Impact of neonatal hypotension/low SBF on neurodevelopmental outcome in the VLBW infant

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Research into blood flow

Perfusion pressure
Autoregulation
Cerebral blood flow
Cerebral oxygen extraction
NIRS

Transitional circulation
Cardiac output
Blood pressure
Peripheral resistance
Effect of other factors
   -Carbon dioxide, ventilation
   -Treatment affects

Peri/intraventricular haemorrhage in preterm infants

Changes in blood flow

Hypotaxic ischaemia
Immature germinal matrix
Genetic

Cardiovascular origins of brain injury

Transitional circulation
Low Systemic Blood Flow
Low Cerebral Blood Flow
Impaired Autoregulation
High Risk for Brain Injury
Risk Long-term Disability

Summary

- Incidence of hypotension/low systemic blood flow
- Pathophysiology
- Short term morbidity associated with hypotension/low systemic blood flow
- Impact on neurodevelopmental outcome
- Randomised controlled trials to assess efficacy of treatments on ND outcome
  ZERO!

Definition of hypotension

- Statistical
  Defined on population norms
- Physiological
  Defined on physiological endpoint such as the autoregulation threshold
- Pathological
  Defined as failure to perfuse end organs resulting in anaerobic metabolism
Normal Mean Blood Pressure

- Cut off at 30mmHg irrespective of GA (Maat Allen 1987)
- Nomograms based on 10th centile for each GA - approx = GA in weeks (Watkins 1989)
- Gestational/Postnatal age dependent nomograms (Nuntharumit et al, Clin Perinatol 1999;26:981-996)

Blood pressure nomogram

Nuntharumit et al, Clin Perinatol 1999;26:981-996

Incidence

- Depends on definition
- Recent review of NICU’s showed that
  - 30% of VLBW diagnosed with hypotension
  - 16-52% of these received Rx with volume expansion
  - 39% received vasopressors – usually in first 24 hours
  - Practice variation is large (ELGAN study) 32% to 98% treatment rates

Low RV output common on day 1 (mean 19 hrs), Resolved by 3 days

Evans et al Arch Dis Child 1996
Changing incidence of low SVC flow

- Recent cohort in randomised trial (2005) – incidence of low SVC flow only 18%
- Half of what it was in 1995
- What has happened?
  - Changes in obstetric management
  - Changes in ventilation management – more CPAP, earlier surfactant, lower ventilatory pressures
  - Changes in cardiovascular management as a result of more information available (ECHO)

Hypotension/Low systemic blood flow - risk factors

- More common
  - Immature infants
  - In first days of life
  - If no antenatal steroids
  - If large PDA
  - If higher pressure ventilation
  - Kluckow & Evans Arch Dis Child 2000

Pathophysiology of hypotension_LOW SBF on Day 1

- Delay in adaptation of immature myocardium to increased SVR at birth
- Peripheral vasodilatation and hyperdynamic myocardial function (esp. VLBW infant with mother who has infection)
- Perinatal depression with secondary myocardial dysfunction and/or abnormal peripheral vasoregulation

Pathophysiology of hypotension_LOW SBF on Day 1

- Simply measuring the blood pressure in a sick neonate will not allow differentiation between these presentations
- Information from
  - History
  - Physical examination
  - CXR
  - Functional echocardiography – cardiac output, shunts and direction

Hypotension cf Shock

- Shock is a physiological state where oxygen supply does not meet oxygen demand
- Appearance of shock is therefore dependent on
  - Systemic blood flow
  - Oxygen content of blood
  - Tissue oxygen demands

The relationship between blood pressure and LV output

<table>
<thead>
<tr>
<th>Mean BP at scan (mmHg)</th>
<th>LV output (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>50</td>
<td>90</td>
</tr>
</tbody>
</table>

R=0.38


Other studies have also found a poor relationship between blood pressure and blood flow
Hypotension cf Shock

- Potential predictors of outcome
- Evidence of poor tissue oxygenation
  - Lactate (Cheung PY 1996)
  - Increased CFOE
  - Intracellular pH
  - Changes in cerebral electrical activity

Cerebral electrical activity and hypotension

- Parameters of cerebral electrical activity begin to change at MBP < 23 mm Hg

Early low blood flow
Associated with compromised aEEG

- Intraventricular haemorrhage
- White matter damage
- Long term neurodevelopmental outcome
- Hyperkalaemia/Other organ damage

Clinical correlates of low systemic blood flow/hypotension

- Intraventricular haemorrhage
- White matter damage
- Long term neurodevelopmental outcome
- Hyperkalaemia/Other organ damage

Early PIVH

- Risk factors include
  - Lower GA, Lower BW, No steroids, vaginal delivery, vaginal breech, low Apgar scores
  - 3 studies have assessed the association between postnatal blood flow and early PIVH
  - 2 measured RVO & SVC flow – no association found Kluckow 2000, Osborn 2003
  - 1 measured CBF using Xenon – observed an association between low CBF & early PIVH Ment 1984
  - Timing & mechanism uncertain – no studies have assessed flow PRIOR to early PIVH

Late PIVH

- Almost 60% of babies with PIVH develop it “late” – after about 6 hours postnatal
- Risk factors include
  - Caesarean section, low CBF, low SVC flow
- 3 studies have demonstrated a relationship between preceding low blood flow and late PIVH Kluckow 2000, Osborn 2003, Meek 1999
- This association suggests a hypoperfusion-reperfusion aetiology for late PIVH.
Cerebral injury in the preterm infant

- Early PIVH (HUS in first 6 hours)
- Vaginal delivery
- Peripartum complications
- Late PIVH (after 6 hours)
  - Multifactorial
  - Cardiovascular maladaptation
  - White matter changes (Flares, PVL, Cysts, Loss of volume)

Haemodynamic basis of IVH.

- What is to blame?
  - Too much blood flow.
  - Too little blood flow.
  - Fluctuating blood flow.
- Association with hypotension.
- Originate in watershed area of GM.
- Animal model: (Ment 1983)
  - Hypoperfusion-reperfusion leads to IVH.
  - Just reperfusion ---- no IVH.

Model for IVH in preterm infants

Beagle Puppy Model for IVH


Possible human model for IVH.

Late IVH: SVC flows in the four babies who developed grade 3 IVH.

Kluckow & Evans. Arch Dis Child 2000
Low systemic blood flow and IVH

Perinatal risk factors for late IVH

| Cohort 1995-1996, n = 126 | OR 20.4 (2.5 - 164.0) |
| Cohort 1998-1999, n = 128 | OR 5.2 (1.6 - 16.7) |

Oelborn et al. Pediatrics 2003

Low SVC flow on Day 1 vs adverse outcome

- 40 VLBW infants
- 21% had low SVC flow in first 24 hrs and this was associated with early neonatal death/IVH

<table>
<thead>
<tr>
<th>Low SVC</th>
<th>Normal SVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-sided p value</td>
<td></td>
</tr>
<tr>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Levitton 1999

NIRS studies of cerebral blood flow

- Evidence of a period of early low CBF on NIRS in extreme preterm infants with brain injury
  - Meek et al. 1999

White matter damage

- Clinical risk factors are multiple
  - T1 bleeding, maternal UTI, histological CA, PPROM, no maternal antibiotics, MSL, fetal acidosis, neonatal hypo/hypercarbia, symptomatic PDA, hypotension after first 24 hrs, twin-twin transfusion syndrome
  - Several studies have NOT found any association with hypotension in early postnatal period and WMD

White matter damage

- Small study reported 7 infants with early low CBF – one developed parenchymal PIVH and two PVL
  - Grossen 1999
- Two other studies with small numbers of infants with PVL also reported low SVC flow in 3/4 and 2/4 babies with PVL
  - Kluckow 2000, Oelborn 2002
- Role of postnatal hypocarbia in development of PVL? Mechanism via changes in blood flow

- Animal models have produced lesions similar to WMD in preterm infants from insults involving
  - Hypoxia/ischemia
  - Marumo 2001, Ohya 1999
  - Inflammation
  - Duncan 2002, McHard 2003
  - Both
  - Hegberg 2002
- Clinical/Epidemiological studies support infective/inflammatory aetiology of PVL, particularly chorioamnionitis
  - de Lee 2000, Lenkin 1999
Blood pressure and neurodevelopmental outcomes

- Normal values/nomograms show
  - BP is lower in more immature infants
  - BP is lower in ventilated or asphyxiated infants
  - BP increases with postnatal age
- Poor relationship between measures of blood flow and blood pressure
- Concept of a critical pressure below which injury may occur (?30mmHg) Muno 2004

Blood pressure and morbidity

- Associations often seen between hypotension and morbidity
  - Hypotension occurs in the same timeframe as vulnerability to brain injury (IVH)
  - Lower BP norms in smaller higher risk infants so by definition fall into hypotensive group if absolute numbers are used to define low MBP

Blood pressure and morbidity

- Grade of IVH related to hypotension (MBP<10th centile) >2 hrs n=131 <1500gms (Watkins et al, Early Hum Dev 1991)
  - Severe cerebral ultrasound changes related to mean blood pressure <30mmHg (4kPA) n=33 (Neal Allen et al, 1987)
  - Infants with lower mean BP at higher risk of IVH n=?? (Bada et al 1990)
  - May also have effects on other organs such as the gastrointestinal tract and kidney

Hypotension - consequences

- Associated with poor outcomes
  - Intraventricular haemorrhage
  - White matter damage
  - Long term neurodevelopmental outcome
- May also have effects on other organs including the GIT and kidney

Blood pressure and morbidity

- Initial concerns raised by Lou et al (1979) in term infants with perinatal distress. Demonstrated
  - Low arterial blood pressure
  - Low cerebral blood flow
  - Increased risk of cerebral injury and adverse ND outcome (n=19, 7 with BW<1500gm)

Blood pressure and morbidity

- Large population based studies - systemic hypotension is NOT an independent risk factor for PIVH or for PVL Heuchan et al Arch Dis Child 2002, DeVries Am J Dis Child 1988
- Some population based studies have shown a relationship between early hypotension and poor neurodevelopmental outcome Low et al Acta Paediatrica 1983, Goldstein Pediatrics 1995
Blood pressure and morbidity

- Treated hypotension vs no treatment
- ND outcome at 20 mo CA

Faranoff JM et al Pediatrics 2006

### Table: Hemodynamic Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treated for Hypotension</th>
<th>No Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP readings &lt; GA in weeks</td>
<td>0.75 ± 0.5</td>
<td>0.77 ± 0.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean BP readings at 24 hrs</td>
<td>76 ± 15</td>
<td>76 ± 15</td>
<td>2.0</td>
</tr>
<tr>
<td>Number of mean BP measures &lt; GA</td>
<td>10</td>
<td>13</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Note: 10 infants in the study group; 16-infant untreated neurodevelopmental testing, and 10 infants in the control group had neurodevelopmental testing. Baseline parameters at 24 hour were exchanged at individual centers age.*

Blood pressure and morbidity

- Plenty of data associating low blood pressure with morbidity, particularly cerebral injury
- 9 Prospective cohorts
- 8 RETRO cohorts
- 3 Case control studies
- Most studies fail to adjust for perinatal confounders
- Only one study reported simultaneous SBF and BP on the first day
- No association between average mean BP over first 12 or 24 hours and outcome
- Significant association with death/abnormal outcome and number of mean BP measures < GA in weeks

Low flow and long term neuro-developmental outcome

- 126 Preterm Infants born <30 weeks
- 23 Died in the neonatal period
- Follow up information on 96 babies
- 86 formal Griffiths Assessment (83%)
- 10 information from treating specialists
- 7 lost to follow up
- Outcomes assessed at 3 years
- Abnormal Motor
- Abnormal Developmental Quotient (DQ)

Hunt et al. J Pediatrics 2004

### Table: Relationship between average SVC flow and outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.71</td>
<td>0.56-0.90</td>
<td>0.004</td>
</tr>
<tr>
<td>Abnormal DQ</td>
<td>0.67</td>
<td>0.51-0.89</td>
<td>0.005</td>
</tr>
<tr>
<td>Abnormal Motor</td>
<td>0.73</td>
<td>0.55-0.97</td>
<td>0.03</td>
</tr>
<tr>
<td>Abnormal DQ + Death</td>
<td>0.77</td>
<td>0.64-0.94</td>
<td>0.008</td>
</tr>
<tr>
<td>Abnormal Motor + Death</td>
<td>0.75</td>
<td>0.61-0.92</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Hunt et al. J Pediatrics 2004

### Table: Relationship between number of times SVC flow <30 ml/kg/min and outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.005</td>
</tr>
<tr>
<td>Abnormal DQ</td>
<td>0.18</td>
</tr>
<tr>
<td>Abnormal Motor</td>
<td>0.01</td>
</tr>
<tr>
<td>Abnormal DQ + Death</td>
<td>0.04</td>
</tr>
<tr>
<td>Abnormal Motor + Death</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Hunt et al. J Pediatrics 2004

SBF, Pressure and 3 yr Outcome

- Average SVC flow over 24 hrs significantly related to
  - Death
  - Abnormal DQ
  - Abnormal Motor development
- Lowest SVC flow
  - Not significantly related
- Average MBP (12 or 24 hrs)
  - No significant relationship with death or disability
- Percent MBP readings less than GA
  - Significant relationship to combined death and disability (p=.02), mainly related to death (p=.002)
Low CBF and neurological outcome

- 71 infants <1500gm, \(^{133}\)Xe CBF measures x 3 (Meaned)
- Measured at age 2 hrs – 10 days
- Outcome – survival, 18 months Bayley assessment

Blood pressure/Blood flow and neonatal outcomes

- Early low systemic blood flow is associated with mortality, late PIVH, NEC and longer term neurodevelopmental impairment
- Associations between low systemic blood flow and adverse outcome is early (first 12 hrs)
- Associations between blood pressure and adverse outcomes has been reported predominantly for measures taken after 12 hours

Blood pressure/Blood flow and neonatal outcomes

- Supports the hypothesis of cardiovascular maladaptation previously put forward by our group regarding VLBW infants
- Initial compensated shock with high SVR, normal BP and poor myocardial function presenting as low SBF early
- Progresses to decompensated shock and hypotension
- Targeting treatment of hypotension only may delay treatment of infants with low systolic blood flow

Evidence that treatment of hypotension/low SBF improves mortality/morbidity in preterm

- Delayed cord clamping
- Cyclooxygenase inhibitors to close PDA
- Volume
- Vasopressor/Inotropes
- Milrinone
- Post natal corticosteroids
- iNO

Cerebral Blood Flow/BP NIRS Data conflicts

- Correlation (Loss of autoregulation):
  - Correlation between MBP and cerebral oxygenation in subgroup with more IVH/Mortality
  - Munro et al, 2004
  - Correlation between CBF and MBP in those with MBP<30mmHg
- No Correlation:
  - Tyszczuk et al, 1998
  - No relationship between CBF and MBP on day 1
  - Kissack et al, 2004
  - No correlation between cerebral oxygen extraction and MBP – but correlates with decreased LV output and lower CO2

Autoregulation

- 28 wks, 1 day old
  - Cranial Ultrasound normal
- 27 wks, 1 day old
  - Cranial Ultrasound abnormal
Cerebral fractional oxygen extraction  

Suggested mechanism
- There is an integral relationship between the cardiovascular system and cerebral circulation in preterm infants
- A unique set of factors results in impaired cardiac function in the first days of life
- Reduced cardiac output can reduce cerebral blood flow
- Autoregulation is impaired by this early impaired blood flow/hypotensive insult

Suggested mechanism
- Infants with impaired autoregulation are at higher risk of brain injury (including IVH)
- As blood flow increases the increase in cerebral blood flow can result in IVH (reperfusion injury)
- This brain injury may be preventable if attention is directed toward the maintenance of cardiac function

Speculation & further research
Timing issues are crucial
- Damage to autoregulation may be done in the first hours of life
- Early recognition of cardiovascular impairment
  - Role of echocardiogram
  - Not only diagnosis of low flow, but up to 60% of babies with low flow eventually develop hypotension requiring treatment as well (often 8-10 hours later? treatment delayed)

Where to next?
- Identification of high risk infants
- Use of other measures
  - NIRS/CBF measures
  - Neonatal echocardiography
  - Electrophysiology
  - Tissue oxygenation measures
- Possible treatments
  - Early/Prophylactic
  - Effective for pathophysiology
  - Pharmacokinetics
- Clinical trials & long term outcomes

Research into brain injury
Heart  Brain

Timelines & further research
- Identification of high risk infants
- Use of other measures
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