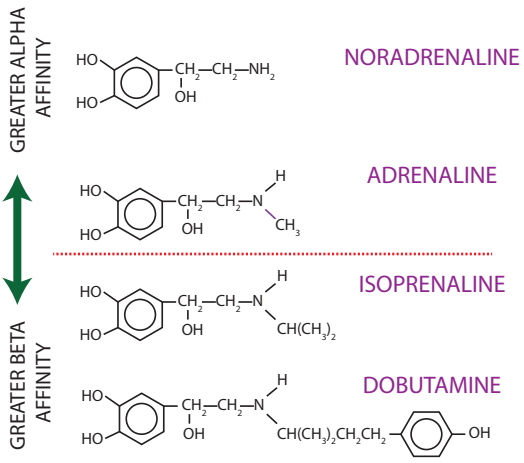
INOTROPES AND VASOPRESSORS

Inotrope An alters the force of contraction of cardiac muscle without changing preload or afterload. Positive inotropes increase cardiac contractility whilst negative inotrops decrease cardiac contractility. **Vasopressors** are drugs that have a predominantly vasoconstrictive action on the peripheral vasculature, both arterial and venous. These drugs are used primarily to increase mean arterial pressure. Many of the commonly used agents such as the catecholamines have both inotropic and variable effects on the peripheral vasculature that include venoconstriction, arteriolar vasodilatation and constriction. Vasoregulatory agents may modulate the responsiveness of the peripheral vasculature to vasoactive drugs in pathological states such as sepsis. These agents include vasopressin and corticosteroids. Given the overlap of pharmacodynamic effects of these drugs, the term 'vasoactive therapy' is a more appropriate description. The ideal inotrope; Is pharmaceutically suitable; Non-toxic, cost effective, stable preparation, compatable with other drugs, peripherally deliverable, Has beneficial pharmacodynamic properties: Increases contractility, Increases mean arterial pressure, Maintenance of diastolic blood pressure, Increases cardiac output, Improves regional perfusion, without pharmocodynamic costs No increase in myocardial oxygen consumption, Avoidance of tachycardia, Non-arrhythmogenic, suitable in pregnancy and paediatric populations has an excellent pharmocokinetic profile Does not develop tolerance, Titratable, Rapid onset, Rapid termination of action, metabolised independent of liver and kidney function, doesn't require concentration monitoring.

Classification of Inotropes and Vasopressors The common ultimate cellular mechanism of action of these agents involves an influence on the release, utilisation or sequestration of intracellular calcium. These agents are divided into two main groups based on whether or not their actions depend upon increases in intracellular cyclic adenosine 3,5-monophosphate (cAMP).

cAMP Dependent Inotropes	cAMP Independent Inotropes	Selective Vasopressors
Catecholamines (Beta Adrenegric Agonists) Natural Adrenaline Noradrenaline Dopamine Synthetic Dobutamine Isoprenaline Phosphodiesterase inhibitors Milrinone Levosimendan Calcium Sensitisers Levosemindan Glucagon	Catecholamines (Alpha$_1$ Adrengeric Agonists at higher doses) Adrenaline Noradrenaline Dopamine Other Digoxin Calcium Thyroid hormone	Vasopressin Metaraminol [The catecholamines have variable vasopressor activity and are not usually considered here]

Catecholamines consist of an aromatic ring attached to a terminal amine by a carbon chain. The configuration of each drug is important for determining affinity to respective receptors. Dopamine is hydroxylated to form noradrenaline, which is the predominant peripheral sympathetic chemotransmitter in humans, acting at all adrenergic receptors. The release of noradrenaline from sympathetic terminals is controlled by reuptake mechanisms mediated via alpha$_2$-receptors and augmented by adrenaline released from the adrenal gland at times of stress. Noradrenaline is converted to form adrenaline that is subsequently metabolised in liver and lung. All catecholamines have very short biological half-lives (1–2 minutes) and a steady state plasma concentration is achieved within 5–10 minutes after the start of a constant infusion. This allows rapid titration of drug to a clinical end-point such as mean arterial pressure. Adrenaline and noradrenaline infusions produce blood concentrations similar to those produced endogenously in shock states, whereas dopamine infusions produce much higher concentrations than those naturally encountered. Dopamine may exert much of its effect by being converted to noradrenaline, thus bypassing the rate limiting (tyrosine hydroxylase) step in catecholamine synthesis. The synthetic catecholamines are derivatives of dopamine. These agents are characterised by increased length of the carbon chain, which confers affinity for beta-receptors. Dobutamine is a synthetic derivative of isoprenaline. These agents have relatively little affinity for alpha receptors due to the configuration of the terminal amine, which differs from the endogenous catecholamines. As a general rule, the longer the terminal amine, the more beta adrenergic effects predominate, the shorter the chain, alpha effects predominate (relatively). From a drug specific perpective at low doses with the natural catecholamines it is the beta effects that are more significant, alpha effects kicking in at higher doses.



Phosphodiesterase inhibitors and **Calcium Sensitisers** are compounds that cause non-receptor mediated competitive inhibition of phosphodiesterase isoenzymes (PDE), resulting in increased levels of cAMP. Importantly, cAMP also affects diastolic heart function through the regulation of phospholamban, the regulatory subunit of the calcium pump of the sarcoplasmic reticulum. This enhances the rate of calcium re-sequestration and thereby diastolic relaxation. For cardiovascular tissue, inhibition of isoenzyme PDE III is responsible for the therapeutic effects. Cardiac effects are characterised by positive inotropy and improved diastolic relaxation. The latter is termed lusitropy and may be beneficial in patients with reduced ventricular compliance or predominant diastolic failure. These agents also cause potent vasodilatation with reductions in preload, venous return and afterload as well as a reduction in pulmonary vascular resistance. The term 'inodilation' has been used to describe this dual haemodynamic effect. Tolerance is not a feature. Titration pharmacokinetics of phosphodiesterase inhibitors are markedly different from catecholamines. Drug half-lives may be prolonged and excretion is predominantly renal. Hypotension may result from vasodilatation, and combined use with catecholamines (e.g. noradrenaline or adrenaline) may be necessary and complementary to maintain mean arterial pressure. Milrinone is currently used in clinical practice, exhibiting more inotropic effects than vasodilatation. Levosimendan is a dose-dependent selective phosphodiesterase inhibitor with a unique action on myocardial calcium metabolism. By increasing myofilament calcium sensitivity throughout the cardiac cycle by binding to cardiac troponin C, associated conformational changes induce improved inotropic and lusitropic function. Vasodilatation is also induced through ATP-sensitive potassium channels. Calcium-sensitive actions predominate at low doses, whilst PDE-inhibition effects predominate at higher doses. The half-life of levosimendan is shorter than older PDE III inhibitors (approximately 1 hour) and it may be given by infusion. Glucagon is a naturally occurring polypeptide that directly stimulates adenyl cyclase via specific receptors to increase cAMP concentration in myocardial cells resulting in positive inotropy without producing myocardial excitability. Large doses are required to achieve this effect which is associated with a high incidence of metabolic side-effects.

cAMP independent inotropes The direct effect of digoxin is via Inhibition of Na^+/K^+ ATPase is considered to be the primary biochemical mechanism of action. Then higher intracellular Na reduces action of the Na-Ca pump leading to decreased calcium extrusion and therefore increased intracellular Ca therefore increased inotropy. Thyroid hormone is required for synthesis of contractile proteins and normal myocardial contraction. It is also a regulator of the synthesis of adrenergic receptors. Preliminary studies suggest that treatment with thyroid hormone in these patients may reduce the need for vasoactive therapy to achieve satisfactory haemodynamics. When injected intravenously, calcium produces an intense positive inotropic effect lasting 10 to 20 minutes and manifesting as increases in stroke volume and decreases in left-ventricular end-diastolic pressure. Heart rate and systemic vascular resistance decrease. Calcium chloride, at 5 to 10 mg/kg IV to adults, may be administered to improve myocardial contractility and stroke volume at the conclusion of cardiopulmonary bypass.

Selective Vasopressors Metaraminol is a direct-acting a2-agonists that are selective vasoconstrictors, both venous and arterial, with minimal b-activity. They have similar pharmacokinetics to catecholamines and may be given by infusion. In patients with normal sympathetic tone, these drugs may cause reflex bradycardia, particularly following bolus administration. Vasopressin Specific vasopressinergic receptors (V1, V2) have been identified in association with sympathetic terminals. Vasopressin is a naturally occurring peptide secreted by the posterior pituitary gland. Reduced serum levels of vasopressin have been demonstrated in septic shock and following cardiopulmonary bypass, suggesting an inflammatory mediated mechanism. Levels are maintained during cardiogenic shock. A proportion of patients with severe septic shock requiring high levels of catecholamines to support the circulation may respond to low doses of infused vasopressin (0.04 U/hour) significantly reducing doses of infused catecholamine. This phenomenon appears to be independent of any directly attributable vasopressor effect; rather it is a supplemental 'catecholamine sparing' strategy, particularly in patients with mild to moderate shock states. The impact in severe shock or on mortality has not been substantiated in a large clinical trial (VASST Study)

Christopher Andersen 2012