APNEA AND CONTROL OF BREATHING
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DIOMEL DE LA CRUZ, M.D.
OBJECTIVES

- Define Apnea
- Review Causes and Appropriate Evaluation of Apnea in Neonates
- Review the Pathophysiology of Breathing Control and Apnea of Prematurity
- Review Management Options for Apnea of Prematurity
  - The Clinical Evidence for Caffeine
  - The Role of Gastroesophageal Reflux
DEFINITION OF APNEA

- Cessation of breathing for greater than 15 (or 20) seconds
  - Or if accompanied by desaturations or bradycardia

- Differentiate from periodic breathing
  - Regular cycles of respirations with intermittent pauses of >3 S
  - Not associated with other physiologic derangements
  - Benign and self-limiting
TYPES OF APNEA

CENTRAL
- Total cessation of inspiratory effort
- Absence of central respiratory drive

OBSTRUCTIVE
- Breathing against an obstructed airway
- Chest wall motion without nasal airflow

MIXED
- Obstructed respiratory effort after a central pause
- Accounts for majority of apnea in premature infants
APNEA IS A SYMPTOM, NOT A DIAGNOSIS

Martin RJ et al. Pathogenesis of apnea in preterm infants.
### APNEA IN THE NEONATE: DIFFERENTIAL

<table>
<thead>
<tr>
<th>Central Nervous System</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intraventricular Hemorrhage</td>
<td>• Airway Obstruction</td>
</tr>
<tr>
<td>• Seizure</td>
<td>• Inadequate Ventilation / Fatigue</td>
</tr>
<tr>
<td>• Cerebral Infarct</td>
<td>• Hypoxia</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Infection</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>• Sepsis</td>
<td>• Necrotizing Enterocolitis</td>
</tr>
<tr>
<td>• Meningitis</td>
<td>• Gastroesophageal Reflux</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Drug Exposure</td>
</tr>
<tr>
<td>• Anemia</td>
<td>• Perinatal (Ex: Magnesium, Opioids)</td>
</tr>
<tr>
<td>• Polycythemia</td>
<td>• Postnatal (Ex: Sedatives, PGE)</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Cardiovascular</td>
<td>Other</td>
</tr>
<tr>
<td>• Patent Ductus Arteriosus</td>
<td>• Temperature instability</td>
</tr>
<tr>
<td></td>
<td>• Metabolic derangements</td>
</tr>
</tbody>
</table>
Detailed History and Physical Examination

- Gestational age, post-natal age, and birth history
- Other new signs or symptoms
- Careful attention to neurologic, cardiorespiratory, and abdominal exam
APNEA IN THE NEONATE: EVALUATION

- **Laboratory Studies**
  - CBC/diff and CRP
  - Cultures, consideration of LP
  - Electrolytes including magnesium
  - Blood gas and lactate

- **Radiologic Studies**
  - Head ultrasound vs. MRI
  - Chest and/or abdominal films
  - Cardiac studies (EKG, echo)
Apnea of Prematurity (AOP) is a **diagnosis of exclusion**

- Peak onset is at 5-7 days of post-natal age

- The likelihood of AOP increases with decreasing gestational age and weight

- The pathophysiology of AOP is multifactorial
  - Understanding is extrapolated from basic science and animal models
RESPIRATORY HOMEOSTASIS

- Medullary and Pontine Respiratory Centers
  - Central Chemoreceptors
  - Peripheral Chemoreceptors
  - Carotid Body
  - Laryngeal Chemoreflex
- Mechanoreceptors
- Pulmonary Stretch Receptors
- Pharyngeal Afferents

Output to Muscles of Respiration: Excitatory or Inhibitory
CHEMICAL CONTROL OF BREATHING

- Peripheral CO2 Sensitivity (carotid body)
- Central CO2 Sensitivity (ventrolateral medulla)
- Hypoxic Chemosensitivity (carotid body)
- Genetic Regulation
Central Chemoreceptors
- Located on ventral medulla
- Detects changes in CSF pH
- Sensitive to CO2 and H+
- Maintain CO2 and pH in narrow physiologic range
THE CAROTID BODY

- Carotid Body
  - Primary peripheral chemoreceptor
  - Sensitive primarily to hypoxia
  - Can also detect changes in CO2, pH, temperature
  - Hypoxia triggers increase in minute ventilation
DYSREGULATION IN THE NEONATE

- Enhanced inhibitory responses
- Hypoxic respiratory depression
- Decreased response to hypercapnia
- Upper airway collapse

Apnea of prematurity
RESPONSE TO HYPERCAPNIA

RESPONSE TO HYPOXIA

- Abnormal biphasic response to hypoxia
  - Initial increase in ventilation followed by a decline
  - Likely represents depression of central respiratory center due to hypoxia

- Theoretical role of ‘Diving Reflex’ in bradycardia
  - In diving mammals, results in bradycardia during episodes of hypoxia
  - ‘Diving Reflex’ persistent in humans until around 6 months of age
VENTILATORY RESPONSE TO 15% FIO2 HYPOXIA IN PRETERM INFANTS

INITIATION OF BREATHING AFTER RESUSCITATION OF RAT PUPS

IMMATURITY OF THE CNS

- Immaturity of pre-term brain present in histologic samples
  - Fewer synaptic connections
  - Paucity of myelin
  - Less dendritic arborization

- Auditory evoked responses impaired in preterm infants with AOP
Increased presence and activity of inhibitory neural pathways and neurotransmitters

- **GABA**
  - Major inhibitory neurotransmitter
  - Increased number of GABA-A receptors in early post-natal life
    - Implicated in hypoxic ventilatory depression

- **Adenosine**
  - Depresses neural function and respiration
  - Indirect evidence for role in AOP from animal studies
  - Methylxanthines are competitive antagonists at the adenosine receptor
Upper airway obstruction is a prominent component of AOP

- Delay in activation of tone-maintaining airway musculature during hypercapneic episodes
- Theoretical ‘overactive’ vagal inhibition of airway dilator muscles
Mainstay of therapy for AOP since the 1970s
- Studies showed decrease in apnea frequency when on theophylline and caffeine

Competitive antagonist at adenosine receptors

Initial concerns about safety
- Increased metabolic demand and impact on growth
- Adenosine as a neuroprotective agent in hypoxia
The CAP Trial
- Large, multi-center RCT comparing caffeine to placebo
- Originally designed to evaluate safety
- Published follow-up at discharge, 18 months, and 5 years

Initial results at hospital discharge
- Decreased GA at last extubation and cessation of PPV
- Decreased rates of BPD
- Slower weight gain in 3 weeks after therapy initiated

## Table 2. Primary Outcome of Death or Neurodevelopmental Disability.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Caffeine Group</th>
<th>Placebo Group</th>
<th>Unadjusted Odds Ratio</th>
<th>Odds Ratio Adjusted for Center (95% CI)</th>
<th>P Value</th>
<th>Odds Ratio Adjusted for Center and Patient Characteristics (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or disability</td>
<td>377/937 (40.2)</td>
<td>431/932 (46.2)</td>
<td>0.78</td>
<td>0.77 (0.64–0.93)</td>
<td>0.008</td>
<td>0.79 (0.65–0.96)</td>
</tr>
<tr>
<td>Components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death before 18 mo†</td>
<td>62/974 (6.4)</td>
<td>63/970 (6.5)</td>
<td>0.98</td>
<td>0.97 (0.67–1.40)</td>
<td>0.87</td>
<td>0.99 (0.65–1.50)</td>
</tr>
<tr>
<td>Cerebral palsy‡</td>
<td>40/909 (4.4)</td>
<td>66/901 (7.3)</td>
<td>0.58</td>
<td>0.58 (0.39–0.87)</td>
<td>0.009</td>
<td>0.59 (0.39–0.89)</td>
</tr>
<tr>
<td>Cognitive delay§§</td>
<td>293/867 (33.8)</td>
<td>329/858 (38.3)</td>
<td>0.82</td>
<td>0.81 (0.66–0.99)</td>
<td>0.04</td>
<td>0.83 (0.67–1.02)</td>
</tr>
<tr>
<td>Severe hearing loss¶¶</td>
<td>17/909 (1.9)</td>
<td>22/905 (2.4)</td>
<td>0.77</td>
<td>0.77 (0.40–1.45)</td>
<td>0.41</td>
<td>0.81 (0.43–1.55)</td>
</tr>
<tr>
<td>Bilateral blindness¶¶</td>
<td>6/911 (0.7)</td>
<td>8/905 (0.9)</td>
<td>0.74</td>
<td>0.74 (0.26–2.15)</td>
<td>0.58</td>
<td>0.79 (0.27–2.31)</td>
</tr>
</tbody>
</table>

Table 2. Primary Outcome of Death or Disability

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Caffeine Group, No./Total (%)</th>
<th>Placebo Group, No./Total (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>OR Adjusted for Center (95% CI)</th>
<th>P Value</th>
<th>OR Adjusted for Center and Patient Characteristics (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Death or disability</td>
<td>176/833 (21.1)</td>
<td>200/807 (24.8)</td>
<td>0.81 (0.65-1.02)</td>
<td>0.82 (0.65-1.03)</td>
<td>.09</td>
<td>0.86 (0.67-1.09)</td>
</tr>
<tr>
<td>Components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death before 5 y</td>
<td>59/867 (6.8)</td>
<td>58/837 (6.9)</td>
<td>0.98 (0.67-1.43)</td>
<td>0.98 (0.70-1.43)</td>
<td>.92</td>
<td>1.03 (0.69-1.52)</td>
</tr>
<tr>
<td>Motor impairment</td>
<td>13/803 (1.6)</td>
<td>21/773 (2.7)</td>
<td>0.59 (0.29-1.18)</td>
<td>0.59 (0.29-1.18)</td>
<td>.20</td>
<td>0.63 (0.31-1.28)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>38/768 (4.9)</td>
<td>38/750 (5.1)</td>
<td>0.98 (0.62-1.55)</td>
<td>0.97 (0.61-1.55)</td>
<td>.89</td>
<td>1.11 (0.68-1.80)</td>
</tr>
<tr>
<td>Behavior problem</td>
<td>42/773 (5.4)</td>
<td>53/748 (7.1)</td>
<td>0.75 (0.50-1.14)</td>
<td>0.75 (0.49-1.15)</td>
<td>.18</td>
<td>0.78 (0.51-1.20)</td>
</tr>
<tr>
<td>Poor general health</td>
<td>32/805 (4.0)</td>
<td>33/775 (4.3)</td>
<td>0.93 (0.57-1.51)</td>
<td>0.92 (0.56-1.52)</td>
<td>.75</td>
<td>0.95 (0.57-1.58)</td>
</tr>
<tr>
<td>Severe hearing loss</td>
<td>22/798 (2.8)</td>
<td>25/773 (3.2)</td>
<td>0.85 (0.47-1.52)</td>
<td>0.85 (0.47-1.52)</td>
<td>.58</td>
<td>0.91 (0.51-1.64)</td>
</tr>
<tr>
<td>Bilateral blindness</td>
<td>7/792 (0.9)</td>
<td>7/763 (0.9)</td>
<td>0.96 (0.34-2.75)</td>
<td>0.96 (0.34-2.75)</td>
<td>.94</td>
<td>1.04 (0.35-3.02)</td>
</tr>
</tbody>
</table>

### Table 3. Secondary Outcomes of Motor and Cognitive Impairment

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Caffeine Group, No./Total (%)</th>
<th>Placebo Group, No./Total (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>OR Adjusted for Center (95% CI)</th>
<th>P Value</th>
<th>OR Adjusted for Center and Patient Characteristics (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross motor function GMFCS level&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Normal</td>
<td>728/803 (90.7)</td>
<td>666/773 (86.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>56/803 (7.0)</td>
<td>78/773 (10.1)</td>
<td>0.66 (0.46-0.94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6/803 (0.7)</td>
<td>8/773 (1.0)</td>
<td>0.69 (0.24-1.99)</td>
<td>0.64 (0.47-0.88)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.006</td>
<td>0.66 (0.48-0.91)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>5/803 (0.6)</td>
<td>5/773 (0.6)</td>
<td>0.91 (0.26-3.17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4/803 (0.5)</td>
<td>10/773 (1.3)</td>
<td>0.37 (0.11-1.17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4/803 (0.5)</td>
<td>6/773 (0.8)</td>
<td>0.61 (0.17-2.17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full scale IQ &lt;85</td>
<td>137/764 (17.9)</td>
<td>144/742 (19.4)</td>
<td>0.91 (0.70-1.18)</td>
<td>0.90 (0.69-1.17)</td>
<td>.44</td>
<td>0.96 (0.73-1.26)</td>
</tr>
</tbody>
</table>

MANAGEMENT OF AOP - CPAP

- Provides distending pressure in airway
  - May prevent upper airway collapse and obstruction

- Improves oxygenation
  - May blunt hypoxic ventilatory depression
Postulated link between apnea GER in pre-term infant
- Rate of GER is high in pre-term infants
- Physiologic mechanism via laryngeal chemoreflex

Many studies over decades with inconsistent results
APNEA AND GER IN PRETERM INFANTS

APNEA AND GER IN PRETERM INFANTS

Long-term risks of AOP are unclear

- Difficult to separate from other comorbid problems
- Particularly confounded by BPD/CLD
LONG-TERM OUTCOMES OF AOP

INTERMITTENT EPISODIC HYPOXIA

- Acute morbidity [e.g., retinopathy of prematurity]
- Cardiovascular instability [e.g., hypertension]
- Respiratory instability [e.g., sleep disordered breathing]
- Neurodevelopmental disability
Prolonged AOP is correlated with more severe neurodevelopmental handicaps

AOP AND RECEPTIVE LANGUAGE

2014 retrospective chart review of ELBW babies with AOP

- Followed at 8 and 20 months
- Frequency of AOP was related to worse language scores at 8 months
- Severity of AOP related to worse language at 20 months CA

Apnea is a symptom, not a diagnosis
- New onset apnea requires thoughtful evaluation

Respiratory control relies on complex interplay of central and peripheral receptors and reflexes
- Abnormal in the neonate

Caffeine and CPAP are both effective therapies for AOP
- Caffeine improves neurodevelopmental outcomes

The link between AOP and GER remains controversial
- Most studies suggest no benefit to reflux and promotility medications
THANK YOU. QUESTIONS?
RESPIRATORY CENTER NEUROANATOMY
PERIPHERAL CHEMORECEPTORS

- In utero – carotid receptor sensitivity to O2 is adapted to low PaO2.
- At birth – fourfold increase in PaO2
- Postnatal Hyperoxia
- Decrease in peripheral chemosensitivity

- Postnatal hypoxia
- Decreased respiratory drive
- Increased peripheral chemosensitivity
APNEA AND RESPONSE TO HYPEROXIC TEST

Cardot, Pediatric Res 2007
## PATHOGENESIS

<table>
<thead>
<tr>
<th>Central Mechanisms</th>
<th>Peripheral Reflex Pathways</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased central chemosensitivity</td>
<td>Decreased carotid body activity</td>
<td>Genetic predisposition</td>
</tr>
<tr>
<td>Hypoxic ventilatory depression</td>
<td>Increased carotid body activity</td>
<td>Sepsis and cytokines</td>
</tr>
<tr>
<td>Upregulated inhibitory neurotransmitters, e.g., GABA, adenosine</td>
<td>Laryngeal chemoreflex Excessive bradycardiac response to hypoxia</td>
<td>Bilirubin</td>
</tr>
</tbody>
</table>
DECREASED RESPIRATORY DRIVE

APNEA, HYPOVENTILATION

Bradycardia

Inhibitory reflexes

 Decreased O₂ delivery

Desaturation

Carotid body
SEPSIS

Hofstetter, PNAS 2007
EFFECT OF LPS ON MINUTE VENTILATION DURING EXPOSURE TO 10% FIO2 IN RATS

Balan, Resp Physiology and Neurobiology, 2011
Di Fiore, J of Pediatrics, 2010
Di Fiore, J of Pediatrics, 2010
### Table 3. Other Outcomes.

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Caffeine Group</th>
<th>Placebo Group</th>
<th>Unadjusted Odds Ratio</th>
<th>Odds Ratio Adjusted for Center (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy of prematurity — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stages*</td>
<td>382/966 (39.5)</td>
<td>417/955 (43.7)</td>
<td>0.84</td>
<td>0.83 (0.69 to 1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Severe retinopathy†</td>
<td>49/965 (5.1)</td>
<td>75/955 (7.9)</td>
<td>0.63</td>
<td>0.61 (0.42 to 0.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cerebral palsy with a GMFCS level of 3 to 5 — no./total no. (%)‡‡</td>
<td>12/905 (1.3)</td>
<td>19/898 (2.1)</td>
<td>0.62</td>
<td>0.62 (0.30 to 1.29)</td>
<td>0.20</td>
</tr>
<tr>
<td>Seizure disorder — no./total no. (%)‡‡</td>
<td>13/907 (1.4)</td>
<td>12/903 (1.3)</td>
<td>1.08</td>
<td>1.08 (0.49 to 2.38)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Mean Difference</th>
<th>Mean Difference Adjusted for Center (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height percentile‡</td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40.7</td>
<td>40.5</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>38.5 (14.5 to 64.9)</td>
<td>36.8 (14.6 to 64.0)</td>
</tr>
<tr>
<td>Weight percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>27.9</td>
<td>28.5</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>16.8 (3.9 to 46.1)</td>
<td>16.8 (3.7 to 48.5)</td>
</tr>
<tr>
<td>Head circumference percentile**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>54.3</td>
<td>52.1</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>56.4 (27.0 to 83.8)</td>
<td>51.1 (25.0 to 81.8)</td>
</tr>
</tbody>
</table>

Schmidt B et al. Long-Term Effects of Caffeine Therapy for Apnea of Prematurity. 