Which inotropes and when in NICU?

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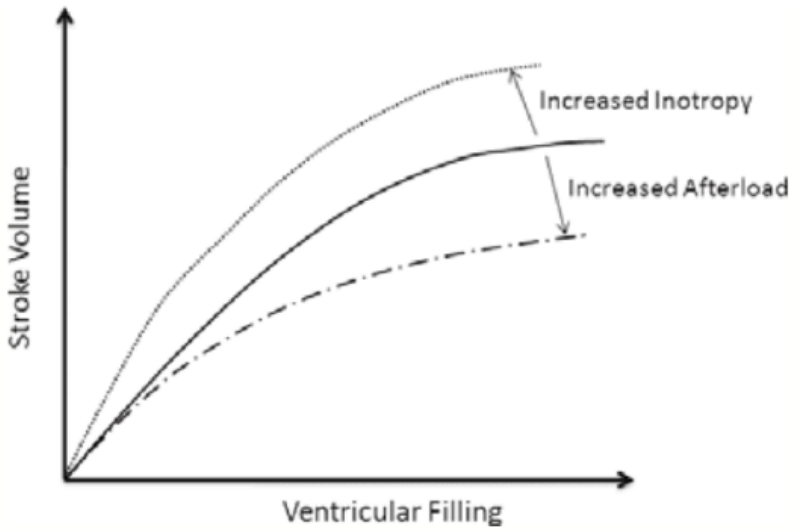
Introduction

- Significant uncertainty of optimal circulatory management of preterm infants
- High variability in inotrope use amongst clinicians
- No trial of inotrope use in neonates has ever shown benefit in clinically significant outcomes

Circulatory changes after birth

- Dramatic changes in preload, myocardial contractility , SVR and PVR immediately after birth
- This results in a period of low systemic blood flow
- This low SBF has been associated with IVH, WM injury and adverse neurodevelopmental outcomes

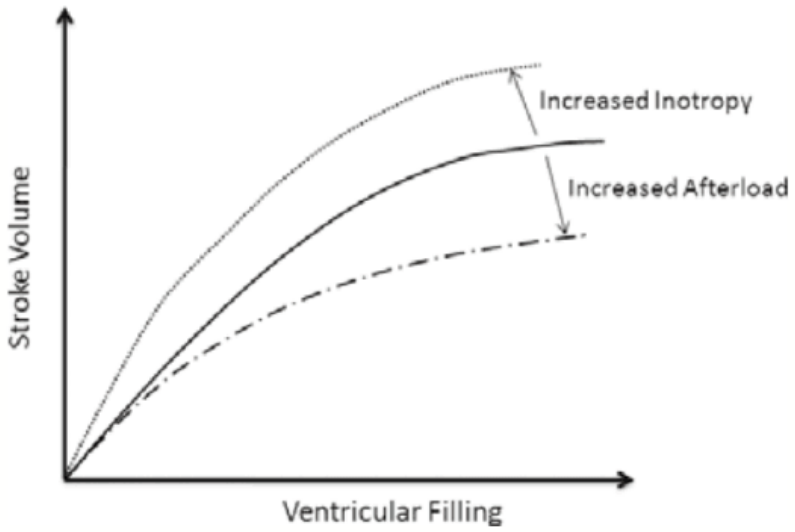
Frank-starling Law



Preload

- Until the top of the curve is reached, increased ventricular filling produces increased myocardial distention and increased stroke volume.
- Inotropes influence preload inducing constriction in peripheral venous capacitance vessels (alpha2).

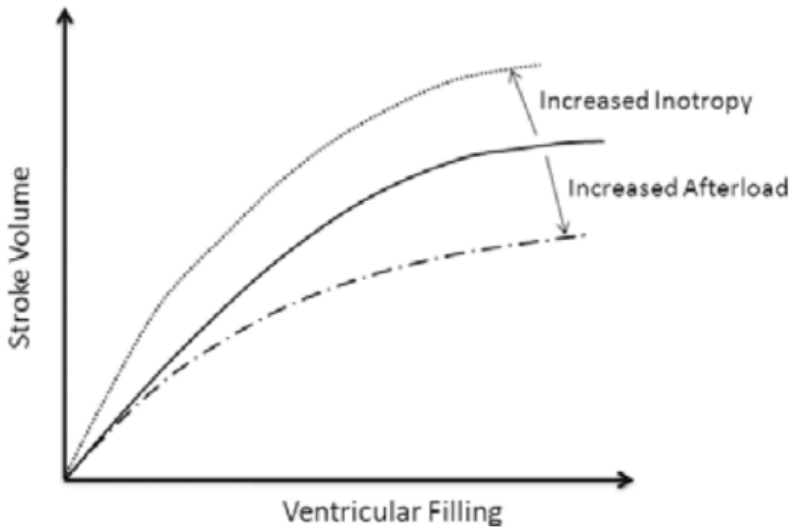
Frank-starling Law



Afterload

- Dependent of peripheral arteriolar tone mediated by alpha 1 and alpha2 receptors.
- Increased afterload reduces the SV for any given end-diastolic volume

Frank-starling Law



Myocardial contractility

- Inotropic drugs influence myocardial contractility by acting on alpha 1 and beta 1 receptors.

Factors affecting hemodynamic response to shock and its management in neonates

- Presence of patent ductus arteriosus
- Perinatal asphyxia
- Persistent pulmonary hypertension
- Low preload- High HR, Low % cardiac cycle spent in diastole
- Poor myocardial contractility- fewer myofibrils, decreased adrenergic receptors
- High SVR- loss of low resistance placenta circulation, increased peripheral beta receptors
- Transient adrenal insufficiency of prematurity
- Poor correlation between blood pressure and systemic blood flow in preterm infants

Catecholamine receptor function

Receptor	Location	Action	Effect
α1	Myocardium	Inotropy	↑Contractility
α1	Peripheral vasculature	Vasoconstriction	↑Afterload, ↑Preload
β1	Myocardium	Inotropy	↑Contractility
β2	Peripheral vasculature	Vasodilatation	↓Afterload ↓ Preload

Inotropes

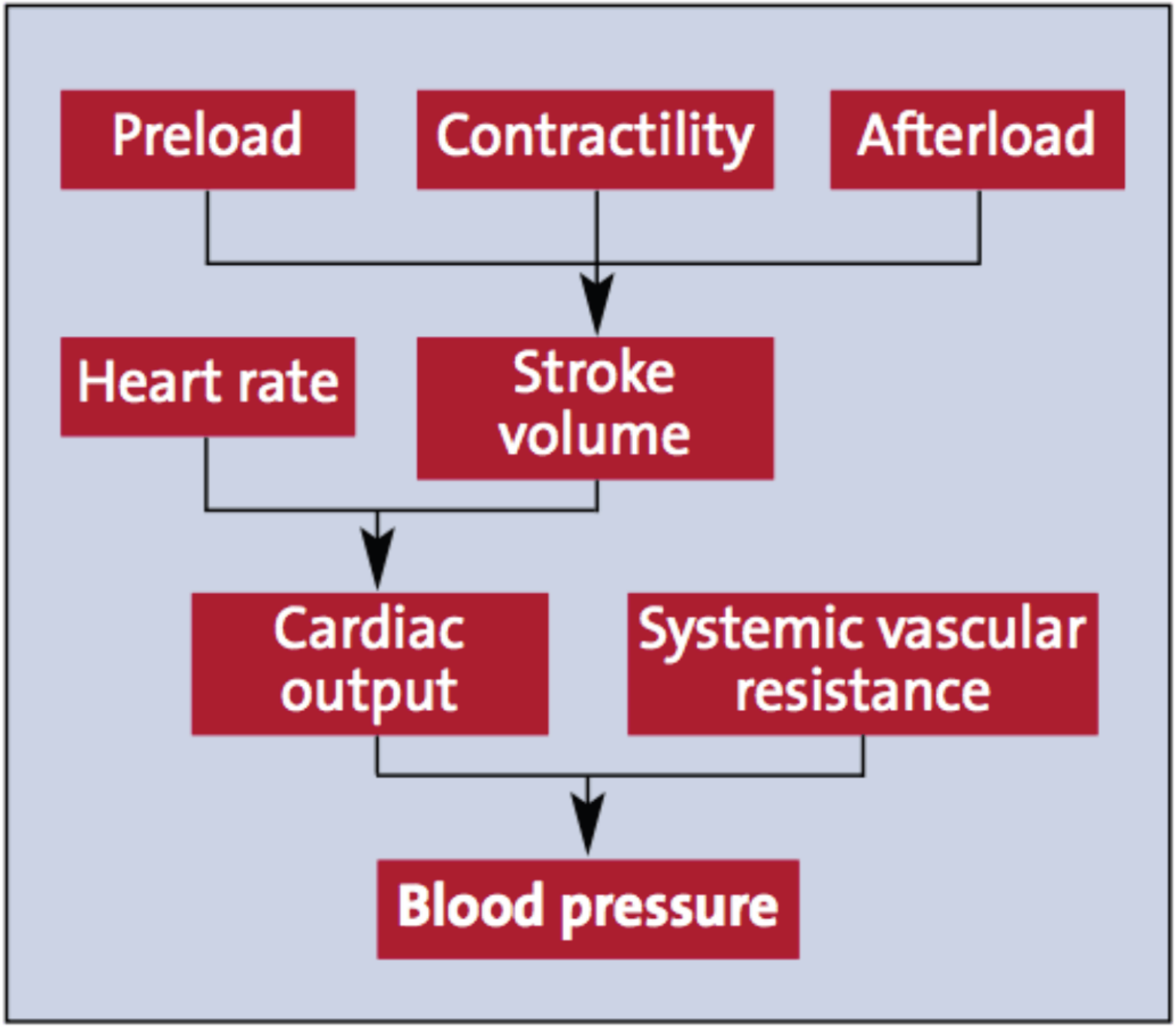
- Dopamine- Primarily a vasopressor through action on α receptors. Increases BP. Dose-2.5-20 µg/kg/min.
- Dobutamine- Inotropic and Vasodilatory through β receptors. Increases systemic blood flow. Decreases IVH. Dose 2.5-20 µg/kg/min.
- Adrenaline- Low dose 0.01-0.1 µg/kg/min- inotropic, high dose >0.1 µg/kg/min –vasopressor. Adverse effects- tachycardia, elevated lactate
- Noradrenaline- Potent vasopressor. Dose 0.05-0.5 µg/kg/min.
- Milrinone- Inodilator and decreases PVR.
- Vasopressin- Potent vasopressor. Also decreases PVR.

Common indications of Inotropes in NICU

- Neonatal Shock
- Heart Failure
- PPHN
- Low BP in very preterm

What is shock during transitional circulation?

- Arterial BP- minimal predictive value for low systemic perfusion or low cerebral blood flow
- Color
- Activity
- CFT
- UOP
- Perfusion Index
- Lactate


Preload
Contractility
Afterload
Heart rate
Stroke volume
Cardiac output
Systemic vascular resistance
Blood pressure

Hypovolemic shock

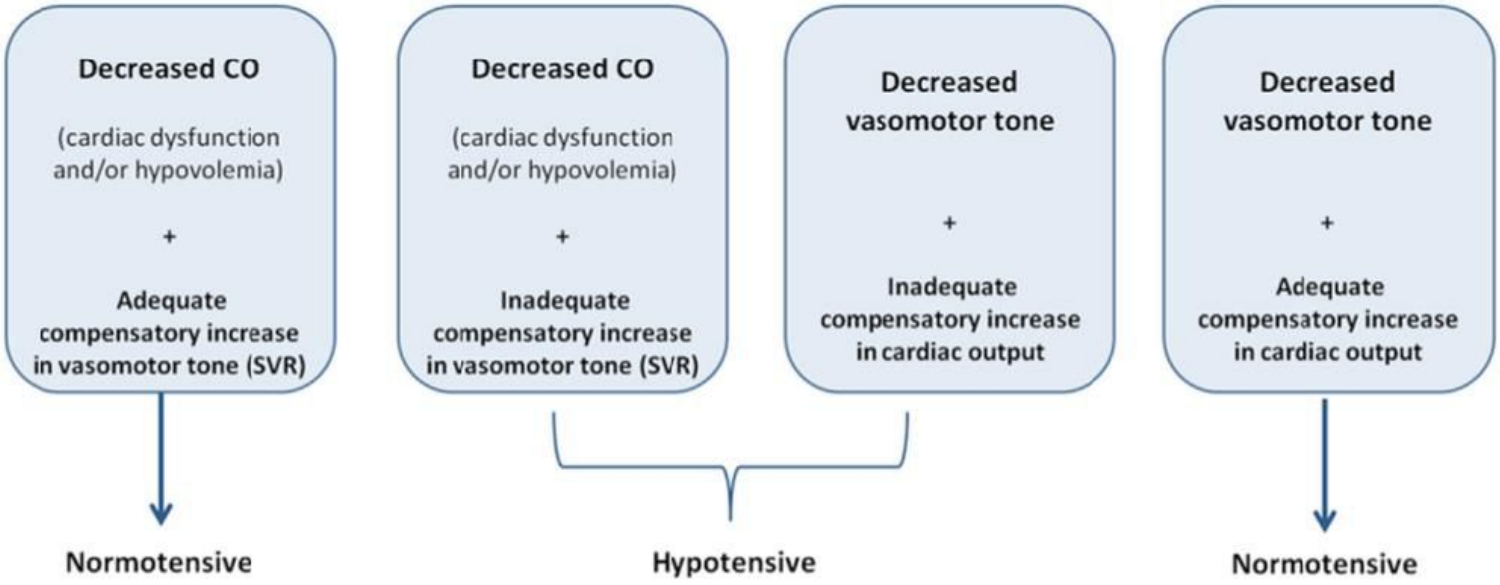
- Massive pulmonary haemorrhage
- Acute surgical emergencies
- Intracranial/subgaleal haemorrhage
- DIC
- Dehydration: insensiblewater losses/polyuria
- Third space losses - NEC
- Decreased venous return
- – Air leak syndromes
- – High positive end expiratory pressure (PEEP)/

Cardiogenic shock

- Birth asphyxia
- Congenital heart disease
  - Duct dependant lesions with closure of the duct
  - Total anomalous pulmonary venous connection
- Postoperative cardiac surgery
- Cardiomyopathy
- Myocarditis
- Arrhythmias

Neonatal shock: other causes

- SEPTIC SHOCK
- ENDOCRINE
  - Adrenal haemorrhage
  - Congenital adrenal hyperplasia
- DRUGS: Sedation


Decreased CO
(cardiac dysfunction and/or hypovolemia)
+
Adequate compensatory increase in vasomotor tone (SVR)
Normotensive
Decreased CO
(cardiac dysfunction and/or hypovolemia)
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Inadequate compensatory increase in vasomotor tone (SVR)
Decreased vasomotor tone
+
Inadequate compensatory increase in cardiac output
Hypotensive
Decreased vasomotor tone
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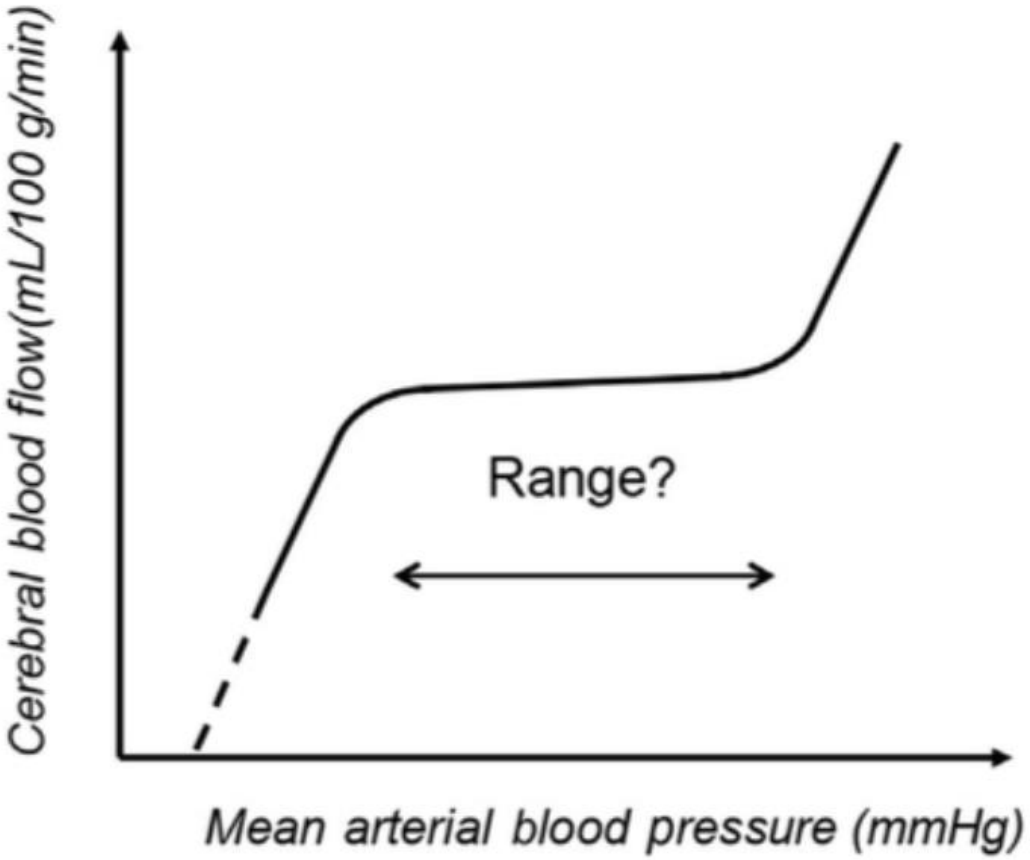
Cerebral autoregulation in neonates



Hypotension

- Mean arterial BP should be maintained at or greater than the gestational age in weeks.
- In the extreme preterm, it is associated with increased mortality, IVH, PVL and neurodevelopmental morbidity.
- In preterm infants, dopamine is the most studied drug, and is more effective in increasing BP than dobutamine.
- All evidence points towards the fact that dopamine can be considered as a first line inotrope in preterm neonatal hypotension (Bhayat SI et al . Inotropes in neonatal hypotension: Systematic review. *World J Clin Pediatr* 2016 May 8; 5(2): 212-222)

Hydrocortisone as an inotrope

- Combined early treatment with hydrocortisone and dopamine for refractory hypotension in preterm newborns.
- Initial dose of 2 mg/kg, 6 h after 1 mg/kg q6h for 3 doses, followed by 0.5 mg/kg q6h for 4 doses.
- Not associated with more adverse effects, but rather showed a trend toward association with better outcome (*Adding Hydrocortisone as 1st Line of Inotropic Treatment for Hypotension in VLBW Infants. Indian J Pediatr 2013*).

Functional Echocardiography

- Preload assessment- IVC volume, Ventricular filling
- Myocardial contractility- Eye-balling, Fractional Shortening
- Output- LVO, RVO, SVC flow (in v/o shunts)

Administration of Inotropes

- Ensure adequacy of ventricular filling
- Administer inotropes through accurate infusion devices
- Use a dedicated lumen of a central line or PICC line. Single strength dobutamine can be infused peripherally.
- Never flush the infusion line.
- Infusions should be written as per the unit protocols and should be changed regularly (at least every 24 hours). Changeover of the new syringe should be according to the unit policy.
- Check compatibilities with other drugs being given simultaneously.
- Use inotropes for short term circulatory support, but weaning should be a slow process.
- Extravasations may produce extensive tissue necrosis. Follow unit policy for management.
- When infusion rates of stronger agents fall below 0.5mL/hr, tiny boluses can cause massive pressure changes. Consider half strength solutions.
- If the inotrope appears to be ineffective, check delivery apparatus. Make up new infusion.

How safe are inotropes?

- Batton et al. Early blood pressure, anti-hypotensive therapy and outcomes at 18 to 22 month corrected age in extremely preterm infants. Arch Dis Child Fetal Neonatal Ed. 2016 May ; 101(3): F201–F206

- There was an increased risk of death/NDD with anti-hypotensive therapy versus no treatment (odds ratio: 1.836, 95% confidence interval: 1.092 – 3.086).