The Pharmacology of Hypotension: Vasopressor Choices for HIE patients

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Objectives

• Review the pathophysiology of hypotension in neonates
• Discuss the role of vasopressors and inotropes in neonates with hypotension
• Compare vasopressor choices in neonates with HIE
Pathophysiology-Based Approach

Blood Pressure $\propto$ Cardiac output x Systemic Vascular Resistance

Heart Rate x Stroke Volume

- Arrhythmia

Preload

- Hypovolemia
  - Diastolic dysfunction
  - Volume overload

- Poor contractility
  - Hyperdynamic myocardium

Contractility

Afterload

- High afterload
  - Low afterload

- Vasodilation
  - Vasoconstriction

Neuroendocrine and paracrine regulatory mechanisms
Vascular Tone

• Vasodilation is one of the most frequent cases of shock in neonates
  • Sepsis, necrotizing enterocolitis
• Decrease in vascular tone most often due to dysregulated production of local nitric oxide and direct vascular cytokine effect
  • Decrease in perfusion pressure
  • Hypotension develops despite normal or elevated CO
• Preterm infants who do not survive shock only significantly dropped CO prior to death
• Gram-negative sepsis and late stages of septic shock also cause myocardial dysfunction
Impaired Contractility

• Systolic dysfunction also a common cause of circulatory failure in neonates

Etiologies:
• Asphyxia most common
  • 1/3 have clinical or electrographic evidence of cardiac involvement
• Premature infants after PDA ligation
  • 10-30% develop hypotension following surgery
  • Poor myocardial performance/contractility
  • Prophylactic milrinone shown to reduce post-ligation hypotension with CO<200 mL/kg/min
Decreased Preload

- Inappropriately high mean airway pressure, pneumothorax, pericardial effusion, pneumopericardium significantly reduce venous return
  - Reduced preload \(\rightarrow\) reduced CO
- Insensible water losses through skin
- Capillary leak: sepsis, NEC, post-abdominal surgery
- Myocardial diastolic dysfunction from hypertrophic cardiomyopathy
  - 1/3 of poorly controlled IDMs
Increased Afterload

• High afterload worsens poor myocardial contractility in infants with dilated cardiomyopathy
  • Not as common
Heart Rate

• Neonates have higher dependence on HR to maintain CO compared to older children and adults
• Bradycardia tends to be transient, secondary to apnea and/or hypoxia
• Tachyarrhythmia more common
  • SVT and atrial flutter
  • Circulatory failure
Pharmacology of Hypotension

- **Vasopressor**
  - Increases vascular tone
  - Peripheral action: vasoconstriction via alpha-1 adrenergic and vasopressin receptors

- **Inotrope: dobutamine**
  - Increases myocardial contractility

- **Vasopressor-inotrope: dopamine, epinephrine**

- **Phosphodiesterase inhibitors: milrinone**
Vasoactive Medications

- Isoproterenol
- Dopexamine
- Dobutamine
- Dopamine
- Epinephrine
- Norepinephrine
- Phenylephrine
Normal Saline Bolus

• Useful when hypovolemia is present
  • Increased intravascular volume, increased CO
• 10 mL/kg NS = 1.54 mEq/kg of normal saline
• Limited efficacy when pathophysiology is not related to hypovolemia
Isoproterenol

- Indications:
  - Improve cardiac output in patients with cardiovascular shock
  - Pulmonary vasodilator (older infants)
- Dosing: 0.05 to 0.5 mcg/kg/min (max = 2 mcg/kg/min)
- Monitoring: BP, blood glucose
- Toxicity: cardiac arrhythmia (tachycardia causing CHF), hypoglycemia, hypoxemia
Dobutamine

• Indications:
  • Hypotension/hypoperfusion related to myocardial dysfunction
  • Severe sepsis/shock in full term neonates unresponsive to fluid resuscitation
• Dosing: 2 to 20 mcg/kg/min (max 25 mcg/kg/min)
• Monitoring: heart rate, BP
• Toxicity: hypotension, tachycardia, vasodilation
Dopamine

- Most commonly used cardiovascular medication in the NICU
- Dose-dependent stimulation of alpha, beta, and dopaminergic receptors
  - Low (≤0.5 mcg/kg/min)
    - Vascular dopaminergic receptors selectively expressed
    - Renal, mesenteric, coronary circulations
  - Moderate (2-4 mcg/kg/min)
    - Alpha receptor activation-vasoconstriction, inotropy
  - High (≥ 4 – 8 mcg/kg/min)
    - Beta receptor activation-inotropy, chronotropy, peripheral vasodilation
Dopamine-Clinical Considerations

• At least 50% of positive inotropic effects caused by inducing release of norepinephrine (NE) stores in the peripheral sympathetic nerve endings in the myocardium
  • Myocardial NE depletes within 8-12 hours
• Dopamine in the premature neonates
  • Decreased NE stores
  • Immature expression of alpha, beta receptors → alpha receptors likely to be activated at low-to-medium doses
  • Cardiovascular adrenergic receptor expression regulated by corticosteroids, higher risk of vasopressor-dependence with adrenal insufficiency
Dopamine-Systemic Blood Pressure

- Dopamine consistently increases blood pressure in neonates
  - Normal saline
  - Hydrocortisone
  - Dobutamine
Dopamine-Cardiac Output

- Increased cardiac output caused by drug-induced increases in myocardial contractility, increased ejection fraction
- Premature infants
  - May cause excessive increases in SVR
  - Decreased cardiac output
Dopamine-Pulmonary Vasculature

• In premature infants on dopamine, 50% will experience an increase in pulmonary vascular resistance (PVR)

• PDA with left-to-right shunt
  • Increased PVR may be helpful to improve systemic circulation

• PDA with right-to-left shunt
  • Increased PVR may be harmful because additional blood would flow away from the lungs
Dopamine Dosing Information

- Usual dosing range: 5-20 mcg/kg/min
  - Titration: 2.5-5 mcg/kg/min every 5-10 minutes

- Monitoring:
  - MAPs, oxygen saturations, urine output

- Concerns:
  - worsening pulmonary status when used in patients with pulmonary hypertension (i.e. PDA with right-to-left flow)

- Administration:
  - NEVER through arterial line, central venous access preferred
Epinephrine

• Dose-dependent stimulation of alpha and beta adrenergic receptors
• Low dose (0.01 to 0.1 mcg/kg/min)
  • Stimulates cardiac and vascular beta 1 and 2 receptors
  • Increased inotropy, chronotrophy, peripheral vasodilation
• Higher dose (>0.1 mcg/kg/min)
  • Stimulates vascular and cardiac alpha 1 receptors
  • Vasoconstriction, increased inotropy
• Net effect: increased blood pressure, systemic blood flow via drug-induced increases in SVR and cardiac output
Epinephrine

• Compared to dopamine
  • Similar efficacy in improving blood pressure and increasing cerebral blood flow
  • Epi group more likely to develop increased serum lactate levels, hyperglycemia requiring insulin

• Clinical considerations
  • Beta-2 stimulation in liver and muscle causes decreased insulin release and increased glycogenolysis (elevates lactate)
  • May be unable to use serum lactate as clinically useful marker of overall perfusion
  • Insulin infusion may be necessary
  • Most useful with low vascular resistance with or without myocardial contractility impairment
Epinephrine Dosing Information

• “Low-dose”: 0.01-0.1 mcg/kg/min
• “High dose”: >0.1 mcg/kg/min
  • No documented true maximum dose
  • Dose-limiting side effects: tachycardia, peripheral ischemia, lactic acidosis, hyperglycemia
• Titration: 0.01-0.02 mcg/kg/min every 3 to 5 minutes
• Monitoring:
  • MAP, heart rate, glucose, lactates
• Administration:
  • NEVER through arterial access, central venous access preferred
Vasopressin

- Primary physiologic role is extracellular osmolarity
- Vascular effects mediated by stimulation of vasopressin 1A and 2 receptors in the cardiovascular system
  - V1A: vasoconstriction
  - V2: vasodilation
- Most useful with vasodilatory shock, deficiency of endogenous vasopressin production with septic shock, infants after cardiac surgery
Vasopressin Clinical Considerations

- Increases
  - MAP, SVR
- Decreases
  - PVR, oxygenation index, iNO requirement, vasopressor requirement
- At high doses, increased SVR may impair cardiac contractility
Vasopressin Dosing Information

- **“Low dose”**: 0.17 - 0.7 milli-units/kg/min
  - Decreased in catecholamine requirement
- **“High dose”**: 1-20 milli-units/kg/min
  - Effective for reducing catecholamine requirement, but more side effects
- **Titration**: 0.05-0.1 milli-units/kg/min every 15-30 minutes
- **Monitoring**:
  - Blood pressure, serum sodium (hyponatremia), weight gain, urine output (decreases), liver enzymes
Norepinephrine

• Endogenous catecholamine that activates alpha 1,2 and beta 1 receptors
  • Increases systemic vascular resistance >> pulmonary vascular resistance
  • Increases cardiac output by increasing contractility via beta 1 receptors
• First-line treatment for septic shock in adult patients
• Neonatal data
  • Sepsis: increased MAP, decreased oxygen requirement, improved tissue perfusion
  • PPHN: produced pulmonary vasodilation, decreased oxygen requirement, increased cardiac output, improved blood flow to lungs without evidence of peripheral ischemia
Norepinephrine Dosing Information

- Dosing range: 0.05-0.7 mcg/kg/min
  - Max: 3.3 mcg/kg/min
  - Titration: 0.05-0.1 mcg/kg/min every 5-10 minutes

- Monitoring:
  - MAP, oxygen saturations, tissue perfusion

- Administration:
  - NEVER through arterial line, central venous access preferred
Milrinone

- Selective phosphodiesterase-III inhibitor
  - Exerts cardiovascular effects through preventing breakdown of cAMP
  - Enhances myocardial contractility, promotes myocardial relaxation, decreases vascular tone in systemic and pulmonary vascular beds

- Disease states
  - Post-operative cardiac repair, PPHN as an adjunct to iNO
  - Post PDA-ligation to prevent hemodynamic instability in 24 hours after procedure
Milrinone-PPHN

- In cases unresponsive to iNO, oxygenation may be improved with addition of milrinone
- Exogenous NO upregulates PDE-III in smooth muscle cells of pulmonary vasculature
  - Decrease or loss of cAMP-dependent vasodilation
- Addition of milrinone to iNO restores pulmonary vasodilation mechanisms dependent of cAMP
  - Increased pulmonary vasodilation, improved oxygenation
• Dosing range: 0.25-0.99 mcg/kg/min
  • Dose reduce for renal impairment
• Titration: 0.2-0.4 mcg/kg/min every 2-4 hours
• Monitoring:
  • MAP: can initially decrease, usually returns to baseline within 1-2 hours
  • Heart rate: can initially decrease, may increase if bolus used (not recommended)
  • UOP: improved
  • Oxygen saturations: improved
Hydrocortisone

• Decreases breakdown of catecholamines, increases calcium in myocardial cells, upregulate adrenergic receptors

• Delayed onset of action for hypotension
  • Inferior as first-line treatment to dopamine

• Relative adrenal insufficiency in premature infants may play a role in need for supplementation

• Timing
  • Prophylactic: prevents adrenal insufficiency, subsequent complications of uninhibited inflammation
  • Refractory hypotension: effectively increases BP and reduces catecholamine requirement
Biophysical Effects of Asphyxia

- Direct cardiovascular effects
- Cardiovascular and CNS injury interaction
- Cerebral blood flow
- Impact of therapeutic hypothermia
Hypothermia Cardiovascular Effects

• TH alone is not associated with increased risk of hypotension
  • Normal or slightly increased BP related to hypothermia-induced vasoconstriction

• Reduction in heart rate after TH leads to 60-70% decrease in LV output compared to normothermic controls
  • Often sufficient because of decreased metabolic activity

• Sinus bradycardia
  • Slowed diastolic repolarization in SA node
  • Diminished influence of sympathetic autonomous nervous system on heart rate

• Normal heart rate despite low temperature may reflect subclinical systemic hypoperfusion and contribute to ongoing brain injury
Hypothermia Pulmonary Vascular Effects

- Severity of brain injury may be associated with dysregulation of vascular tone in pulmonary vascular bed
- Concurrent HIE and pulmonary hypertension more likely to have abnormal brain MRI despite TH
  - Greater disease severity-severe/prolonged hypoxia increases risk of impaired transition, persistent pulmonary hypertension
Hypothermia Pulmonary Vascular Effects

• Reduced pulmonary blood flow
  • Lower preductal cardiac output + systemic hypotension = worsened ischemic insult

• Use of rapidly-acting pulmonary vasodilators (iNO)
  • Increased pulmonary venous return + augmentation of preductal cardiac output = reperfusion injury
Effects of Rewarming

- Augmentation of cardiac output and systolic blood pressure + concurrent decrease in systemic vascular resistance and DBP
  - Overall reduction in mean BP by ~8 mmHg
- Changes in drug volume of distribution, metabolism, and clearance
  - High Vd medications mobilized from sequestered tissue and can have exaggerated effects during rewarming
- Adjustment of cardiovascular medications
  - CNS hemorrhage during rewarming associated with greater degree of hemodynamic instability
  - Avoid iatrogenic hypertension and excessive unregulated cerebral blood flow
### Clinical Considerations/Confounders

<table>
<thead>
<tr>
<th>Variables</th>
<th>Change Seen</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Sinus bradycardia</td>
<td>Decreased SA node repolarization</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Increased DBP</td>
<td>Systemic vasoconstriction</td>
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<tr>
<td></td>
<td>Decreased SBP</td>
<td>Decreased cardiac output</td>
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<tr>
<td>Color</td>
<td>Pallor</td>
<td>Decreased skin perfusion</td>
</tr>
<tr>
<td>Capillary refill time</td>
<td>Prolongation</td>
<td>Decreased skin perfusion</td>
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<tr>
<td>Lactate</td>
<td>Lactic acidosis</td>
<td>Lactate washout after initiation insult, sequestering</td>
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<tr>
<td>Blood gas</td>
<td>Metabolic acidosis</td>
<td>Residual perinatal acidosis</td>
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<tr>
<td>Urinary output</td>
<td>Oliguria or Anuria</td>
<td>Acute renal injury</td>
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</tbody>
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Approach to Cardiovascular Care

• Consider pathophysiology, phase of intervention, and impact of concomitant treatments
  • Isolated transient myocardial ischemia may not require intervention

• Weigh impact of treatment for impaired function/low cardiac output against consequences of reperfusion injury
### Table V. Echocardiography findings, pathophysiology, and suggested therapy in neonates with HIE and hemodynamic instability

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Echocardiography findings</th>
<th>Management principles</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low SAP, normal oxygenation</td>
<td>LV/RV systolic dysfunction</td>
<td>(+) Inotropy</td>
<td>1st line: dobutamine</td>
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<td></td>
<td></td>
<td></td>
<td>2nd line: epinephrine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Hydrocortisone (if refractory)</td>
</tr>
<tr>
<td>Low SAP, impaired oxygenation</td>
<td>PPHN</td>
<td>Pulmonary vasodilation and ↑SBF</td>
<td>1st line: iNO, optimum ventilation</td>
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<td></td>
<td></td>
<td></td>
<td>2nd line: vasopressin or norepinephrine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- PGE₁ (if restrictive DA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hydrocortisone (if refractory)</td>
</tr>
<tr>
<td>LV dysfunction + PPHN</td>
<td>(+) Inotropy, maintain R → L ductal shunt to support SBF</td>
<td>1st line: dobutamine, PGE₁ (if restrictive DA)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2nd line: epinephrine (caution if severe oxygenation failure)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1st line: dobutamine, iNO</td>
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<tr>
<td>RV dysfunction + PPHN</td>
<td>(+) Inotropy, reduce RV afterload, maintain adequate RV preload</td>
<td>2nd line: PGE₁ (if restrictive DA) 3rd line: vasopressin or norepinephrine</td>
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</tbody>
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Hypovolemia Hypotension

- Aggressive volume resuscitation should be avoided
  - Association between increased cerebral blood flow and poor outcome
  - Exception: direct evidence of acute hypovolemia

- Blood transfusions for anemia + pulmonary hypertension
  - Increased oxygen carrying capacity
Isolated Hypotension

• Presentation
  • Low systolic BP and evidence of end organ hypoperfusion

• Treatment goals
  • Increase stroke volume and cardiac output

• Treatment options
  • Epinephrine
  • Dobutamine
Hypotension + Increased Afterload

- **Presentation**
  - Low pulmonary blood flow, impaired oxygenation, low cardiac output

- **Treatment goals**
  - Sedation, +/- muscle relaxation, ventilation, iNO
  - Avoid excessive mean airway pressure—further impairment of pulmonary venous return

- **Treatment options**
  - Dobutamine
  - Milrinone
  - Vasopressin
  - Norepinephrine
Refractory Hypotension

- Adrenal insufficiency can occur independently or in combination with other causes of hypotension
- Refractory
  - Persistent hypotension despite catecholamine therapy
  - Hypoglycemia, hyponatremia
  - Adrenal injury
- Treatment
  - Hydrocortisone
Summary

• Pathophysiology of hypotension in neonate is diverse
  • Gestational age, patient factors
• Treatment for hypotension should consider pathophysiology
• HIE/TH represents unique treatment considerations
Questions