The Challenge of Immature Respiratory Control in a Developing Lung

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Before 1972

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After 1974

Rock ‘n’ Roll Hall of Fame
Cleveland, Ohio, USA
The Challenge of Immature Respiratory Control in a Developing Lung

- Where have we been?
  - The challenge of ongoing respiratory morbidity
  - Linking immature respiratory control and respiratory morbidity
  - Exploring underlying mechanisms
Advice for an Entry Level Neonatologist in the 1970s

“A solution for prematurity is at hand”. Implication: this is a risky career move.

“All the respiratory problems have been solved”. Implication: avoid respiratory research.
Surface Properties in Relation to Atelectasis and Hyaline Membrane Disease

Mary Ellen Avery, M.D., and Jere Mead, M.D., Boston
Treatment of the Idiopathic Respiratory-Distress Syndrome with Continuous Positive Airway Pressure

George A. Gregory, M.D., Joseph A. Kitterman, M.D., Roderic H. Phibbs, M.D., William H. Tooley, M.D., and William K. Hamilton, M.D.

PULMONARY DISEASE FOLLOWING RESPIRATOR THERAPY OF HYALINE-MEMBRANE DISEASE*
Bronchopulmonary Dysplasia

WILLIAM H. NORTHWAY, JR., M.D.,† ROBERT C. ROSAN, M.D.,‡ AND DAVID Y. PORTER, M.D.§

PALO ALTO, CALIFORNIA
ASSISTED VENTILATION
IN TERMINAL HYALINE MEMBRANE DISEASE

BY
MARIA DELIVORIA-PAPADOPoulos and PAUL R. SWYER

Reprinted from Archives of Disease in Childhood, Vol. 39, No. 207 October 1964
APNEA IN PREMATURE INFANTS: MONITORING, INCIDENCE, HEART RATE CHANGES, AND AN EFFECT OF ENVIRONMENTAL TEMPERATURE

William J. R. Daily, M.A., M.D., Marshall Klaus, M.D., and H. Belton P. Meyer, M.D.

ABSTRACT

“...Continuous monitoring of respiration in small infants is now clinically feasible.”

Pediatrics 1969
The Challenge of Immature Respiratory Control in a Developing Lung

- Where have we been?

- The challenge of ongoing respiratory morbidity

- Linking immature respiratory control and respiratory morbidity

- Exploring underlying mechanisms
The BPD Challenge

- Incidence in ELBW infants approaches 40%
- No clear definition
- Animal models remain a challenge
- Strong relationship with neurodevelopmental handicap
Neonatal Morbidities at 22-28 Weeks’ Gestation [1993-2012]

Stoll BJ et al: JAMA 2015
Limitations of Current Definitions of BPD for the Prematurity and Respiratory Outcomes Program

Association between BPD Incidence and IQ Deficit

Twilhaar ES et al: JAMA Pediatr 2018
Ventilation
(baro/volutrauma)

Oxygen
(oxidant/antioxidant balance)

Infection
(pre/postnatal)

Structural Immaturity

Inflammatory Response

Biochemical Imbalance

Alveolar remodeling

Altered pulmonary vasculature
Impaired Airway Structure and Function
Airway Hyperresponsiveness in School Children Born Very Preterm

FEV₁%

BPD  Non-BPD  Controls

p<0.0001  p<0.0001

Adult Progression of Bronchial Responsiveness after Term and Extremely Preterm [EP] Birth

Ventilation in Extremely Preterm Infants and Respiratory Function at 8 Years

Lex W. Doyle, M.D., Elizabeth Carse, M.D., Anne-Marie Adams, Ph.D., Sarath Ranganathan, Ph.D., Gillian Opie, M.B., B.S., Jeanie L.Y. Cheong, M.D., for the Victorian Infant Collaborative Study Group

N Engl J Med
Volume 377(4):329-337
July 27, 2017
Days of Respiratory Support in Extremely Preterm Infants [\(<28\) wk]

<table>
<thead>
<tr>
<th></th>
<th>1997 [n=151]</th>
<th>2005 [n=170]</th>
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<tbody>
<tr>
<td><strong>Endotracheal ventilation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>8–32</td>
<td>2.5–23.5</td>
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<tr>
<td>Mean</td>
<td>23.1±21.0</td>
<td>19.9±28.6</td>
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<tr>
<td><strong>Nasal CPAP</strong></td>
<td></td>
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<tr>
<td>Median</td>
<td>24</td>
<td>31.5§</td>
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<tr>
<td>Interquartile range</td>
<td>14–36</td>
<td>16.8–42§</td>
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<tr>
<td>Mean</td>
<td>26.0±15.3</td>
<td>33.3±26.0§</td>
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<tr>
<td><strong>Supplemental oxygen</strong></td>
<td></td>
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<tr>
<td>Median</td>
<td>45</td>
<td>53.5</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>10.5–88</td>
<td>9.8–106</td>
</tr>
<tr>
<td>Mean</td>
<td>65.1±48.0</td>
<td>75.1±68.0</td>
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Expiratory Flows at 8 Years of Age in Each Period

<table>
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<tr>
<th>Variable</th>
<th>1997 (N=112)</th>
<th>2005 (N=123)</th>
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<tr>
<td><strong>FEV</strong>₁</td>
<td></td>
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<tr>
<td>Raw value — liters</td>
<td>1.43±0.30</td>
<td>1.25±0.28</td>
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<tr>
<td>z score</td>
<td>-0.65±1.30</td>
<td>-1.19±1.17†</td>
</tr>
<tr>
<td>Percent of predicted value</td>
<td>92.0±15.7</td>
<td>85.4±14.4†</td>
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</tbody>
</table>
Lung Parenchymal Injury

↓ Bronchoalveolar attachments

↓ Airway caliber

Airway Constrictor/Dilator Imbalance

Excessive constriction

Altered Airway Smooth Muscle Properties

↑ Airway smooth muscle

↑ Contractility

Airway hyperreactivity
The Challenge of Immature Respiratory Control in a Developing Lung

- Where have we been?
- The challenge of ongoing respiratory morbidity
- *Linking immature respiratory control and respiratory morbidity*
- Exploring underlying mechanisms
Physiologic Pathways Leading to Mechanisms of Action

Apnea of Prematurity

- Chemo-mechano receptors
- CPAP
- Xanthines
Apnea of Prematurity

- Chemo-mechano receptors
- CPAP
- Xanthines

Intermittent Hypoxia

Longer Term Neurorespiratory Morbidity
All Roads Lead to Apnea

- Immature respiratory control
  - ↓ inhibitory neurotransmission
  - ↓ peripheral chemosensitivity
  - ↓ central chemosensitivity

- Poor respiratory function
  - ↓ FRC
  - ↑ resistance
  - ↓ compliance

- Unstable upper airway
- Low O₂ reserves

- Apneic episodes

↓ or ↑ peripheral chemosensitivity
↓ central chemosensitivity
Immature Respiratory Control

Compromised Lungs and Airways

Pulmonary Hypertension

Low Baseline Oxygenation

INTERMITTENT HYPOXIC EPISODES

POSSIBLE ADVERSE NEURORESPIRATORY OUTCOMES

Dylag A: in press 2019
Risk of Bronchopulmonary Dysplasia

“The only treatments that have reduced the incidence of BPD in randomized trials without serious adverse events in premature infants are caffeine and vitamin A”.

Laughon: JAMA Pediatr 2014
Mean Number of Desaturation Episodes in Infants of 24 to 28 Weeks’ Gestation Over the First 8 Weeks

Mean ± 95% confidence interval

J Di Fiore: J Pediatr 2010
Incidence of Intermittent Hypoxia at Various Gestational Ages

Di Fiore JM: PAS 2019
Duration of Intermittent Hypoxia at Various Gestational Ages

Di Fiore JM: PAS 2019
Neonatal Intermittent Hypoxemia Events are Associated with Diagnosis of Bronchopulmonary Dysplasia at 36 Weeks Postmenstrual Age

Raffay TM: Pediatr Res, in press, 2019
“Measures of desaturation, but not bradycardia, significantly added to the predictive model. Desaturation metrics also added to clinical risks for prediction of severe intraventricular hemorrhage, retinopathy of prematurity and prolonged length of stay in the NICU”.

POTENTIAL CAUSAL PATHWAYS BETWEEN INTERMITTENT HYPOXIA AND BRONCHOPULMONARY DYSPLASIA

Direct

IH

Oxidant stress, Inflammation

BPD

Confounding

IH

Pre/Postnatal precursors

BPD

Effect Modification

IH

Supplemental oxygen, Ventilatory support

BPD
The Challenge of Immature Respiratory Control in a Developing Lung

- Where have we been?
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Potential Consequences of Immature Respiratory Control

Apnea of Prematurity

Enhanced ventilatory support

Intermittent hypoxia

Inflammation

Respiratory morbidity

Oxidant stress

Neurodevelopmental disability

Shah V, Di Fiore JM, Martin RJ: In: Bancalari E, Keszler M, Davis P [eds]: The Newborn Lung, 2019
Longer Term Sequelae

Postnatal Intermittent Hypoxia/Reoxygenation

Oxidative Stress \(\xrightarrow{\text{inflammation}}\) Inflammation

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

Ryan: Circulation 2005

Controls
OSAS
OSAS 6 weeks on CPAP

p<0.001
p=0.002
Proposed Central Role for Respiratory Control in Mediating Inflammatory Responses

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

Neural Systemic
Immature or impaired respiratory control

Proinflammatory response

Intermittent hypoxia/reoxygenation
The Risk for Hyperoxaemia after Apnoea, Bradycardia and Hypoxaemia in CPAP-treated Preterm Infants

van Zanten HA: Arch Dis Child 2014
Intermittent Hypoxia during Recovery from Neonatal Hyperoxic Lung Injury Causes Long-term Impairment of Alveolar Development: A New Rat Model of BPD

Intermittent Hypoxia during Recovery from Neonatal Hyperoxic Lung Injury Causes Long-term Impairment of Alveolar Development: A New Rat Model of BPD


→ = secondary crests
The Contribution of Intermittent Hypoxemia to Late Neurological Handicap in Mice with Hyperoxia-induced Lung Injury

Ratner V, Kishkurno SV, Slinko SK, Sosunov SA, Sosunov AA, Polin RA, Ten VS

“Our results suggest that intermittent hypoxia associated with hyperoxia-induced lung injury, but not lung injury itself, results in significant neurological handicap in neonatal mice with BPD”.

Neonatology 2007; 92(1):50-58
Longer-term Effects of Intermittent Hypoxia [IH]±Hyperoxia on Respiratory System Resistance in Neonatal Mice

Oxygen & Free Radicals: Protein Inflammation

HYPOXIA – REOXYGENATION

HYPEROXIA

NADPH (NOX)- OXIDASES

MITOCHONDRIA

Chemokines

Granulocytes

Alveolar space

Structural/Functional Proteins

H2O2

NO•

Peroxynitrite

NO-Tyrosine

3-Chlor-Tyrosine

Vento M et al: Redox Biol 2017
Oxygen & Free Radicals: Lipid Peroxidation Biomarkers

Pericas et al: Analytica Chimica Acta 2015
Rainbow Mouse Pup NICU
Potential Maturational Parallels?

- OSA
- COPD
- Adverse Outcomes

- Apnea
- BPD
- Adverse Outcomes

Adults

Neonates
Prematurity-related Ventilatory Control [PreVent] 2016-

An NHLBI sponsored multicenter observational study to investigate mechanisms of ventilatory control that contribute to the risk of respiratory morbidity in preterm infants

Case Western • Northwestern • UAB
Univ Miami • Washington Univ • UVA
Thank you to My Research Collaborators

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Anna Maria Hibbs  
YS Prakash

NHLBI, NICHD