Neonatal Shock

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Objectives

• Review the initial evaluation and differential diagnosis of neonatal shock
• Review the pharmacology of treatment of shock
• Apply the above information to a clinical case
Neonatal Shock

• Imbalance between tissue oxygen delivery and oxygen consumption

• Syndrome with diverse group of life threatening and multifactorial conditions

• Not regarded as a single pathologic entity
Oxygen Delivery and Consumption

Oxygen Delivery must remain > 2-3 times consumption

J.A. GUTIERREZ AND A.A. THEODOROU

OXYGEN DELIVERY AND OXYGEN CONSUMPTION IN PEDIATRIC CRITICAL CARE
Blood Pressure

Preload → Heart rate → Cardiac output → Blood pressure

Contractility → Stroke volume → Systemic vascular resistance → Blood pressure

Afterload
Hypotension

• Associated risks preterm > term infants
  – Inability to regulate cerebral blood flow (CBF)
• Paucity of data on reference values for arterial blood pressure in newborns
• Mean arterial blood pressure ≈ GA (weeks)
• BP tends to increase with:
  – Advancing GA
  – Birth weight
  – Postnatal age (esp within first 5 days of life)
“Normal” Blood Pressure Ranges

Blood Pressure “Rule of Thumb”

- Lower acceptable mean blood pressure (mmHg) on DOL 1 should be ≈ GA wks
- DOL 2-3 increases by ~ 5-7mmHg
- By DOL 3, 90% infants 23-26 wks GA will have mean blood pressure >30mmHg

Cerebral Blood Flow and Autoregulation

No autoregulation with blood pressure changes (as may occur with severe asphyxia)

Autoregulation with blood pressure changes (normal state; may be dampened in premature newborns and with specific disease states)

(A) with decreasing gestational age, mean arterial blood pressure approaches the lower limit of the autoregulation plateau; this predisposes the premature brain to decreased cerebral blood flow with changes in blood pressure.

Shock
Case

- 4.1kg 39 wk male born via c-section for failure to progress
- Pregnancy complicated by gestation DM on glyburide, screens negative including GBS
- Floppy, poor respiratory effort → PPV → CPAP
- Inability to obtain pulse oximetry and pale
- APGARs: 2, 5, 6
- Vital signs: HR 171; RR 31; Sat 85%; Blood Pressure unable to register
Is this baby in shock?
If so, which phase of shock?
What type of shock?
Phases of Neonatal Shock

• Compensated
• Uncompensated
• Irreversible
Phase 1: Compensated Shock

- Vital organ function maintained
  - Neurohormonal compensatory mechanism
- Redistribute blood flow to heart, brain and adrenals
- Decreased: stroke volume, central venous pressure and urine output
- Normal blood pressure
  - Increased myocardial contractility and HR so CO remains ~normal
Compensated Shock, cont.

*Blood pressure may not always appropriately reflect status of organ blood flow*
Phase 2: Uncompensated Shock

- Failure of intrinsic neurohormonal compensatory mechanisms
- Decreased:
  - microvascular perfusion
  - myocardial contractility
  - stroke volume
  - blood pressure
- Decreased tissue perfusion → lactic acidosis
- Multiorgan failure if untreated
Uncompensated Shock, cont.

Diagram:

- **Preload** → **Heart rate** → **Cardiac output** → **Blood pressure**
- **Contractility** → **Stroke volume**
- **Afterload** → **Systemic vascular resistance**
Phase 3: Irreversible Phase

• Cellular damage → complete organ failure
• Death invariably
Cellular and Molecular Pathophysiology of Shock

- Reactive oxygen species $\rightarrow$ cell injury
- Nitric oxide overproduction $\rightarrow$ hypotension
- Eicosanoids $\rightarrow$ vasomediators and inflammatory mediators
- $K_{ATP}$ channels $\rightarrow$ vascular smooth muscle tone
Down-Regulation of Adrenergic Receptors

• Occurs with critical illness and exogenous catecholamine administration
• Absolute or relative adrenal insufficiency
• Leads to “pressor-resistant shock”
  – Glucocorticoids
Back to our case…

- Intubated, lines placed
  - Code event requiring epinephrine and compressions during placement
- VBG: <6.8/37/113 Lactate 13.8 Hct 24
- NS bolus and PRBCs
- Oscillator, 100% oxygen, iNO 20
- Saturations now mid 90s, HR 140s
- Echocardiogram done
Echocardiogram
Types of Shock

• Hypovolemic
• Cardiogenic
• Distributive

• More than one type may be involved
Hypovolemic Shock

• Uncommon primary cause of neonatal shock
• Hypovolemia $\rightarrow$ low CO and $\downarrow$ preload $\rightarrow$ $\downarrow$ BP
• Causes
  – Fetomaternal hemorrhage
  – Massive hemorrhage
  – Inappropriate increase in vascular capacitance
  – Surgical/GI losses (gastrochisis)
  – Decreased venous return (air leaks, PEEP)
  – DIC
  – Dehydration (insensible losses/polyuria)
Cardiogenic Shock

• Neonate have immature myocardial structure and function
  – Greater dependence on extracellular $[\text{Ca}^{2+}]$
  – Greater sensitivity to increased afterload
  – ELBW seem to be more sensitive
Immature Myocyte
Cardiogenic Shock, cont.

• Increase in afterload \(\rightarrow\) myocardial dysfunction and decreased cardiac output

• Transitional circulation
  – Placenta low resistance \(\rightarrow\) cut the cord \(\rightarrow\) immediate increase in SVR
    • Can lead to increased LV afterload
    • Decrease in cardiac output
    • Development of shock
Other Causes of Cardiogenic Shock

- Perinatal asphyxia
- Prolonged septic shock
- PDA ligation
- Cardiomyopathies
- Myocarditis
- Ductal-dependent heart defects
- Arrhythmias
Distributive Shock

- Most common cause of early neonatal shock
- Impaired regulation of vascular tone +/- myocardial dysfunction
- SEPSIS
  - Inflammatory mediators (TNF-α)
Distributive Shock, cont.

- Two hemodynamic patterns
  - Warm shock
    - Loss of vascular tone
    - Increased systemic blood flow
    - Hypotension
  - Cold shock
    - Increased vascular tone
    - Low systemic blood flow
    - Falling blood pressure
Pressor-Resistant Systemic Hypotension

- Normal to high systemic blood flow
  – ? Supranormal cardiac output
- More likely to be ≤ 27wks gestation or critically ill or perinatal asphyxia
- Down-regulation of cardiovascular adrenergic receptors, cytokine release, excess NO synthesis
- Exacerbated by immaturity, relative adrenal insufficiency
Returning to Our Case…
What do we do next?

• Echo demonstrating small ventricles (decreased preload)
  – Poor function
• Mean arterial blood pressure 31mmHg
• Lactic acidosis
Treatment of Neonatal Shock
Treatment Modalities

- Volume
- Cardiovascular pharmacologic therapies
- Corticosteroids

- Tailored to primary cause and effect
Volume

- Relatively uncommon in 1\textsuperscript{st} day
- Replace the fluid that is lost
- Excessive volume $\rightarrow$ worsen status if myocardial dysfunction
- Morbidities: PDA, lung dysfunction, ?IVH
Indications for Volume Resuscitation

- Known blood loss
- Insensible losses
- Declining central venous pressure
- Volume repletion in distributive shock
- Before starting pharmacologic support
  - 10mL/kg Normal Saline over ~30 minutes
  - May repeat
Crystalloid vs. Colloid?

  - Randomized hypotensive preterm and term to normal saline vs. 5% albumin
  - No difference in magnitude of BP response
  - No difference in need for 2nd bolus
  - NS is safe, readily available, cheaper
  - NS better than albumin
Crystalloid vs. Colloid?

- Randomized hypotensive preterm infants to NS vs. 5% albumin
- No difference in BP response
- No difference in need inotropic support
- NS just as effective
Volume Expansion

• Normal saline first choice
• Unless known anemia/blood loss
Pharmacologic Therapies

• Inotropes - drugs that improve myocardia contractility
  – Increase peak force of contraction under isometric conditions

• Chronotropes – drugs that increase HR

• Lusitropes – drugs that increases the rate of myocardial relaxation

• Limited evidence as to which to use, doses and monitoring
Inotropes

• Stimulate myocardial
  – α-adrenergic receptors
  – β-adrenergic receptors
  – Dopaminergic receptors
Mechanisms of Action

R, receptor; Gs and Gi, stimulatory and inhibitory G-proteins; AC, adenyl cyclase; PK-A, protein kinase A; SR, sarcoplasmic reticulum; α and β, alpha and beta-adrenoceptors; Epi, epinephrine; NE, norepinephrine; ACh, acetylcholine; M2, muscarinic receptor; A1, adenosine (Ado)

R, receptor; Gq, phospholipase C-coupled Gq-protein; PL-C, phospholipase C; PIP2, phosphatidylinositol biphosphate; IP3, inositol triphosphate; DAG, diacylglycerol; SR, sarcoplasmic reticulum; NE, norepinephrine; AII, angiotensin II; ET-1, endothelin-1; α1, alpha1-adrenoceptor; AT1, type 1 angiotensin receptor; ETA, type A endothelin receptor.

α- and β-Receptor Stimulation

[Diagram showing the pathways and mechanisms of α- and β-receptor stimulation, including changes in membrane proteins, intracellular signaling, and resulting effects on vasconstriction and vasodilation.]
## Properties of Receptors

<table>
<thead>
<tr>
<th>Adrenergic, Dopaminergic, and Vasopressin Receptors</th>
<th>$\alpha_1/\alpha_2^a$</th>
<th>$\beta_2$</th>
<th>$\alpha_1$</th>
<th>$\beta_1/\beta_2$</th>
<th>DA$_1$/DA$_2$</th>
<th>V$_{1a}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vasoconstriction</td>
<td>++++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++++</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>0</td>
<td>++++</td>
<td>0</td>
<td>0</td>
<td>++++</td>
<td>0</td>
</tr>
<tr>
<td>+Inotropy</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+++</td>
<td>+/+</td>
<td>0</td>
</tr>
<tr>
<td>+Chronotropy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cond. velocity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Table 1: Cardiovascular actions mediated by adrenergic, dopaminergic, and vascular vasopressin receptors*

*Clin Perinatol 39 (2012) 221–238*
Subsets categorize vasoactive agents by presence or absence of inotropic effects and effects on vasculature.
Trends in Neonatal Hypotension

• All Infants

• ELBW Infants

Arch Dis Child Fetal Neonatal Ed 2006;91:F213-F220.
# Receptor Activity

<table>
<thead>
<tr>
<th>Drug</th>
<th>$\alpha_1$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>DA$_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>0 – 3+</td>
<td>1 – 4+</td>
<td>0 – 2+</td>
<td>0 – 4+</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>2 – 4+</td>
<td>3 – 4+</td>
<td>1 – 3+</td>
<td>0</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>4+</td>
<td>2+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>1+</td>
<td>3 – 4+</td>
<td>1 – 2+</td>
<td>0</td>
</tr>
<tr>
<td>Milrinone</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## Hemodynamic Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>HR</th>
<th>MAP</th>
<th>CI</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>↑ - ↑↑</td>
<td>↑ - ↑↑</td>
<td>0 - ↑</td>
<td>↓/↑</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑ - ↑↑</td>
<td>↑ - ↑↑</td>
<td>↑↑</td>
<td>↓/↑↑</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0 - ↑</td>
<td>↑↑↑</td>
<td>0 / ↓/↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0 - ↑↑</td>
<td>↓/↑</td>
<td>↑</td>
<td>0 / ↓</td>
</tr>
<tr>
<td>Milrinone</td>
<td>↑↑</td>
<td>0 / ↓/↑</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
Dopamine

- Most commonly used in NICU
- Stimulates α- and β-adrenergic, dopaminergic and serotinergic receptors
- Maturational differences in α- and β-adrenergic receptors → and thus dose-dependent responses
- Effective in shock due to myocardial dysfunction and shock due to altered vasoregulation
Dose-dependent Effects of Dopamine in Neonates

DOPAMINE

≥ 0.5 μg/kg/min

Dopamine Receptors
Renal, Mesenteric & coronary > pulmonary circulation, heart

+ Vasodilation in kidneys*, intestine#, coronary arteries
+ Increase in GFR*
+ Direct renal tubular effects*
+ Positive inotropy*
+ Endocrine effects

≥ 2-4 μg/kg/min

Alpha Receptors
More homogenously distributed

+ Vasoconstriction*
+ Positive inotropy*
+ Metabolic effects*

≥ 4-8 μg/kg/min

Beta Receptors
More homogenously distributed

+ Positive inotropy*
+ Positive chronotropy*
+ Peripheral vasodilation
+ Metabolic effects*

* Without adrenoreceptor down-regulation
# Demonstrated effects in preterm neonates

Thoughts…

• Hemodynamic effects and response altered by downregulation of adrenergic receptors
  – Prolonged endogenous and exogenous receptor stimulation
  – May see attenuated response
Dobutamine

• Relatively cardioselective
• 2 enantiomers with different affinity for adrenergic receptors
• Negative isomer $\alpha_1$-receptor agonist
  – Increases myocardial contractility and SVR
• Positive isomer $\beta_1$- and $\beta_2$-receptor agonist
  – Increases myocardial contractility, HR and conduction velocity, decreases SVR
• Net effect – increase myocardial contractility, HR (lesser extent), no effect or decrease SVR
Cardiovascular Effects of Dobutamine in Neonates

**DOBUTAMINE**

≥ 5µg/kg/min

**Beta Receptors**
- More homogenously distributed
- Positive inotropy*
- Decreased myocardial compliance (diastolic)
- Improved myocardial QO₂
- Positive chronotropy
- Peripheral vasodilation
- Metabolic effects

**Alpha Receptors**
- More homogenously distributed
- Positive inotropy*
- Decreased myocardial compliance (diastolic)
- Vasoconstriction

* Without adrenoreceptor down-regulation
# Demonstrated effects in preterm neonates

Cardiovascular Effects

• Myocardial dysfunction, normal SVR → drug of choice
  – Increases CO (more effective than dopamine)
  – Example: Asphyxia

• Not appropriate 1st line if vasodilatory shock is primary cause (low SVR)
  – May add to dopamine
Dopamine vs. Dobutamine?

• If BP is low, dopamine better than dobutamine in increasing SVR
• Dobutamine without an $\alpha_1$-adrenergic agonist may worsen hypotension
• If impaired myocardial function $\rightarrow$ adding dobutamine may be beneficial
Dopamine vs. Dobutamine

• Randomized, double-blind, crossover trial

• Preterm infants < 32 weeks (N = 20)

• Dopamine
  – Median dose 12.5 mcg/kg/min
  – 100% achieved MAP > 30 mmHg
  – Increased SVR while maintaining SV

• Dobutamine
  – Median dose 20 mcg/kg/min
  – 40% achieved MAP > 30 mmHg
  – Dobutamine increased CO, less impact on MAP

Dopamine vs. Dobutamine

[Graphs showing comparison of MAP (mm Hg) with Dobutamine and Dopamine.]
Epinephrine

• Dose dependent stimulation of α- and β-adrenergic receptors

• Net effects
  – Significant increase in BP
  – Increases systemic blood flow by increasing SVR and CO

• 100-fold more potent than dopamine or dobutamine as inotrope
EPINEPHRINE

**Beta Receptors**
- More homogenously distributed
- Positive inotropy# (direct)
- Positive chronotropy#
- Peripheral vasodilation (renal, mesenteric. muscle)
- Metabolic effects#

**Alpha Receptors**
- More homogenously distributed
- Vasoconstriction#
- Positive inotropy#
- Metabolic effects#

0.01-0.1 μg/kg/min

> 0.1 μg/kg/min
Epinephrine Clinical Use

- Refractory shock, second line agent
  - Hyperglycemia
  - Renal vasoconstriction

- Free from myocardial damage and ischemia
  - Potent β- activity
  - Direct cardiac toxicity
    - Damage to arterial walls
    - Myocardial contraction band necrosis
    - Myocyte apoptosis
Norepinephrine

• Potent vasopressor
  – Increases HR
  – Increases myocardial contractility
  – Increases SVR

• 100-fold more potent than dopamine or dobutamine as inotrope

• Lacks $\beta_2$ effects

• Use if diastolic pressure low
  – If systolic pressure low, epinephrine
Milrinone

• Lusitope – aiding in diastolic relaxation
• Prevents degradation of cAMP → improves myocardial contractility, decreases PVR and SVR
  – Inotropy : vasoldilation = 1:20
• Limited studies in neonates
• Benefit when added to epi or norepi
• Caution with renal failure
Milrinone – Phosphodiesterase 3 Inhibitor

\[
\begin{align*}
\beta \text{ agonist} & \rightarrow \beta \text{ receptor} \\
& \downarrow \\
& \downarrow \text{Gs-GTP} \\
& \downarrow \text{adenyl cyclase} \\
& \downarrow \uparrow \text{cAMP} \\
\text{Phosphodiesterase Inhibitors} & \rightarrow \text{PDE3} \\
& \downarrow \text{AMP}
\end{align*}
\]
Corticosteroids

• Relative or absolute adrenal insufficiency
  – Especially sick preterm infants

• Glucocorticoids involved in regulating expression of cardiovascular adrenergic receptors

• If not enough receptors → decreased response to vasopressors
Adrenocortical Function

- 24-36 wk GA inverse relationship between GA and [cortisol]
  - Illness has significant negative effect on [cortisol]
  - ELBW requiring more respiratory support and inotropic support had lower cortisol levels
- Several studies shown that many stressed newborns fail to synthesize cortisol, have low levels
Adrenocortical Function in VLBW Infants

Ng et al. Arch Dis Child Fetal Neonatal Ed 2001;84:F122–F124
How Does Hydrocortisone Increase BP?

• Non-genomic effects:
  – Inhibits rate limiting enzyme in catecholamine break down
  – Decreases NE reuptake at nerve endings
  – Increases cytosolic Ca^{2+} availability
  – Inhibits vasodilatory effects of inflammatory response
  – Improves capillary integrity
  – 1-2 hrs

Seri and Evans
How Does Hydrocortisone Increase BP?, cont.

• Genomic Effects:
  – Upregulation of cardiovascular adrenergic receptors
  – Induction of second messenger systems
    • Synthesis and membrane assembly of new receptor proteins
  – Requires 8-12 hrs
Preterm Infants’ Response to Hydrocortisone

Seri and Evans, Pediatrics; May 2001
What About Late Preterm and Term Infants?

• Not well studied in term infants
  – Used frequently with paucity of evidence

• Currently being studied through NRN
  – RCT evaluating the effects of a course of hydrocortisone therapy on morbidity and cardiovascular function and long-term neurodevelopment and mortality of ill term and late preterm infants diagnosed with cardiovascular insufficiency

Clinical trials.gov: NCT 01954056
ECMO

• Refractory hypotension
• Failure of medical therapy
Back to Our Case

• Continued to fluid resuscitate
  – NS, blood products (coagulopathy)

• Started dopamine
  – Acute hypotensive episode with desaturation
  – More fluid, increased dopamine and added hydrocortisone

• Repeated echocardiogram
Repeat Echocardiogram
Case Conclusion

• Once intravascular volume improved, cardiac function improved → oxygenation improved, lactatic acidosis started to improve

• Able to wean off support over then next few days
Conclusions

• Early recognition of neonatal shock is imperative
  – Remember low BP ≠ low organ perfusion
• Volume resuscitation may not be indicated in preterm infant unless known cause for hypovolemia
  – Normal saline is preferred unless blood loss
Conclusions, cont.

• Pharmacologic therapies may be necessary
  – Dopamine is most common inotrope used by neonatologist, but depending on etiology of hypotension, others may be more appropriate

• Glucocorticoid therapy should be considered

• More data is needed to determine efficacy and long term outcomes
Thank You
Selected References


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