Inotropes in Preterm Infants - Evidence For and Against

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What we don’t know -

• What is the relationship between blood pressure and cerebral perfusion?
• Does increasing blood pressure improve overall, and particularly cerebral perfusion?
• Which inotrope should we use when?
• Does any circulatory intervention improve outcome?
Circulatory Physiology

- Preload
- Contractility
- Afterload
- Balance of pressure and flow
- Control of cardiovascular function
- Fetal shunt pathways
### Adrenergic Control of Contractility and Vascular Tone

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Action</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>Myocardium</td>
<td>↑ Inotropy</td>
<td>↑ Contractility</td>
</tr>
<tr>
<td>α1</td>
<td>Peripheral Vasc</td>
<td>↑ Constriction</td>
<td>↑ Afterload (↑ Preload)</td>
</tr>
<tr>
<td>α2</td>
<td>Peripheral Vasc</td>
<td>↑ Constriction</td>
<td>↑ Afterload (↑ Preload)</td>
</tr>
<tr>
<td>β1</td>
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Assessment of the Newborn Circulation

- History
- Overall clinical status
- Capillary refill
- Lactate (and trend)
- Urine output
- Blood pressure
- Toe-core temperature gap

- Echocardiography:
  - IVC Filling
  - Cardiac Filling
  - Eyeball contractility
  - LVO and RVO
  - SVC flow
  - Ductal steal (diastolic DAo reversal)
  - Raised pulmonary resistance
Volume support

- Increases preload
- Likely increases output, irrespective of prior hypovolaemia
- 10-20 ml/kg
- Likely short duration of action
- 0.9% saline
- Consider blood and FFP

Osborn J Ped 2002;140:183-191
Dopamine is a Vasopressor

- Also has inotropic action
- Risk of vasopression ‘trumping’ inotropy
- Doesn’t increase overall perfusion
- Cerebral impact uncertain
- Pharmacodynamics very variable
- Endocrine effects – TRH, GH, prolactin
- ‘Titrate to response’ seems reasonable, but be ready to wean dose as BP rises
Dobutamine

- Synthetic isoprenaline analogue
- Clearance considered less gestation-dependent
- Less peripheral alpha effect

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<tr>
<td></td>
<td>$\alpha_1$†</td>
</tr>
<tr>
<td></td>
<td>$\beta_1$ ($\beta_2$)†</td>
</tr>
<tr>
<td></td>
<td>↑contractility</td>
</tr>
<tr>
<td>Dopamine**</td>
<td>++‡</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>++</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+</td>
</tr>
<tr>
<td>Dobutamine‡</td>
<td>++</td>
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- Less vasoconstriction
- Potential for peripheral vasodilatation
Epinephrine

- Endogenous catecholamine
- Dose range 100 – 1,000 nanogram/kg/min
- Non-selective for all receptor types
- Potentially more effective inotrope than dopamine

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*Note: + indicates increasing effect, # indicates decreasing effect, Ø indicates no effect.
Norpinephrine

- Endogenous catecholamine
- Dose range 100 – 1,000 nanogram/kg/min
- Less peripheral beta effect

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<th>Peripheral vascular receptors</th>
<th>Vasodilation in renal, mesenteric, and coronary circulation</th>
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Cardiovascular adrenergic and dopaminergic receptors

- $^+$: Slight effect
- $^+$ $^+$: Moderate effect
- $^+$ $^+$ $^+$: Strong effect
- $^\#$: Indeterminate effect
- $\emptyset$: No effect
Corticosteroids

• Relative adrenal insufficiency is common
  – Extreme preterms
  – Term septic infants

• Genomic actions of corticosteroids
  – Up-regulation of adrenergic receptors
  – Inhibition of nitric oxide synthase
  – Inhibition of vasodilatory prostaglandins

• Non-genomic actions of corticosteroids
  – Increase intracellular calcium levels
  – Inhibit catecholamine breakdown
  – Decrease capillary leak

Noori Pediatrics 2006;118:1456-1466
Milrinone

- Phosphodiesterase III inhibitor
- Enhances intracellular cAMP
- Inotrope and vasodilator
- May be pulmonary vasodilator

Which Inotrope for Which Baby?

- **Newborn preterm (transitional circulation)**
  - Hypotensive, ? hypoperfusion
  - Normotensive, but circulatory failure
- **Ex-preterm (post-transitional)**
  - Circulatory collapse
  - PDA
- **Term**
  - Sepsis
  - PPHN
In each scenario -

• Comprehensive Assessment
  – History, Clinical and Echocardiographic
• Identify the pathophysiology
• Identify what you’re trying to achieve
• Institute intervention
• Assess response
  – Preload
  – Output
  – Tissue Perfusion
‘Late’ preterm circulatory collapse

In these infants new hypotension is a very worrying sign.
Until then...

• Comprehensive clinical assessments
• Define the pathophysiology
• Define aims of intervention
• Which inotrope?
  – Dobutamine for inotropy
  – Dopamine for vasopresston
  – Adrenaline and Noradrenaline if struggling
  – Volume, nitric, hydrocortisone as judged
• Monitoring and reacting to response to intervention is critical
Any questions?

Suggested Literature Reviews

• Barrington, Seminars F&N, 2008;13:16-23
• Evans, ADC F&N Ed 2006;91:F213-220
• Seri and Noori, EHD 2005;81:405-411
• Osborn, EHD 2005;81:413-422