.01–0.3 μg/kg/min IV infusion; may increase by 0.05–0.1 μg/kg/min every 15 min until target BP is achieved 0.03–0.1 μg/kg/min to optimize renal perfusion in patients with preoperative renal dysfunction
Onset of action:	10 min (adult)

Duration of action:	1 h
Half-life:	5 min
Hemodynamic effects:	Decreases BP without increasing heart rate or contractility; increases renal perfusion
Clinical usage:	Severe hypertension requiring prompt control to optimize renal perfusion in patients with preoperative renal dysfunction
Side effects:	Dose-related tachycardia, especially in doses >0.1 μg/kg/min; increase in intraocular pressure; hypokalemia (monitor potassium within 6 h of administration)

Clinical Pearls

1. Use caution in patients with coronary artery disease or ongoing angina pectoris, as it can increase myocardial oxygen demand due to dose-dependent tachycardia.
2. May transiently increase intraocular pressure (caution in patients with glaucoma).
3. Avoid concomitant use with beta-blockers due to their negative chronotropic effects.

Prostaglandin E2 (Iloprost)

Prostaglandin E2 dilates systemic and pulmonary arterial vascular beds. It has been used in cardiothoracic surgical patients who have pulmonary hypertension, hypoxemia, or right heart dysfunction to decrease mean pulmonary artery pressure without altering MAP.

Epoprostenol (Flolan, Veletri)

Epoprostenol is a naturally occurring prostacyclin. It dilates systemic and pulmonary arterial vascular beds and inhibits platelet aggregation. It is used for long-term intravenous treatment of primary pulmonary hypertension and, in the nebulized form, in cardiothoracic surgical patients with pulmonary hypertension and right heart dysfunction. The aerosolized dose is 3–50 ng/kg/min.

Nitric Oxide, inhaled (NO, iNO, INOmax)

Nitric oxide is a naturally occurring vasodilator made by vascular endothelial cells.

Mechanism of action:	Decreases vascular smooth muscle tone by increasing intracellular cGMP through activation of guanylate cyclase
Dose:	20–40 parts per million

Onset of action:	10 min (adult)
Duration of action:	1 h
Half-life:	5 min
Hemodynamic effects:	Lowers right ventricular afterload; selective pulmonary vasodilation
Clinical usage:	Pulmonary hypertension associated with acute right ventricular dysfunction post CPB; treatment of right ventricular failure after heart transplantation

Antiarrhythmics

Antiarrhythmic drugs are used to prevent and treat cardiac conduction abnormalities. Antiarrhythmic drugs are classified by mechanism of action into four groups (Table 3.1). They alter the velocity of conduction and the duration of the refractory period, and they suppress abnormal automaticity. Cardiac surgery patients often develop supraventricular arrhythmias, such as atrial fibrillation, whereas ventricular arrhythmias usually occur in the presence of injury to the cardiac muscle. Continuous electrocardiographic monitoring is necessary, especially during the parenteral administration of these drugs.

Sodium Channel Blocker

Procainamide (Pronestyl)

Procainamide is a class Ia antiarrhythmic that blocks sodium channels. It is the antiarrhythmic of choice in preexcitation syndromes with accessory pathways, such as Wolff-Parkinson-White syndrome. It is contraindicated in the prolonged QT syndrome.

Table 3.1 Vaughan-Williams classification of antiarrhythmic drugs according to their mechanism of action

Mechanism of action	Class	Drug
Fast sodium channel blocker	Ia	Procainamide
	Ib	Lidocaine
Beta-blocker	II	Metoprolol
Potassium channel blocker	III	Amiodarone
Calcium channel blocker	IV	Diltiazem
Other	N/A	Adenosine
		Magnesium
		Atropine/glycopyrrolate
		Digoxin

Lidocaine (Xylocaine)

Mechanism of action:	Class Ib antiarrhythmic that blocks sodium channels and decreases automaticity
Dose:	1–1.5 mg/kg (usually 100 mg dose)
Onset of action:	45–90 s
Duration of action:	10–20 min
Half-life:	90–120 min; eliminated by hepatic metabolism
Hemodynamic effects:	Therapeutic doses do not affect myocardial contractility and rarely reduce BP, but high doses depress myocardial contractility.
Clinical usage:	Indicated for ventricular arrhythmias and is the preferred medication in patients with ventricular arrhythmias that have a prolonged QT interval
Side effects:	Lidocaine central nervous system toxicity manifests as nausea, vomiting, mental status changes, and seizure.

Clinical Pearls

1. Lidocaine is contraindicated in patients with documented immune-mediated hypersensitivity to an amide local anesthetic.
2. Lidocaine has antiarrhythmic activity in ischemic myocardial tissue.
3. Contraindicated in Wolff-Parkinson-White and Stokes-Adams syndromes.

Beta-Blockers (Class II Antiarrhythmics)

Beta-blockers bind to beta-adrenergic receptors and have negative inotropic and chronotropic effects, and they slow AV conduction. Thus, they reduce BP and myocardial oxygen demand. Beta-blockers suppress renin activity and can reduce insulin release in hyperglycemia and mask initial symptoms of hypoglycemia, especially in labile diabetics. In cardiac surgery, indications include control of postoperative hypertension with a satisfactory cardiac output. Intravenous beta-blockers should be avoided when hypertension is accompanied by impaired cardiac output. Contraindications include cardiogenic shock, metabolic acidosis, hypotension, bradycardia, second- or third-degree heart block, sick sinus syndrome, and pheochromocytoma that has not been treated with alpha-blocking agents.

Atenolol (Tenormin)

Mechanism of action:	Selective beta$_1$ adrenoceptor antagonist
Dose:	Bolus: 2.5–10 mg IV push at a rate not to exceed 1 mg/min
Onset of action:	Effects are seen in 1 h with maximum effects in 2–4 h
Duration of action:	Up to 24 h
Half-life:	6–7 h; significantly prolonged in renal dysfunction

Hemodynamic effects:	Decreases BP by decreasing heart rate
Clinical usage:	In patients undergoing cardiac surgery, postoperative prevention of atrial fibrillation is important. Atenolol is used in hypertension, angina, acute myocardial infarction (with stable BP and heart rate), and tachyarrhythmias.
Side effects:	Hypotension, heart block, bradycardia, bronchospasm, heart failure

Esmolol (Brevibloc)

Mechanism of action:	Cardioselective $beta_1$ receptor blocker with a very short duration of action
Dose:	Bolus: 150 μg/kg over 30 s; then start infusion at 50 μg/kg/min; titrate to a maximum dose of 300 μg/kg/min for desired heart rate
Onset of action:	30 s
Duration of action:	10–30 min; metabolized by erythrocyte cholinesterase
Half-life:	2–9 min
Hemodynamic effects:	Decreases BP by decreasing heart rate
Clinical usage:	Perioperative hypertension; treatment of supraventricular tachycardia; atrial fibrillation (ventricular rate control); acute myocardial ischemia
Side effects:	Hypotension, heart block, bradycardia, bronchospasm, heart failure

Clinical Pearls

1. Contraindications include sinus bradycardia and heart block greater than first degree. Use with extreme caution in hypertensive patients who have marginal cardiac output.
2. Esmolol competitively prolongs neuromuscular blockade by succinylcholine due to the cholinesterase metabolism of both drugs.

Labetalol (Normodyne, Trandate)

Mechanism of action:	Selective $alpha_1$-adrenergic blocker and nonselective $beta_1$, $beta_2$-adrenergic blocker with a ratio of 1:7 IV
Dose:	Bolus: 5–10 mg IV push Infusion: 1–4 mg/min
Onset of action:	Rapid onset of action with maximal effects after 5 min
Duration of action:	2–6 h
Half-life:	6–8 h
Hemodynamic effects:	Negative inotropic and chronotropic effects; therefore, reduces BP
Clinical usage:	Used as a long-acting antihypertensive medication
Side effects:	Contraindications include overt cardiac failure, greater than first-degree heart block, and severe bradycardia.

Clinical Pearls

Labetalol is the only intravenous beta-blocker with alpha blocking activity.

Metoprolol (Lopressor)

Mechanism of action:	Selective beta$_1$ receptor blocker
Dose:	Bolus: 2.5–5 mg IV push
Onset of action:	1–5 min
Duration of action:	IV: 5–8 h
Half-life:	3–4 h; prolonged to 7–9 h in those with poor CYP2D6 metabolism
Hemodynamic effects:	Decreases heart rate and therefore BP
Clinical usage:	Intravenous use is indicated with myocardial ischemia and slowing of the ventricular response to atrial arrhythmias.
Side effects:	Hypotension, heart block, bradycardia, bronchospasm, heart failure

Potassium Channel Blocker (Class III Antiarrhythmic)

Amiodarone (Cordarone)

Mechanism of action:	Amiodarone is a class III antiarrhythmic with many pharmacodynamic effects. Amiodarone blocks sodium and potassium channels and exhibits calcium channel and adrenergic-blocking effects. Amiodarone prolongs the action potential by delaying repolarization.
Dose:	Malignant ventricular arrhythmia: 150 mg IV push followed by an infusion of 1 mg/min x 6 h Pulseless ventricular arrhythmia: 300 mg IV push
Onset of action:	Rapid control of ventricular rates; rhythm control requires higher cumulative doses.
Duration of action:	A bolus of amiodarone is rapidly distributed out of the intravascular space, resulting in a duration of action that is significantly shorter than the pharmacologic half-life (approximately 10–15 min).
Half-life:	IV single dose: mean range 9–36 days
Hemodynamic effects:	Slows conduction throughout the sinoatrial and atrioventricular nodes, resulting in negative chronotropic and dromotropic (conduction speed) effects
Clinical usage:	Indicated for the treatment of atrial fibrillation, polymorphic ventricular tachycardia without a prolonged QTc, and ventricular fibrillation
Side effects:	Prolonged QT, hypotension, atrioventricular block

Clinical Pearls

Hypotension associated with amiodarone administration may be mitigated by lengthening the infusion time.

Calcium Channel Blockers (Class IV Antiarrhythmics)

Nicardipine (Cardene)

Mechanism of action:	Inhibits calcium influx into vascular smooth muscle cells, including coronary arteries; no sinoatrial/atrioventricular nodal activity
Dose:	5 mg/h IV infusion; titrate by 2.5 mg/h increments every 5–15 min to a maximum infusion of 15 mg/h.
Onset of action:	1–2 min
Duration of action:	8 h; upon discontinuation of continuous infusion, a 50% reduction in effect occurs after 30 min, with a gradual reduction in effect over 50 h.
Half-life:	Alpha half-life of 3 min, with a rapid early distribution phase, an intermediate phase; beta half-life of 45 min; and terminal half-life of 14 h
Hemodynamic effects:	Reduces BP without negative inotropic effects or influence on sinoatrial or atrioventricular nodal conduction
Clinical usage:	Postoperative hypertension in the presence of reduced ventricular function; prevention of radial artery spasm if used in coronary artery bypass graft as an arterial conduit; coronary vasodilator
Side effects:	Hypotension, reflex tachycardia, vasodilation and flushing, headache

Clinical Pearls

1. Nicardipine is contraindicated in patients with advanced aortic stenosis.
2. Use with caution in patients with angina and heart failure.
3. Drug should be administered through large peripheral veins or central veins. Change site every 12 h to reduce the risk of venous thrombosis and local irritation.
4. Do not dilute with sodium bicarbonate or lactated Ringer's solution.

Clevidipine (Cleviprex)

Mechanism of action:	Short-term calcium channel blocker; inhibits calcium influx into vascular smooth muscle cells, producing a substantial reduction in BP; no sinoatrial/atrioventricular nodal activity
Dose:	1–2 mg/h, doubling the dose at 90 s intervals to achieve BP goal. Usual maintenance dose: 4–6 mg/h; maximum 21 mg/h
Onset of action:	1–4 min
Duration of action:	5–15 min
Half-life:	Biphasic: initial, 1 min; final, 15 min
Hemodynamic effects:	Potent BP reduction; no effect on heart rate
Clinical usage:	Emergency control of BP
Side effects:	Hypotension, atrial fibrillation, nausea, fever

Clinical Pearls

1. For every 1–2 mg/h increase in dose, an approximate reduction of 2–4 mm Hg in systolic blood pressure may occur.
2. Drug metabolism and elimination are not affected by hepatic or renal disease, and there are no significant drug-drug interactions.
3. Use with caution in patients with angina and heart failure.
4. Formulated in an oil-in-water emulsion containing 200 mg/mL of lipid (2 kcal/mL); contains soybean oil, egg yolk, phospholipid, and glycerin; contraindicated in patients with hypersensitivity to any of the components.

Diltiazem (Cardizem)

Mechanism of action:	Benzothiazepine calcium channel blocker that acts by preventing the influx of calcium into the slow channels of vascular smooth muscle and myocardium during depolarization
Dose:	Bolus: 0.25 mg/kg over 2 min. If no adequate response is noticed after 15 min, a repeat bolus of 0.35 mg/kg over 2 min is given. Infusion: start at 5–15 mg/h IV, using a 125 mg/125 mL mix for up to 24 h.
Onset of action:	3 min (IV)
Duration of action:	1–3 h (IV bolus); 0.5–10 h (after discontinuation of continuous infusion)
Half-life:	3–4 h (IV bolus); 4–5 h (continuous infusion). Administration with midazolam or triazolam can increase effects.
Hemodynamic effects:	Reduces BP; reduces heart rate
Clinical usage:	Used for slowing the ventricular response to atrial fibrillation and flutter (pacemaker backup must be readily available); treatment of systemic hypertension; prevention of arterial graft spasm and radial artery and coronary artery spasm
Side effects:	Arrhythmia, atrioventricular block, hypotension

Clinical Pearls

1. Avoid in cases with marginal cardiac output due to effects on slowing heart rate.
2. Contraindicated in patients with sick sinus syndrome, second- or third-degree AV block (except if functioning ventricular pacemaker is present), hypotension SBP <90 mm Hg, and ventricular tachycardia.
3. Concomitant use with beta-blockers, digoxin, or clonidine can lead to additive effects on cardiac conduction. Avoid administration in proximity of other conduction-altering agents.

Endogenous Nucleoside

Adenosine (Adenocard)

Mechanism of action:	Adenosine is a nucleoside that acts by slowing the conduction through the atrioventricular node.
Dose:	Bolus: 6 mg rapid IV push over 1–2 s followed immediately by a saline flush; may repeat 12 mg twice within 1–2 min
Onset of action:	10–20 s
Duration of action:	3–7 s
Half-life:	Metabolized in blood in less than 10 s
Hemodynamic effects:	Reduces BP and heart rate
Clinical usage:	Used for treatment and conversion to sinus rhythm of paroxysmal supraventricular tachycardias with atrioventricular reentry
Side effects:	Adenosine can produce a short heart block; do not give the second dose if a high-grade block develops after the first dose.

Electrolytes

Magnesium Sulfate

Hypomagnesemia is common after CPB due to dilution and diuresis and is associated with an increased risk of cardiac arrhythmias. While the efficacy of magnesium for the prevention of supraventricular and ventricular arrhythmias is controversial, the administration of magnesium at the conclusion of CPB (2 g over 15 min) and on the first morning after surgery is common practice, given the detrimental effects of postoperative hypomagnesemia. In patients with torsades de pointes, administer magnesium sulfate 25–50 mg/kg IV push.

Potassium Chloride (KCl)

Mechanism of action:	Crucial for resting membrane potential and action potential that are necessary for myocardial contraction and nerve conduction
Dose:	Infusion: 20–40 mEq IV over 30–60 min
Onset of action:	Immediate
Duration of action:	Variable
Half-life:	Variable; depends on the kidney for elimination
Hemodynamic effects:	At high concentration, decreases atrioventricular conduction and myocardial contractility
Clinical usage:	Prevention and treatment of arrhythmias associated with hypokalemia (serum potassium <3.5 mEq/L)
Side effects:	Phlebitis in the peripheral IV, so central line administration is preferable; rapid administration may cause cardiac arrest in diastole; caution in end-stage renal disease, as it accumulates in the circulation.

Clinical Pearls

1. Metabolic and respiratory alkalosis exacerbate hypokalemia, with intracellular shift of potassium. There is a tendency to hyperventilate the patient with the Ambu bag, causing respiratory alkalosis during transport to the intensive care unit; caution is warranted since hypokalemic patients can develop a serious cardiac arrhythmia.
2. Potassium should be administered to hypovolemic patients only after hydration and diuresis are established.
3. Chronological ECG changes of hyperkalemia (serum potassium >5.5 mEq/L): tall tented T-waves, prolongation of PR interval, widening QRS complex, flattening and disappearance of P-waves, development of a sine wave pattern, and, finally, asystolic cardiac arrest.

Anticholinergic

Atropine sulfate (Atropine)

Atropine is an anticholinergic antimuscarinic agent.

Mechanism of action:	It antagonizes the muscarinic actions of acetylcholine at smooth muscle parasympathetic locations, salivary glands, and the central nervous system. It stops the effects of acetylcholine on the sinoatrial and atrioventricular nodes.
Dose:	Bolus: 0.01 mg/kg IV (usually 0.5–1 mg IV); can be administered intramuscularly
Onset of action:	1–4 min
Duration of action:	15–30 min
Half-life:	3–4 h; metabolized by the liver and excreted renally
Hemodynamic effects:	Low dose may cause bradycardia, but higher dose produces tachycardia.
Clinical usage:	Indicated for treatment of bradyarrhythmia; sinus bradycardia if atrioventricular pacing wires fail or were not placed at the end of cardiac surgery; adjunct to the reversal of neuromuscular blockade; bronchodilation
Side effects:	Acute glaucoma; pyloric obstruction. In patients with prostatic hypertrophy, it can lead to complete urinary retention. Central anticholinergic syndrome is associated with delirium, stupor, and coma.

Glycopyrrolate (Robinul)

Glycopyrrolate is an anticholinergic antimuscarinic agent with a longer duration than atropine. It does not cross the blood-brain barrier.

Mechanism of action:	Antagonizes the muscarinic actions of acetylcholine at smooth muscle parasympathetic locations and salivary glands
Dose:	0.1–0.2 mg/dose IV every 2–3 min; can be administered intramuscularly
Onset of action:	Within 1 min
Duration of action:	2–3 h as a vagal blockade; 7 h as anti-sialagogue
Half-life:	0.5–1.5 h
Hemodynamic effects:	Tachycardia
Clinical usage:	Bradyarrhythmia; premedication as anti-sialagogue; adjunct to the reversal of neuromuscular blockade
Side effects:	Severe allergic reactions, mental confusion, urinary retention

Cholinergic

Neostigmine (Prostigmin)

Neostigmine, a reversal agent of non-depolarizing neuromuscular blocking agents, can be used in cardiac surgery to slow the heart rate in supraventricular tachycardia without affecting myocardial contractility, especially in patients coming off CPB. In this situation, caution should be exercised (pacing wires at the time of administration of neostigmine should be functional) as neostigmine might cause severe bradycardia or asystole. Also, when using neostigmine to slow the HR, redosing of neuromuscular blocking agents is necessary.

Diuretics

Numerous elements play a role in the development of kidney injury during CPB, including exposure to nephrotoxins, either exogenous from administered drugs or endogenous from iron or heme pigments released from traumatized red blood cells. Also, factors such as ischemia-reperfusion injury, embolization, hemodynamic perturbation, neurohormonal activation, non-pulsatile flow, and the activation of the systemic inflammatory response may impair renal function. Oliguric acute kidney injury is associated with more severe injury than is nonoliguric acute kidney injury. However, intraoperative diuretic administration in oliguric states does not reduce the risk of postoperative renal dysfunction, although diuretics can be used in the short term for volume control through their effects on urine output. Diuretics decrease preload and reduce vascular congestion. Given the potential for adverse effects, use of these medications should be reserved for compelling indications, such as hyperkalemia or significant volume overload.

Loop Diuretic

Furosemide (Lasix)

Mechanism of action:	Furosemide prevents sodium and chloride reabsorption in the loop of Henle and proximal and distal tubules by slowing or stopping the action of the sodium-potassium-chloride transport protein (symporter).
Dose:	Incremental doses from 10 mg IV (max 200 mg/dose). Consider higher initial doses in patients on chronic diuretic therapy or with poor renal perfusion.
Onset of action:	5 min; peak effect at 30 min
Duration of action:	1.5–2 h
Half-life:	0.5–2 h; prolonged up to 9 h in end-stage renal disease
Hemodynamic effects:	Hemodynamic effects should be minimal, although excessive diuresis resulting in hypovolemia may cause hypotension.
Clinical usage:	Increases urine output in severe volume overload, increases potassium excretion in hyperkalemia
Side effects:	Electrolyte disturbances: hypokalemia, hypomagnesemia; ototoxicity

Clinical Pearls

1. The maximum concentration for IV administration is 10 mg/mL.
2. Infusion rate should not exceed 4 mg/min to minimize the risk of ototoxicity.

Osmotic Diuretic

Mannitol (Osmitrol)

Mechanism of action:	Mannitol is an osmotic diuretic that reduces cell swelling and tissue edema during hemodilution by increasing oncotic pressure. It is an oxygen-free radical scavenger that reduces ischemia-reperfusion injury in vital organs.
Dose:	Mannitol 25% solution – 12.5 g added to the CPB circuit prime
Onset of action:	Diuresis: 1–3 h
Half-life:	0.5–2.5 h; 6–36 h in renal failure
Hemodynamic effects:	Hypotension if given quickly
Clinical usage:	Often added to the CPB priming solution. It reduces cell swelling after cardioplegic arrest and improves urine output.
Side effects:	Exacerbation of congestive heart failure by expanding intravascular volume

Clinical Pearls

1. Do not use solutions that have visible crystals.
2. Administer via a ≤5-micron filter set to avoid administration of crystallized particles.
3. Crenation and agglutination of red blood cells may occur if mannitol is administered with whole blood.

Anticoagulants, Prothrombotics, and Pharmacological Blood Conservation

Normal coagulation is a delicate equilibrium between the procoagulant pathway, which is responsible for thrombus formation at the damaged or exposed surface of the vascular system, and the processes that keep thrombus from forming elsewhere. There is a high incidence of hematological complications in the perioperative period of cardiac surgery because of the imbalance of the coagulation system. The goal is to prevent and treat coagulopathies. Many patients are at risk for developing coagulopathy, which leads to increased perioperative bleeding. The causes of coagulopathy can be either patient-related or procedure-related. Causes of patient-related coagulopathies are advanced age, preoperative anemia, liver disease, renal insufficiency, and antiplatelet or long-acting anticoagulant therapy at the time of surgery.

The use of hypothermic CPB necessitates full anticoagulation. Additionally, the hemodilution effects of coagulation factors and exposure of the blood elements to the artificial CPB circuit lead to platelet consumption and activation of the coagulation cascade, including fibrinolysis. The hematologic agents discussed in this section variably affect the coagulation cascade, either promoting or inhibiting coagulation.

Before the initiation of CPB, adequate anticoagulation must be accomplished and confirmed by a whole-blood test of anticoagulation, i.e., the activated clotting time. Activated clotting time goals vary, depending on the anticoagulant used and whether the patient is off-pump or on CPB. After the patient is weaned from CPB, anticoagulation must be reversed; heparin is fully reversed with the use of protamine sulfate. Newer drugs that reverse other anticoagulants are now approved by the Food and Drug Administration and commercially available. The risk of excessive perioperative bleeding for the cardiac surgical patient is high, and the anesthesia provider must have pharmacological strategies for blood conservation.

Anticoagulants:

- Heparin
- Bivalirudin
- Argatroban

Prothrombotic agents:

- Protamine
- Coagulation factors
  - Antithrombin III
  - Prothrombin complex concentrates
  - Factor VII
- Antifibrinolytic agents
  - Tranexamic acid
  - ε-Aminocaproic acid
- Reversal of direct oral anticoagulants
  - Idarucizumab
  - Andexanet alfa

Anticoagulants

Indirect Thrombin Inhibitors

Unfractionated Heparin

Mechanism of action:	Heparin binds and activates antithrombin III, causing inactivation of thrombin (factor II) and factor Xa. Heparin also prevents the conversion of fibrinogen to fibrin.
Dose:	300 units/kg prior to the initiation of CPB. Monitor and maintain target activating clotting time per institution standards for CPB and non-CPB operations.
Onset of action:	Immediate. Check activated clotting time 3 min after administration.
Duration of action:	4–6 h
Half-life:	1.5–2.5 h Eliminated via the liver and the reticuloendothelial system
Clinical usage:	Anticoagulation for CPB
Side effects:	Bleeding and heparin-induced thrombocytopenia (HIT), a life-threatening disorder caused by the formation of IgG antibodies to heparin and platelet factor 4

Direct Thrombin Inhibitors (DTIs)

Direct thrombin inhibitors are anticoagulants that inhibit both soluble thrombin and fibrin-associated thrombin. Consequently, they inhibit fibrin formation, activation of factors V, VIII, and XIII, protein C, and platelet aggregation. Since the discontinuation of lepirudin and desirudin, only bivalirudin and argatroban are available in the United States.

Bivalirudin (Angiomax)

Mechanism of action:	Direct thrombin inhibitor
Dose:	Bolus: 1 mg/kg initially Infusion (initiation of 2.5 mg/kg/h, targeting activated clotting time of more than 2.5 times of baseline). Fifty milligrams are added to the priming solution. Additional boluses of 0.1–0.5 mg/kg may be given to maintain an activated clotting time in the therapeutic range. Discontinue infusion 10–15 min prior to weaning from CPB.
Onset of action:	Immediate
Duration of action:	Coagulation times return to baseline about 1 h after the cessation of infusion.
Half-life:	Twenty-five minutes with normal renal clearance. Drug is eliminated by enzymatic deactivation in plasma.
Clinical usage:	Anticoagulation in patients who cannot be treated with heparin (e.g., HIT)
Side effects:	Bleeding

Argatroban (Acova)

Mechanism of action:	Direct thrombin inhibitor
Dose:	Bolus: 6.5 mg initially (0.1 mg/kg) followed by infusion – 5–10 μg/kg/min, with a target activated clotting time more than 500 s. Dosing of argatroban as an alternative to heparin during CPB is associated with failure to provide adequate anticoagulation and clotting of the oxygenator. Argatroban should be restricted to circumstances where other thrombin inhibitors are contraindicated.
Onset of action:	Immediate
Duration of action:	Coagulation times return to baseline about 90 min after infusion.
Half-life:	Dose-dependent, 1.5–2.5 h; eliminated by hepatic metabolism
Clinical usage:	Anticoagulation in the setting of HIT
Side effects:	Bleeding

Antithrombin III (ATryn, Thrombate III)

Antithrombin III is a naturally occurring anticoagulant. Two types of antithrombin are available in the United States: human antithrombin III pooled from human serum (Thrombate III) and recombinant human antithrombin III (ATryn).

Mechanism of action:	Serine protease inhibitor binds to thrombin, XIIa, IXa, and XI to deactivate them.
Dose:	In patients with known antithrombin III deficiency prior to surgery, dosing is individualized according to baseline levels, using formulas provided in the package labeling to achieve antithrombin III levels at 120%. In patients with suspected heparin resistance with inadequate activated clotting time after repeated doses of heparin, antithrombin doses of 500–1000 units have been suggested.
Onset of action:	5 min
Duration of action:	7 min
Half-life:	Plasma-derived antithrombin III, 2.5–3.8 days Recombinant human antithrombin III, 12–18 h
Hemodynamic effects:	Reduces blood pressure; vasodilation
Clinical usage:	Acquired heparin resistance; treatment of hereditary antithrombin III deficiency; prophylaxis of deep-vein thrombosis or pulmonary embolism during surgical or obstetrical procedures
Side effects:	Viral infection; goat milk protein hypersensitivity

Clinical Pearls

In hospitals that do not stock antithrombin III concentrates, fresh-frozen plasma may be used to provide antithrombin III in suspected heparin resistance.

Antiplatelet Agent

Cangrelor (KENGREAL)

Cangrelor, a platelet P2Y12 inhibitor, is a rapidly acting intravenous antiplatelet drug, used in patients with HIT.

Mechanism of action:	Reversibly blocks ADP-induced platelet activation and aggregation
Dose:	Bolus: 30 μg/kg IV; 4 μg/kg/min continuous infusion for 2 h
Onset of action:	2 min after administration by IV bolus
Duration of action:	Normal platelet function is restored in 1 h.
Half-life:	3–6 min; deactivated in the circulation by dephosphorylation
Clinical usage:	Percutaneous coronary intervention
Side effects:	Bleeding, bronchospasm, anaphylactoid reactions, angioedema

Clinical Pearls

HIT results from the production of IgG antibodies directed to heparin-platelet factor 4 complex. A new option used as an alternative to anticoagulation with bivalirudin and argatroban is administration of cangrelor, which inhibits platelets; heparin then can be used for anticoagulation during CPB, since there will be no sites for the HIT antibody to attach.

Procoagulants

Protamine Sulfate

Mechanism of action:	Protamine sulfate is a highly positively charged basic protein molecule that combines with and neutralizes polyacidic negatively charged heparin molecules to form inactive salt aggregates. Historically, protamine sulfate was prepared from salmon sperm, but it is now produced via recombinant biotechnology.
Dose:	1–1.3 mg protamine reverses 100 units of heparin. Alternatively, dosing is calculated by a heparin-protamine titration device (Hepcon). Protamine should be given slowly after a test dose. The dose of protamine should not exceed a ratio of 2.6 mg protamine:100 units heparin, as higher doses can prolong impaired platelet function and paradoxically raise the activated clotting time.
Onset of action:	0.5–1 min
Duration of action:	2 h
Half-life:	Metabolized in blood in less than 10 s
Hemodynamic effects:	Reduces BP (hypotension from histamine release if administered quickly); reduces heart rate (bradycardia)
Clinical usage:	Heparin reversal
Side effects:	Four types of protamine reactions: 1. Hypotension from rapid administration, mediated by nonimmunologic histamine release and direct myocardial depression. Hypotension usually is transient and only necessitates brief support of BP. 2. True anaphylaxis is mediated by antiprotamine IgE antibody in patients sensitized to protamine. Treatment is early recognition followed by discontinuation of protamine and administration of diphenhydramine 25–50 mg IV, famotidine 20 mg IV, epinephrine 10–100 μg IV, hydrocortisone 100 mg IV, and an inhaled bronchodilator. 3. Anaphylactoid-like reactions are mediated by activation of the complement system and direct degranulation of mast cells. Anaphylactoid-like reactions are less dramatic than anaphylaxis, but treatment is the same. 4. Acute pulmonary vasoconstriction with pressure overload results in acute right ventricular failure, pulmonary edema, and circulatory collapse. This is the most severe clinical complication of protamine reactions and is mediated by a massive discharge of thromboxane A_2, in the lungs. Treatment is early recognition followed by discontinuation of protamine, full heparinization, and administration of epinephrine, nitroglycerin, and milrinone. If all fails, hand massage of the heart, re-cannulation, and resumption of bypass are indicated. Mechanical support should be considered. For subsequent CPB, direct administration of protamine into the aorta (bypassing the pulmonary circulation) or letting the heparin metabolize without heparin reversal can be considered.

Clinical Pearls

1. Heparin rebound occurs after adequate neutralization of heparin; 2–3 h after administration, protamine is cleared from the circulation, and non-neutralized heparin dissociated from plasma protein reappears in the circulation, causing anticoagulation and bleeding.
2. Patients who are allergic to fish, diabetics who have been previously treated with insulin preparations containing protamine, and vasectomized men have increased risk of protamine allergic reactions because of the presence of antiprotamine antibodies in the serum.

Prothrombin Complex Concentrates (Kcentra)

Prothrombin complex concentrate (PCC) is indicated for significant bleeding caused by vitamin K antagonist therapy (e.g., warfarin). There are two formulations on the market: 4-factor and 3-factor. All PCCs contain factors II, IX, and X. 4-factor PCCs contain therapeutic levels of factor VII as well as proteins S and C. Activated PCCs contain factor VII in the activated form. Unactivated 4-factor PCC is sometimes used off-label to treat patients with severe coagulopathic hemorrhage after cardiac surgery that involved CPB. PCC restores vitamin K-dependent clotting factors and promotes coagulation.

Mechanism of action:	Administration of 4-factor PCCs rapidly increases plasma levels of vitamin K-dependent coagulation factors II, VII, IX, and X and the anticoagulant proteins C and S.
Dose:	Use in cardiac surgery to a maximum of 50 units/kg or 5000 units
Onset of action:	Rapid; significant INR reduction within 10 min
Duration of action:	6–8 h
Half-life:	Depending on the clotting factor, it ranges from 1.5 to 60 h.
Hemodynamic effects:	Hypotension if given quickly
Clinical usage:	Often added to the CPB priming solution. It reduces cell swelling after cardioplegic arrest and improves urine output.
Side effects:	Thromboembolic complications; 4-factor PCC contains heparin and may provoke HIT.

Clinical Pearls

1. Potency of the available PCC agent is measured by the content of factor IX units.
2. 4-factor PCC contains heparin and is contraindicated in patients with known heparin-induced thrombocytopenia or heparin hypersensitivity.
3. Should not be administered in disseminated intravascular coagulopathy, hypercoagulable disease states, or with other prothrombotic agents, such as antifibrinolytic agents, as administration may predispose to thromboembolic complications.

Factor VII (Novoseven)

Mechanism of action:	rFVIIa attaches to the surface of activated platelets and promotes factor X activation and rapid thrombin generation from prothrombin on the activated platelet surface.
Dose:	Dosing not well-established; 35–70 μg/kg/dose has been recommended in non-prospective studies. Lower doses (10–20 μg/kg) may be preferred to reduce thromboembolic events in patients with left ventricular assist devices.
Dilution:	Reconstitute with histidine diluent provided by the manufacturer according to prescribing information.
Onset of action:	Immediate
Duration of action:	Up to 6 h
Half-life:	2.8–3.1 h
Clinical usage:	Consider off-label use for management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after surgery involving CPB.
Side effects:	Thrombotic complications, including stroke

DESMOPRESSIN ACETATE (DDAVP)

Desmopressin is a synthetic analog of antidiuretic hormone produced in the posterior pituitary gland.

Mechanism of action:	Releases factors VIII and XII and von Willebrand factor from vascular endothelium and increases their levels by three- to fivefold
Dose:	Bolus: 0.3 μg/kg IV slowly over 20 min
Onset of action:	Within minutes; peak in 15–30 min
Duration of action:	4–12 h
Half-life:	Biphasic; initial is 7.8 min, and terminal is 75.5 min; renal elimination
Hemodynamic effects:	Increases MAP; tachycardia
Clinical usage:	Platelet dysfunction associated with uremia or recent antiplatelet agent administration in patients undergoing cardiac surgery to reduce bleeding and transfusion; von Willebrand disease; hemophilia A
Side effects:	Thrombotic events, water intoxication, hyponatremia, seizures, allergic reactions, and anaphylaxis

Antifibrinolytic Agents

Contact of blood with the extracorporeal surfaces during CPB initiates a total systemic inflammatory response characterized by activation of inflammation, coagulation, and fibrinolysis. Fibrinolysis occurs from the release of endothelial plasminogen activators and fibrin formation that leads to activation of plasmin. Plasmin then breaks down fibrin into fibrin degradation products. Use of prophylactic antifibrinolytic therapy is one approach that has been used to reduce nonsurgical-related

bleeding. Antifibrinolytics preserve clot integrity through inhibition of fibrinolysis by binding to plasminogen lysine binding sites. Antifibrinolytic agents include tranexamic acid and ε-aminocaproic acid. Both agents increase the risk of arterial and venous thrombotic events. Therefore, antifibrinolytics should not be administered in disseminated intravascular coagulopathy or with other prothrombotic agents, such as factor VIIa or PCC.

Aminocaproic Acid (Amicar)

Aminocaproic acid is a synthetic lysine analog.

Mechanism of action:	Stabilizes clot formation, as explained above
Dose:	Bolus: 100 mg/kg (typically 5–10 g) followed by 5 mg/kg added to CPB circuit priming solution Infusion: 10–15 mg/kg/h (typically 1–1.5 g/h) during cardiac surgery
Onset of action:	Immediate
Duration of action:	3–5 h
Half-life:	2 h; eliminated by kidneys
Clinical usage:	Treatment of bleeding associated with systemic hyperfibrinolysis during cardiac surgery
Side effects:	Increased risk of arterial and venous thrombotic events, hypotension, bradycardia, and renal failure. Contraindicated in disseminated intravascular coagulopathy or with other prothrombotic agents, such as factor VIIa or PCC

Tranexamic Acid (TXA, Cyklokapron)

Tranexamic acid is a synthetic lysine analog that is ten times more potent than ε-aminocaproic acid.

Mechanism of action:	Stabilizes clot formation, as explained above
Dose:	High dose: 30 mg/kg bolus, 2 mg/kg added to CPB circuit priming solution and continuous infusion of 16 mg/kg/h during surgery Low dose: 10 mg/kg bolus, 1–2 mg added to CPB circuit priming solution and continuous infusion of 1 mg/kg/h during cardiac surgery
Onset of action:	Immediate
Duration of action:	3–5 h
Half-life:	3 h; eliminated by renal clearance
Clinical usage:	Bleeding associated with systemic hyperfibrinolysis during cardiac surgery; spine surgery; trauma
Side effects:	Increased risk of arterial and venous thrombotic events, hypotension with rapid infusion, seizures, and renal failure. Contraindicated in disseminated intravascular coagulopathy or with other prothrombotic agents, such as factor VIIa or PCC

Aprotinin (Trasylol)

Aprotinin is a serine protease inhibitor. After a research trial (the BART study) reported increased mortality with aprotinin, the Food and Drug Administration issued a warning, and its use was discontinued in the United States.

Reversal of Direct Oral Anticoagulants

Patients taking oral anticoagulants may need urgent or emergent cardiac surgery. Reversal of anticoagulation is necessary to reduce bleeding and the need for transfusion. Two recently developed agents that are indicated for life-threatening bleeding due to direct oral anticoagulants are discussed here.

Idarucizumab (Praxbind)

Idarucizumab is a monoclonal antibody Fab fragment that is indicated for reversal of the oral direct thrombin inhibitor dabigatran (Pradaxa). Idarucizumab attaches to free and thrombin-bound dabigatran to neutralize its activity. The recommended dose of idarucizumab is 5 g. Side effects include thromboembolic risk and hypersensitivity reactions.

Andexanet alfa (Andexxa)

Andexanet alfa is a modified recombinant factor Xa protein approved for reversal of oral factor Xa inhibitors, including apixaban (Eliquis) and rivaroxaban (Xarelto). Andexanet alfa may be used off-label for reversal of edoxaban (Savaysa), betrixaban (Bevyxxa), and enoxaparin (Lovenox). Depending on the dose and time since the last administration of factor Xa inhibitor, a low-dose (400 mg IV bolus followed by a 4 mg/min continuous infusion for up to 2 h) or high-dose (800 mg IV bolus followed by 8 mg/min continuous infusion for up to 2 h) regimen may be indicated. Side effects include increased thromboembolic risk.

For common cardiac drips, please see Chap. 8.

Further Reading

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