The Challenge of Optimizing Oxygenation: What about Intermittent Hypoxic Episodes?

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Paul Brodnitz

**Born:** June 3 1857  
**Died:** Mar 20 1922 (at age 64)

**In:** Posen (Poznani), Posen (Wielkopolskie), Germany (Poland)

### Immediate family

- Luise Brodnitz (born Silbermann)  
  His wife

- Ilse Charlotte Simon (born Brodnitz)  
  His daughter

- Julia Dorothea Brodnitz  
  His daughter

- Margot Birnholz (born Brodnitz)  
  His daughter

- Max Brodnitz  
  His father

- Louise Brodnitz (born Weißbein)  
  His mother
APNEA OF PREMATURITY
Physiologic Pathways Leading to Mechanisms of Action

Apnea of Prematurity

- Chemo-mechano receptors
- CPAP
- Xanthines
Mid 1970s
Apnea of Prematurity

- Physiologic Mechanisms
- Xanthines
- CPAP

Intermittent Hypoxia
A Role for Intermittent Hypoxia

- Magnitude of the problem
- Intermittent hypoxia, oxidant stress and inflammation
- Proposed morbidity
- Treatment and future directions
Decreased Respiratory Drive

APNEA, HYPOVENTILATION

-incr. vagal tone
-decr. O₂ delivery
-desaturation
-bradycardia
-carotid body
Factors Influencing Arterial $O_2$ Desaturation during Apnea of Prematurity

- Alveolar $O_2$ Stores
- Pulmonary Hypertension
- Total Blood $O_2$ Capacity
Importance of Pulse Oximeter Averaging Time When Measuring Oxygen Desaturation Episodes

The graph illustrates the difference between short and long averaging times. With short averaging time (left), theSaO$_2$ peaks and troughs are more pronounced, indicating more frequent and rapid changes in oxygen saturation. With long averaging time (right), the peaks and troughs are less pronounced, suggesting that the changes are less frequent but may be more severe over a longer period. This highlights the importance of choosing the appropriate averaging time to accurately assess oxygen desaturation episodes.
Importance of Pulse Oximeter Averaging Times

Short averaging time

Long averaging time

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

Number of Hypoxic Events (per week) vs. Postnatal Age (weeks)

J Di Fiore: J Pediatr 2010
A Role for Intermittent Hypoxia

- Magnitude of the problem
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Central Role of Inflammatory Mechanisms on the Immature Lung and Brain

INFLAMMATION

Adverse Respiratory Outcome [BPD]

Adverse Neurodevelopmental Outcome [PVL]
Postnatal Intermittent Hypoxia/Reoxygenation

Oxidative Stress

Inflammation

Longer Term Sequelae

Adapted from Ryan S, et al: Thorax 2009
Inflammatory Pathways Associated with Intermittent Hypoxia in Obstructive Sleep Apnea

Controls

OSAS

OSAS 6 weeks on CPAP

p<0.001

p=0.002

TNF alpha [pg/ml]

Ryan: Circulation 2005
Immature or impaired respiratory control

Proinflammatory response

Intermittent hypoxia/reoxygenation
Exposure to inflammation

Phrenic output \[\downarrow\]

Brainstem

Cytokine induction

Vagal afferents \[\uparrow\]

Diaphragm

Balan KV et al 2012
Effect of Intratracheal LPS on Hypoxic Ventilatory Response

Minute ventilation (% change)

Time (min)

Hypoxia

Recovery

Control

LPS

Balan KV: Respir Physiol Neurobiol 2011
Immature or impaired respiratory control

Proinflammatory response

Intermittent hypoxia/reoxygenation
Apnea of Prematurity

- Physiologic Mechanisms
- Intermittent Hypoxia
- Xanthines
- CPAP

Longer Term Neurorespiratory Disability
The Risk for Hyperoxaemia after Apnoea, Bradycardia and Hypoxaemia in Preterm Infants
A Role for Intermittent Hypoxia

- Magnitude of the problem
- Intermittent hypoxia, oxidant stress and inflammation
- Proposed morbidity
- Treatment and future directions
Proposed Morbidities of Intermittent Hypoxia

- Acute morbidity [e.g., retinopathy of prematurity]
- Respiratory instability [e.g., sleep disordered breathing]
- Neurodevelopmental disability

Martin RJ and Wilson C: J Appl Physiol 2009
Role of Oxygenation in Genesis of ROP

**Hyperoxia**
- ↓VEGF
- ↓EPO
- ↓IGF-1

vessel growth stops

**Hypoxia**
- ↑VEGF
- ↑EPO
- ↑IGF-1

neovascularization

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

Postnatal Age (wks)

LaserROP (n=16)
No LaserROP (n=63)

* p<.05
Mean± 95% confidence Interval

J Di Fiore: J Pediatr 2010
Proposed Morbidities of Intermittent Hypoxia

Acute morbidity [e.g., retinopathy of prematurity]

Respiratory instability [e.g., sleep disordered breathing]

Neurodevelopmental disability

Martin RJ and Wilson C: J Appl Physiol 2009
Anatomy of Carotid Bodies

- PETROSAL GANGLION
- INTERNAL CAROTID
- CAROTID BODY
- SUPERIOR CERVICAL GANGLION
- COMMON CAROTID ARTERY
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
Respiratory Consequences of Chronic Intermittent Hypoxia

Chronic Intermittent Hypoxia

Reactive Oxygen Species

CAROTID BODY gene/protein expression

Sensitization of the Hypoxic Sensory Response

Unstable Breathing

Worsening of Apnea
### Risk for Sleep Disordered Breathing [Combined Apnea, Hypopnea Measure] at 8-11 years

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>3.0 (1.5-6.5)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Very Low Birth Weight Increases Risk for Sleep-Disordered Breathing in Young Adulthood: The Helsinki Study of Very Low Birth Weight Adults

E. Juulia Paavonen, MD, PhD, BSocSc, Sonja Strang-Karlsson, MD, Katri Räikkönen, PhD, Kati Heinonen, PhD, Anu-Katriina Pesonen, PhD, Petteri Hovi, MD, Sture Andersson, MD, PhD, Anna-Liisa Järvenpää, MD, PhD, Johan G. Eriksson, MD, PhD, Eero Kajantie, MD, PhD
Proposed Morbidities of Intermittent Hypoxia

- Acute morbidity [e.g., retinopathy of prematurity]
- Respiratory instability [e.g., sleep disordered breathing]
- Neurodevelopmental disability

Martin RJ and Wilson C: J Appl Physiol 2009
Persistence of Apnea and Bradycardia of Prematurity (ABP) is Associated with Poor Neurodevelopmental Outcome

<table>
<thead>
<tr>
<th>Postmenstrual Age at last ABP episode (complete weeks)</th>
<th>Number of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ABP</td>
<td>18</td>
</tr>
<tr>
<td>31-33</td>
<td>16</td>
</tr>
<tr>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>37-38</td>
<td>8</td>
</tr>
<tr>
<td>39-44</td>
<td>6</td>
</tr>
<tr>
<td>Severe Handicap</td>
<td></td>
</tr>
<tr>
<td>No Severe Handicap</td>
<td></td>
</tr>
</tbody>
</table>

Severe Handicap
No Severe Handicap
More Recent Trials of Oxygen Targeting in ELBWs

- SUPPORT [n=1316]
- BOOST II [n=1187]
- COT [n=1201]

[randomization of preterm infants 24-28 wk GA to 85-89% vs 91-95% O$_2$ saturation]
Association between Intermittent Hypoxemia or Bradycardia and Late Death or Disability [including ROP] in Extremely Preterm Infants

“This association was significant only for prolonged hypoxemic episodes lasting at least 1 minute...Bradycardia did not alter the prognostic value of hypoxemia.”

Poets CF et al: JAMA, 2015
**Time with SpO₂ <80% and Outcome at 18 months of Age**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>IH &lt;1min</th>
<th></th>
<th></th>
<th>IH≥1min</th>
<th></th>
<th></th>
<th>P</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>RR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>RR (95% CI)</td>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late Death or Disability</td>
<td>1.04 (.61-1.77)</td>
<td>1.01 (.77-1.32)</td>
<td>.88</td>
<td>3.4 (1.95-5.93)</td>
<td>1.66 (1.35-2.05)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cognitive/language delay</td>
<td>.96 (.56-1.64)</td>
<td>.96 (.72-1.29)</td>
<td>.87</td>
<td>2.88 (1.65-5.02)</td>
<td>1.61 (1.29-2.03)</td>
<td>&lt;.001</td>
<td></td>
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</tr>
<tr>
<td>Motor Impairment</td>
<td>2.27 (.90-5.74)</td>
<td>1.90 (.90-4.04)</td>
<td>.08</td>
<td>5.20 (2.48-10.92)</td>
<td>3.51 (2.16-5.72)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Severe ROP</td>
<td>1.84 (0.86-3.95)</td>
<td>1.46 (0.86-2.47)</td>
<td>.12</td>
<td>2.95 (1.47-5.90)</td>
<td>1.93 (1.26-2.98)</td>
<td>.002</td>
<td></td>
<td></td>
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*Poets: JAMA 2015*
The Incidence of Intermittent Hypoxia in the Low and High Target Groups

Intermittent Hypoxemic Events During the First 3 Days of Life

- 25% of infants
- Number of IH events
- <80%, 20sec-5 min
- 25% of infants
Effect of Growth Status and Longer IH Events in Days 1-3 on Survival

Di Fiore JM: J Pediatr 2017
Effect of Growth Status and Shorter IH Events in Days 1-3 on Survival

Di Fiore JM: J Pediatr 2017
A Role for Intermittent Hypoxia

- Magnitude of the problem
- Intermittent hypoxia, oxidant stress and inflammation
- Proposed morbidity
- Treatment and future directions
TREATMENT STRATEGIES FOR INTERMITTENT HYPOXIA

**XANTHINES**
- ENHANCE RESPIRATORY CONTROL

**SUPPORTMENTAL OXYGEN**
- Manual vs automated \( \text{FiO}_2 \) control

**RBC TRANSFUSION**
- IMPROVE OXYGEN STORES

- CPAP
  - Stabilize lung volume
  - Splint upper airway

**OPTIMIZE BASELINE \( \text{SaO}_2 \)**
- NOVEL NON-INVASIVE VENTILATION TECHNIQUES
# Neonatal Caffeine Therapy: Unresolved Issues

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
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<tbody>
<tr>
<td><strong>Early onset</strong></td>
<td>• Improves various morbidities</td>
</tr>
</tbody>
</table>
| **Prolongation of therapy**                                        | • Available data are largely based on associations rather than randomized trials  
• How early is too early?                                                                                                                                                               |
| **Higher doses**                                                   | • Decreases duration of intermittent hypoxic episodes  
• May shorten hospitalization [if discharged on caffeine]  
• May provide exposure to unnecessary medication  
• May prolong hospitalization [if discharged off caffeine]                                                                                                                                |
|                                                                    | • More strongly enhance respiratory neural output  
• Adenosine receptor subtype inhibition of inflammation is variable and dose dependent, raising safety concerns  
• Preliminary report of cerebellar injury  
• Likely need for postnatal dose adjustments                                                                                                                                             |
INTERMITTENT HYPOXEMIA (IH)
Dose Dependent: Timing, Frequency, Severity, Duration

"Severe IH"
High Risk Patterns

"Mild IH"
Low Risk Patterns

Inflammation

Neurotransmitter Imbalance

Reactive Oxygen Species

Poor Outcomes

Adaptive Responses?
Growth/Trophic Factors

Unclear Outcomes

Early Postnatal Life

Basal Expression
Inflammatory Signals/Neurotransmitters/ROS/Trophic Factors

Di Fiore et al, in press