Apnea of Prematurity: What’s New?

Richard J. Martin, M.D.
Drusinsky-Fanaroff Chair in Neonatology
Rainbow Babies and Children’s Hospital
Professor of Pediatrics
Case Western Reserve University
Cleveland, Ohio

Apnea of Prematurity

- Pathobiologic mechanisms
- Patterning of cardiorespiratory events
- Therapeutic approaches
- Resolution

Perinatal Modulation of Respiratory Neural Output

Prenatal
- Inhibition
- Placental unit
- Hypoxia
- Adenosine
- Prostaglandin
- Descending pontine inhibition
- Hyperthermia
- Non-REM sleep

Postnatal
- Excitation
Richard J. Martin, MD  
Director, Division of Neonatology

Apnea of Prematurity:  
What's New?  
Belgium 2012

Anatomy of carotid bodies

Modulation of Peripheral Chemoreceptor Function During Development

Proposed Apneic Threshold in Neonates

Decreased Respiratory Drive

Factors Influencing Arterial O₂ Desaturation during Apnea of Prematurity

Mixed Apnea

Richard J. Martin, MD
Director, Division of Neonatology

Physiologic Data From Upper Airway Dilator Muscles During Development

Pathophysiologic Data From Upper Airway Dilator Muscles During Development

Physiologic Data From Upper Airway Dilator Muscles During Development

Physiologic Data From Upper Airway Dilator Muscles During Development

Apnea of Prematurity

- Pathobiologic mechanisms
- Patterning of cardiorespiratory events
- Therapeutic approaches
- Resolution

Characterization of Cardiorespiratory Patterns: Objectives

- To predict natural history (e.g. shortening duration of ventilatory support and/or hospitalization)
- To predict morbidity
  - Early recognition of sepsis
  - Retinopathy of Prematurity

Mortality Reduction by Heart Rate Characteristic Monitoring in Very Low Birth Weight Neonates: A Randomized Trial

“Heart Rate Characteristics monitoring (by early detection) can reduce the mortality rate in very low birth weight infants.”

Mean Number of Desaturation Episodes in Infants of 24 to 28 Weeks Gestation Over the First 8 Weeks of Life (n=79)

Model Based Estimate of Desaturation Episodes in Infants with and without ROP (adjusted for covariates)

Role of Oxygenation in Genesis of ROP

Timing of Intermittent Hypoxic Events

Effect of Time Interval Between Intermittent Hypoxic Events

Postnatal Intermittent Hypoxia/Reoxygenation

Longer Term Sequelae

Adapted from Ryan S, et al. Thorax 2009
Apnea of Prematurity

- Pathobiologic mechanisms
- Patterning of cardiorespiratory events
- Therapeutic approaches
- Resolution

Therapeutic Approaches

Interventions of proven efficacy
- Treat specific etiologies (e.g. Sepsis)
- CPAP
- Xanthine therapy

Other proposed interventions
- Change in baseline SaO₂
- Increase in hematocrit
- Supplemental CO₂
- Anti-reflux therapy

Model for IL-1β-induced Neonatal Respiratory Depression


Effect of CPAP on Incidence of Apnea

(p<0.02)

Before CPAP

During CPAP

Nasal CPAP for Neonatal Apnea

- Decrease in upper airway resistance
- Increase in FRC
- Improvement in oxygenation

Ability of Nasal Cannula Flow to Deliver CPAP of 6 cm H₂O

Sreenan, Pediatrics 2001
Richard J. Martin, MD  
Director, Division of Neonatology

**Apnea of Prematurity: What’s New? Belgium 2012**

---

**Methylxanthine therapy in premature infants: Sound practice, disaster, or fruitless byway?**

*Schmidt B. J. Pediatr 1999*

---

**Effect of Caffeine Therapy for Apnea of Prematurity**

<table>
<thead>
<tr>
<th>Caffeine Group (n=1006)</th>
<th>Placebo Group (n=1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenstrual age at last use of endotracheal tube</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>29.1 weeks</td>
</tr>
<tr>
<td></td>
<td>30.0 weeks</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Postmenstrual age at last use of supplemental oxygen</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>33.6 weeks</td>
</tr>
<tr>
<td></td>
<td>35.1 weeks</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Schmidt, NEJM 2006*

---

**Proposed Beneficial Effects of Xanthine on BPD**

- CAFFEINE
  - Lower concentration
  - Adenosine receptor blockade ($A_1$, $A_{2A}$, $A_{3}$)
  - Higher concentration
  - cAMP (phosphodiesterase inhibition)
  - INCREASED RESPIRATORY DRIVE
  - INFLAMMATORY RESPONSE MODULATION
  - BRONCHODILATION

---

**Caffeine Therapy for Apnea Trial: Outcome at 18-21 Months**

<table>
<thead>
<tr>
<th></th>
<th>Caffeine</th>
<th>Placebo</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or disability</td>
<td>40%</td>
<td>46%</td>
<td>0.77</td>
<td>0.006</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>4.4%</td>
<td>7.3%</td>
<td>0.38</td>
<td>0.009</td>
</tr>
<tr>
<td>MDI&lt;85</td>
<td>34%</td>
<td>38%</td>
<td>0.80</td>
<td>0.035</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>5.1%</td>
<td>7.9%</td>
<td>0.63</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Schmidt, NEJM 2007*
Richard J. Martin, MD  
Director, Division of Neonatology

### Proposed Beneficial Effects of Xanthine on Neurodevelopment

*xanthines*

- Altered CNS neurotransmission (adenosine, GABA)
- Less apnea
- Less hypoxic events
- Downregulation of cytokine release from immune cells

**Improved Neurodevelopmental Outcome**

### Efficacy of Xanthine Therapy

“Infants receiving respiratory support derived more neurodevelopmental benefits from caffeine than infants not receiving support.”

“Earlier discontinuation of any positive airway pressure explained 49% of the beneficial long term drug effect.”

Davis, PG et al. J Pediatr 2010

### Indications for Caffeine Therapy

**Therapeutic**

**Prophylactic**

CAP Trial  
Survey [2010-2011]

### Survival Without Disability to Age 5 Years After Neonatal Caffeine Therapy for Apnea of Prematurity

“Neonatal caffeine therapy was no longer associated with a significantly improved rate of survival without disability in children with very low birth weights who were assessed at 5 years.”

Schmidt, JAMA 2012

### Therapeutic Approaches

**Interventions of proven efficacy**

- Treat specific etiologies (e.g. Sepsis)
- CPAP
- Xanthine therapy

**Other proposed interventions**

- Change in baseline SaO₂
- Increase in hematocrit
- Supplemental CO₂
- Anti-reflux therapy

### The Incidence of Intermittent Hypoxia in the Low and High Target Groups
Effect of Transfusion on Apnea with Associated Bradycardia and Desaturation

Mean Number of Desaturation Episodes in Infants of 24 to 28 Weeks Gestation Over the First 8 Weeks of Life (n=79)

Effect of RBC Transfusion on Intermittent Hypoxia

CO₂ Inhalation as a Treatment for Apnea of Prematurity

Incidence of Cardiorespiratory Events Preceded by GER

Apnea and GER: Common Features
Apnea of Prematurity

- Pathobiologic mechanisms
- Patterning of cardiorespiratory events
- Therapeutic approaches
- Resolution

Cross-Over Trial of Treatment for Bradycardia Attributed to Gastroesophageal Reflux

Efficacy and Safety of Proton Pump Inhibitor Therapy in Infants with GERD


Proposed Approach to Predischarge Management

Infants with ≥ One Extreme Event per 20,000 Monitor Hours
Effect of Apnea on Hospital Discharge

Apnea and Intermittent Hypoxic Episodes: Do They Matter?

Challenges:
- Role of accompanying bradycardia?
- Role of accompanying hypercapnia?
- Role of resaturation (recovery) that inevitably follows desaturation?
- Is a relationship between apnea and outcome causal?

Rainbow Developmental Respiratory Neurobiology Lab
- Peter MacFarlane
- Abdelmadjid Belkadi
- Prabha Kc
- Anjum Jafri
- Christopher Wilson
- Catherine Mayer
- Julie DiFiore
- NHLBI, NICHD