Apnea of Prematurity: Physiologic Basis for Therapies

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Neonatal Case
[everyday in the NICU]
Case

- Male infant born at 26 weeks’ gestation, 680 gm
- Required initial intubation for surfactant when FiO₂ reached 0.5
- Loaded with caffeine on day 2 and extubated to nasal CPAP
- Now on day 8 exhibiting intermittent self-resolving apnea
Questions

- What physiologic mechanism make this infant at risk for apnea of prematurity?

- How are CPAP and xanthine therapy benefitting his apnea?
inhibition of fetal respiratory activity

-hypoxia
-placental unit
-adenosine
-prostaglandin
-descending pontine inhibition
-hyperthermia
-non-REM sleep
Respiratory Reflexes and Neonatal Apnea

IMMATURITY

enhanced inhibitory reflexes

decreased hypercapnic responses

hypoxic stimulation not sustained

APNEA
Reflex Pathways Activated by Lung and Airway Afferents

Brainstem

- INSP NEURONS
- Vagus heart
+ Vagus airways

Phrenic
Respiratory Reflexes and Neonatal Apnea

IMMATURITY

- enhanced inhibitory reflexes
- decreased hypercapnic responses
- hypoxic stimulation not sustained

APNEA
Neonatal Ventilatory Response to Hypercapnia

Krauss, Pediatr Res, 1975
CO₂ Response Curves for Preterm Newborns Without and With Apnea

Controls without Apnea

Newborns with Apnea

Gerhardt, 1984
Proposed Apneic Threshold in Neonates

Actual PCO$_2$
Apneic threshold

Neonates

1.5 Torr

Apneas

Darnall, 2011
Respiratory Reflexes and Neonatal Apnea

IMMATURITY

- enhanced inhibitory reflexes
- decreased hypercapnic responses
- hypoxic stimulation not sustained

APNEA
Anatomy of Carotid Bodies

- Petrosal Ganglion
- Internal Carotid
- Carotid Body
- Superior Cervical Ganglion
- Common Carotid Artery
Neonatal Hypoxic Ventilatory Response

Min Vent (cc/min/kg)

O₂ Saturation (%)

Time (minutes)

Martin: J Pediatr 1998
Modulation of Peripheral Chemoreceptor Function During Development

Postnatal hyperoxia
- Decreased peripheral chemosensitivity
  - Prolongation of Apnea

Postnatal intermittent hypoxia
- Increased peripheral chemosensitivity
  - Generation of Apnea

Respiratory Instability
Questions

- What physiologic mechanism make this infant at risk for apnea of prematurity?

- How are CPAP and xanthine therapy benefitting his apnea?
**Effect of CPAP on Incidence of Apnea**

![Graph showing the effect of CPAP on apnea incidence](image-url)

- **Before CPAP:** 60 episodes / 12 hours
- **During CPAP:** 0 episodes / 12 hours

Statistical significance: \( p < 0.02 \)

*Kattwinkel 1975*
Physiologic Data From Upper Airway Dilator Muscles During Development

- Alae nasi (AN)
- Genioglossus (GG)
- Sternohyoid (SH)
- Posterior Cricoarytenoid (PCA)
Nasal CPAP for Neonatal Apnea

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

Pre

Post

Mean Daily Number of Apneic Episodes

Number of Apneic spells per day

Pre Theophylline

Post Theophylline

Pre Caffeine

Post Caffeine

Uauy, Pediatr 1975

Aranda, J Peds 1977
Methylxanthine therapy in premature infants: Sound practice, disaster, or fruitless byway?

Schmidt B: J Pediatr 1999
CAP TRIAL
### Effect of Caffeine Therapy for Apnea of Prematurity

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

Schmidt, NEJM 2006
## Caffeine Therapy for Apnea Trial: Outcome at 18-21 Months

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

<table>
<thead>
<tr>
<th>Outcome</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>0.58</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
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
Developmental Coordination Disorder

OR [95% CI] = 0.71 [0.52-0.98]

Inflammation

Ventilatory support

Hypoxic episodes

White matter stability

Xanthines

↑ Respiratory neural output

↓ Inflammation

↓ Ventilatory support

↓ Hypoxic episodes

↑ White matter stability

Improved neurorespiratory outcome

Stryker, Dylag, Martin: In: Fetal & Neonatal Lung Development, in press 2015
How long?

*When to start*

*When to end*

How much?
What to Do?

Hanoi · 2015
Indications for Caffeine Therapy

Therapeutic
Prophylactic

Percent Use

CAP Trial

Survey [2010-2011]

Percent of Responders

Abu Jawdeh: J Neonat Perinat Med 2013
**Association of Early* Caffeine and Outcome: Retrospective Cohort Study**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Caffeine Group, Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early (n = 3806)</td>
</tr>
<tr>
<td>Discharged receiving oxygen, No. (%)</td>
<td>931 (24.5)</td>
</tr>
<tr>
<td>Duration of oxygen requirement, d</td>
<td>9 (1-43)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, d</td>
<td>2 (1-9)</td>
</tr>
<tr>
<td>Duration of noninvasive respiratory support, d</td>
<td>1 (1-5)</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>52 (27-88)</td>
</tr>
<tr>
<td>Discharged receiving caffeine, No. (%)</td>
<td>1386 (35.4)</td>
</tr>
</tbody>
</table>

* Within the first two days

Lodha A: JAMA Pediatr 2015
Effect of Caffeine on Intermittent Hypoxia: Randomized Clinical Trial in Preterm Infants

Rhein L: JAMA Pediatr 2014
Rapid Response of Diaphragm EMG to Caffeine Bolus [10 mg/kg caffeine base]

Kraaijenga JV: J Pediatr 2015
Extubation Failure after High vs Low Caffeine Citrate Maintenance Dosage

Randomized Controlled Trial

Steer P: Arch Dis Child Fetal Neonatal Ed 2004
Case [continued]

- He is now three weeks old, in a nasal cannula, on full enteral feeds, and weighs 920 gm
- He develops several new episodes of significant apnea requiring bag/mask ventilation
- Sepsis work-up is performed and antibiotics begun
- Lab values demonstrate borderline neutropenia and a hematocrit of 24%
Questions

- What are potential mechanisms whereby sepsis presents with apnea?
- Would this infant’s episodes benefit from red blood cell transfusion?
Model for IL-1β-induced Neonatal Respiratory Depression

Systemic Immune Response → IL-1β → IL-1R

Blood Brain Barrier: endothelial cell
COX-2 → mPGES-1 → AA → PGH₂ → PGE₂ → PGE₂ → EP₃R

Brain Parenchyma

Respiratory related brainstem regions → Respiratory Depression

Central Role of Inflammatory Mechanisms on the Immature Lung and Brain

Adverse Respiratory Outcome (BPD)

Adverse Neurodevelopmental Outcome (PVL)

INFLAMMATION
Exposure to inflammation

Phrenic output [↓]

Cytokine induction

Vagal afferents [↑]

Diaphragm

Balan KV et al 2012
Proposed Central Role for Respiratory Control in Mediating Inflammatory Responses

- IMMATURE RESPIRATORY CONTROL
- CHORIOAMNIONITIS
- POSTNATAL SEPSIS
- PROINFLAMMATORY RESPONSE
- INTERMITTENT HYPOXIA/REOXYGENATION
- APNEA

Arrows indicate Neural and Systemic connections.
Questions

- What are potential mechanisms whereby sepsis presents with apnea?

- Would this infant’s episodes benefit from red blood cell transfusion?
Effect of Transfusion on Apnea with Associated Bradycardia and Desaturation

Zagol: J Pediatr 2012
Factors Influencing Arterial $O_2$ Desaturation during Apnea of Prematurity

Adapted from Sands SA: PLOS Computational Biology 2009
Intermittent Hypoxic Episodes

- Apneic episodes
- Low baseline SaO₂
- Low O₂ reserves
- Unstable upper airway

Immature respiratory control
Poor respiratory function
Case [continued]

- Our infant boy is now 38 weeks postmenstrual age, weighs 2.2 kg, and is taking all feeds by mouth.
- Supplemental oxygen and caffeine were recently discontinued.
- Baseline oxygen saturation ranged from 92-95% in room air.
- Bedside monitor triggers intermittent desaturation and bradycardia alarms.
Question

- What is the pathophysiological significance of these desaturation and bradycardic events?

- How should discharge planning proceed?
Decreased Respiratory Drive

APNEA, HYPOVENTILATION

 incr. vagal tone

BRADYCARDIA

decr. O₂ delivery
carotid body

DESATURATION
Heart Rate Characteristics and Clinical Signs in Neonatal Sepsis

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.”

Importance of Pulse Oximeter Averaging Time When Measuring Oxygen Desaturation Episodes

<table>
<thead>
<tr>
<th>SaO₂ (%)</th>
<th>100</th>
<th>90</th>
<th>80</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>short averaging time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>long averaging time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time
Importance of Pulse Oximeter Averaging Times

Short averaging time

Long averaging time

SpO2 (%)

Time (min)

Courtesy J. Di Fiore
Intermittent Hypoxic Episodes: What is the Magnitude of the Problem?

- Masimo Radical technology was employed via 2 sec averaging
- Desaturation was defined as <80% (≥10 sec and ≤3 min)
- Pulse oximetry data were continuously recorded from birth to 8 weeks in a preterm cohort
Mean Number of Desaturation Episodes in Infants of 24 to 28 Weeks’ Gestation Over the First 8 Weeks of Life (n=79)

Postnatal Age (weeks)

# of Hypoxic Events (per week)

mean±95% confidence interval

J Di Fiore: J Pediatr 2010
Role of Oxygenation in Genesis of ROP

Adapted from Chow: Pediatrics 2003
Model Based Estimate of Desaturation Episodes in Infants with and without Laser Therapy for ROP

![Graph showing the number of desaturations per week against postnatal age. The graph compares LaserROP (n=16) and No LaserROP (n=63). Mean ± 95% confidence interval.]

* $p < .05$

J Di Fiore: J Pediatr 2010
Lower Baseline Ranges of Oxygen Saturation Decrease ROP but Increase Mortality in ELBW Infants

SUPPORT Trial: NEJM 2010
The Incidence of Intermittent Hypoxia in the Low and High Target Groups

Di Fiore: J Pediatr 2012
Differential Mortality in Low vs High $O_2$ Target Groups

Walsh MC, Di Fiore JM, Martin RJ & SUPPORT Investigators: Manuscript under review
Persistence of Apnea and Bradycardia of Prematurity (ABP) is Associated with Poor Neurodevelopmental Outcome

<table>
<thead>
<tr>
<th>Postmenstrual Age</th>
<th>Severe Handicap</th>
<th>No Severe Handicap</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ABP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>31-33</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>34</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>35</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>36</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>37-38</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>39-44</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Pillekamp: Neonatology 2007
What is the pathophysiologic significance of these desaturation and bradycardic events?

How should discharge planning proceed?
Effect of Apnea on Discharge Timing

Eichenwald, 2011, Pediatrics
Apnea: Predischarge Challenges

- Apnea >20 sec is uncommon and deserves attention
- Predischarge pneumograms should be used selectively, not routinely
- Caffeine can usually be stopped well before discharge: this may need further study
- Home monitor use should be minimized
Apnea: Predischarge Recommendations

- Discontinue pulse oximetry at 36 weeks if no respiratory issues
- Discontinue cardiorespiratory monitoring prior to discharge when infant engaged with parents
- Lower bradycardia alarms to <70 beats/min prior to discharge
Cerebral Tissue Oxygen Saturation $[StO_2]$ via NIRS

Combined hypoxemia and bradycardia

Hypoxemia <75% only

Bradycardia <80/min only

Schmid: Neonatology 2015