Impaired Right Ventricular-Pulmonary Vascular Interactions in Adults Born Premature

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Disclosures: None
When I grow up, I want to be a…?

http://www.nicuhelpinghands.org/
• Prematurity in the US
  – Definitions and epidemiology

• Long-term right ventricular and pulmonary vascular outcomes after preterm birth
  – Newborn Lung Project Cohort
  – Insights from animal models
Objectives

- Identify a history of premature birth as a risk factor for adult pulmonary hypertension and right ventricular dysfunction
- Incorporate screening for key components of birth history in the standard evaluation of pulmonary hypertension patients
Incidence of Premature Birth Is Rising

Preterm Birth, by Completed Weeks of Gestation, 1990–2012*

<table>
<thead>
<tr>
<th>Year</th>
<th>34-36 weeks</th>
<th>32-33 weeks</th>
<th>Less than 32 weeks</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>1.40</td>
<td>1.92</td>
<td>1.40</td>
<td>7.30</td>
</tr>
<tr>
<td>1995</td>
<td>1.42</td>
<td>1.89</td>
<td>1.42</td>
<td>10.99</td>
</tr>
<tr>
<td>2000</td>
<td>1.49</td>
<td>1.93</td>
<td>1.49</td>
<td>11.64</td>
</tr>
<tr>
<td>2006</td>
<td>1.62</td>
<td>2.04</td>
<td>1.62</td>
<td>12.81</td>
</tr>
<tr>
<td>2012</td>
<td>1.49</td>
<td>1.93</td>
<td>1.49</td>
<td>11.54</td>
</tr>
</tbody>
</table>

*Data for 2012 are preliminary.

Incidence of Premature Birth Is Rising

Blencowe, Lancet 2012
• GESTATIONAL AGE:
  – Term: $\geq 37$ wks
  – Moderate to late preterm: 32 to $<37$ wks
  – Very preterm: 28 to $<32$ wks
  – Extremely preterm: $<28$ wks
• **BIRTH WEIGHT:**
  - Low birth weight (LBW):
    <2500 g (5lbs 8oz)
  - Very low birth weight (VLBW):
    <1500 g (3lb 5oz)
  - Extremely low birth weight (ELBW):
    <1000 g (2lbs 3oz)
The First US Neonatal Care Unit

• 1904: Dr. Martin Couney and the Coney Island “Child Incubator Exhibit”
“Growing Pains” in Neonatal Care

• 1930s: Routine use of oxygen for cyanotic infants
• 1960s: First NICUs opened, ventilators in infants with Respiratory Distress Syndrome
Modern Neonatal Care

- 1980s: Initial trials of surfactant
- 1990s: Routine use of surfactant, antenatal steroids, antenatal antibiotics

Vincent, born at 31 wks
Felix, born at 24 wks
Karine, born at 28 wks
Lexiani, born at 25 wks

“Les Premes”
RedM Photography by Red Méthot
https://www.facebook.com/pg/RedMPhoto/photos/?tab=album&album_id=679320625546362
Advances in Neonatal Care Improve Mortality

NICHD Neonatal Research Network - 1986

Mortality

Percent Mortality

501-750 g
751-1000 g
1001-1500 g
Overall

0 10 20 30 40 50 60 70

Adapted from: Fanaroff, Seminars in Perinatology 2003
Major Neonatal Comorbidities: Bronchopulmonary Dysplasia

- **BPD:**
  - Persistent oxygen requirement inappropriate for the GA
  - Arrest in alveolar and vascular development

38 wk infant, non-respiratory death
24 wk stillborn infant
8 mo with BPD, born at 28 wks

Thomas, born at 23 wks
“Les Premes” Collection

Coalson, Seminars in Neonatology 2003
Premature Birth Is a Risk Factor of Neonatal Pulmonary Vascular Morbidity

Adults Born Premature Demonstrate Poorer Respiratory Outcomes

- Lower FEV$_1$ and FEV$_{25-75\%}$
- Increased respiratory symptoms
- Increased airway obstruction/bronchial reactivity
- Reduced diffusing capacity
- Reduced exercise tolerance

- LACKING data on long term pulmonary vascular health

Vrijlandt, AJRCCM 2006.
Gough, CHEST 2012.
Islam, AJRCCM 2015.
Crump, Pediatrics 2011.
Alveolar and Vascular Development are Integrally Linked
Preterm Birth May Limit Adult Pulmonary Vascular Endowment

TIME
Fetal Neonatal Childhood Adulthood

Disrupted Vascular Development
Risk Factors:
- Prenatal
- Genetic
- Epigenetic
- Environmental

Secondary Insults
Potential Insults:
- Tobacco
- Hypoxia
- Infection
- Toxins

Normal Vascular Development and Aging

Disrupted Vascular Development Leads to Decreased Adult Pulmonary Vascular Endowment

Decreased Vascular Development Leads to Increased Susceptibility to Secondary Insults

Goss, Pulmonary Circ 2017.
Right Ventricular Systolic Dysfunction In Young Adults Born Preterm

Cardiac MRI in 102 adults born preterm
Avg GA 30.3 wks; Assessed at 25.1 yr (23-28)
Premature Birth Increases Risk for Pulmonary Hypertension

Case control study of adults in the Swedish Pulmonary Arterial Hypertension Registry

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>p-Value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>p-Value</td>
<td>Lower</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td>26.01</td>
<td>&lt;0.0001</td>
<td>7.26</td>
</tr>
<tr>
<td>Female gender</td>
<td>3.45</td>
<td>0.0002</td>
<td>1.78</td>
</tr>
<tr>
<td>Gestational age ≤ 36 weeks</td>
<td>4.85</td>
<td>0.0047</td>
<td>1.59</td>
</tr>
</tbody>
</table>
Long-term Effects of Premature Birth on the Pulmonary Vasculature?

- **Newborn Lung Project Cohort**
  - Neonates enrolled at birth from 6 NICUs in Wisconsin and Iowa
  - Years 1988-1990
  - Weight ≤ 1500 g
  - Average gestational age 28 wks

- **Healthy controls**

- **All subjects free from adult cardiopulmonary disease**

Long-term Effects of Premature Birth on the Pulmonary Vasculature?

- **Visit 1:**
  - Screening: PFT, VO2 Max (normoxia/hypoxia)
- **Visit 2:**
  - Exercise at 70% $P_{\text{Max}}$ during cardiac MRI
- **Visit 3:**
  - Exercise at 70% $P_{\text{Max}}$ during right heart cath

Rest - Exercise
Normoxia - Hypoxia
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Term</th>
<th>Preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects (male)</strong></td>
<td>10 (7)</td>
<td>11 (5)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>25.8 ± 0.8</td>
<td>26.9 ± 1.1*</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>72.9 ± 9.8</td>
<td>69.4 ± 13.3</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td>1.8 ± 0.1</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td><strong>BMI (m²)</strong></td>
<td>23.3 ± 1.6</td>
<td>23.4 ± 3.2</td>
</tr>
<tr>
<td><strong>Pulmonary function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>4.4 ± 1.0</td>
<td>3.7±/-0.7</td>
</tr>
<tr>
<td>FEV1 % pred</td>
<td>101 ± 17</td>
<td>99 ± 21</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>5.4 ± 1.1</td>
<td>4.6 ± 0.8</td>
</tr>
<tr>
<td>FVC % pred</td>
<td>108 ± 11</td>
<td>107 ± 19</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>0.9 ± 0.3</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>DL_{CO} (ml/min/Torr)</td>
<td>31.0 ± 7.0</td>
<td>23.9 ± 4.2*</td>
</tr>
<tr>
<td>DL_{CO} % pred</td>
<td>106 ± 16</td>
<td>90 ± 1*</td>
</tr>
<tr>
<td>DL_{CO} / VA (ml/min/Torr/L)</td>
<td>5.2 ± 0.6</td>
<td>4.5 ± 0.5*</td>
</tr>
<tr>
<td>DL_{CO} / VA %pred</td>
<td>113 ± 13</td>
<td>96 ± 11*</td>
</tr>
<tr>
<td><strong>Exercise test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO_{2peak} (ml/min/kg)</td>
<td>54.4 ± 17.1</td>
<td>34.4 ± 6.6*</td>
</tr>
<tr>
<td>P_{max} (watt)</td>
<td>246 ± 45</td>
<td>184 ± 41*</td>
</tr>
<tr>
<td>70% P_{max} (watt)</td>
<td>179 ± 27</td>
<td>134 ± 23*</td>
</tr>
</tbody>
</table>
## Neonatal Characteristics

<table>
<thead>
<tr>
<th>Neonatal Characteristics (n=11)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>28.2 ± 2.8</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1071 ± 310.4</td>
</tr>
<tr>
<td>Delivered by C-section (n)</td>
<td>9</td>
</tr>
<tr>
<td>Singleton/multiple</td>
<td>5/6</td>
</tr>
<tr>
<td>Received antenatal steroids</td>
<td>0</td>
</tr>
<tr>
<td>Intubation at 24 hrs. (n)</td>
<td>9</td>
</tr>
<tr>
<td>Received surfactant (n)</td>
<td>4</td>
</tr>
<tr>
<td>Days on mechanical ventilation</td>
<td>16.6 ± 25.1</td>
</tr>
<tr>
<td>Days on oxygen</td>
<td>96.3 ± 159.7</td>
</tr>
<tr>
<td>Days in the NICU</td>
<td>63.8 ± 32.0</td>
</tr>
<tr>
<td>BPD diagnosis (n)</td>
<td>5</td>
</tr>
<tr>
<td>Persistent PDA (n)</td>
<td>8</td>
</tr>
<tr>
<td>Acute pulmonary complications (n)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Diagnosis of PH by echo in the NICU</strong></td>
<td>0</td>
</tr>
<tr>
<td>Discharge home on supplemental oxygen (n)</td>
<td>5</td>
</tr>
</tbody>
</table>
Adults Born Premature Have Elevated Resting Pulmonary Pressures

Arij Beshish, MBBCh

Systolic PAP Rest

Mean PAP Rest

Diastolic PAP Rest

*p=0.02

*p=0.04

Beshish, AJRCCM, in revision
Neonatal Days on Ventilatory Support is Strongest Predictor of Adult PAP

Arij Beshish, MBBCh

Beshish, AJRCCM, in revision
Adults Born Premature Have a Stiffer Pulmonary Vascular Bed
Exercise Reveals Decreased Pulmonary Vascular Recruitability

Arij Beshish, MBCh

Mean PAP Response to Exercise

Total Pulmonary Resistance Response to Exercise

mPAP (mmHg)

TPVR (mmHg/L/min)

Rest Exercise

Term

Preterm

Beshish, AJRCCM, in revision
Adults Born Premature Unable to Augment Stroke Volume During Exercise

Heart Rate
Response to Exercise

Stroke Volume Index
Response to Exercise

Cardiac Index
Response to Exercise

- SVI P=0.04

Term
Preterm

Rest Exercise

Beshish, AJRCCM, in revision
Smaller, Less Efficient RV in Adults Born Premature

Arij Beshish, MBBCh
Cardiac Flow Is Less Laminar in Adults Born Preterm

Term

Male, GA 40 wks
PA 23/10 (mPAP 15)

Preterm

Male, GA 25 wks
PA 30/19 (mPAP 23)
RV Filling Vortex Is Less Structured in Adults Born Preterm
Total kinetic energy in the RV was normalized by each subject’s stroke volume to evaluate energetic efficiency.
Adults Born Premature Demonstrate Impaired Heart Rate Recovery

Heart Rate Recovery (absolute)

Heart Rate Recovery % max

p = 0.03

p = 0.001

Kristin Haraldsdottir, MS

Haraldsdottir, JAP, in revision
Adults Born Premature Demonstrate Impaired Heart Rate Recovery

Kristin Haraldsdottir, MS

Haraldsdottir, JAP, in revision
Adolescents Born Preterm Appear to Have Similar Cardiac Dysfunction

Kristin Haraldsdottir, MS

Heart rate recovery

SVi

SVi MRI

Term
Preterm

* **
 Adults born premature have:
  – Mild elevations in pulmonary arterial pressure
  – Stiffer pulmonary vasculature
  – Impaired cardiac response to exercise (SV limitation)
    • Also seen in adolescent population
  – Impaired heart rate recovery after maximal exercise
Premature Birth Associated with a Markedly Increased Risk for Heart Failure

**CENTRAL ILLUSTRATION:** Risk of HF in Childhood and Young Adult Age in Relation to Gestational Age at Birth

- **37+ weeks**: 1.00 Reference
- **32-36 weeks**: 1.36 (0.87-2.13)
- **28-31 weeks**: 3.58 (1.57-8.14)
- **<28 weeks**: 17.0 (7.96-36.3)

Why such a marked increase risk for heart failure?
Right ventricular dysfunction out of proportion to degree of pulmonary vascular disease?
Animal Models of Chronic Lung Disease of Prematurity

Relevant for cardiac development as well?
Timing of cardiac binucleation
Human: 32 weeks gestation
Rat: PND 4
Postnatal Hyperoxia Exposure in Rats Recapitulates the known RV-PV Phenotype in Humans

**RV Hypertrophy**
- Normoxia: N x-M, N x-F
- Hyperoxia: H x-M, H x-F
  - RV/(LV+S)
  - p<0.001, p<0.01, p=0.06

**Cardiac Output**
- Normoxia: N x-M, N x-F
- Hyperoxia: H x-M, H x-F
  - CO (mL/min)
  - p<0.001, p<0.01

**RV Ejection Fraction**
- Normoxia: N x-M, N x-F
- Hyperoxia: H x-M, H x-F
  - Ejection Fraction (%)
  - p=0.01, p<0.01

**RV Systolic Pressure**
- Normoxia: N x-M, N x-F
- Hyperoxia: H x-M, H x-F
  - Pressure (mmHg)
  - p<0.001, p=0.005

Goss, AJRCMB 2017.
Postnatal Hyperoxia Exposure in Rats Results in RV Dysfunction and RV-PV Uncoupling

![Graphs showing ESPVR (Ees), Arterial Elastance (Ea), and Ventriculovascular Coupling (Ees/Ea)]

- ESPVR (Ees): Normoxia vs. Hyperoxia
  - Normoxia: White bars
  - Hyperoxia: Black bars
  - Significance: p=0.04

- Arterial Elastance (Ea)
  - Normoxia: White bars
  - Hyperoxia: Black bars
  - Significance: p=0.01

- Ventriculovascular Coupling (Ees/Ea)
  - Normoxia: White bars
  - Hyperoxia: Black bars
  - Significance: p<0.01

Goss, AJRCMB 2017.
RV Dysfunction is “Out of Proportion” to a Mild Chronic Pressure Overload State

- Adaptive RV hypertrophy gene expression persists
  - ↑ VEGF and Apelin, ↓ Hexokinase 1
- Absence of fibrosis or impaired autophagy
- BUT appear to have increased mitochondrial dysregulation
  - Increase in RV mitochondrial number
  - Decreased mitochondrial biogenesis
  - Evidence of mitochondrial DNA damage
  - Mitochondrial dysfunction not typical of rat PAB models

Goss, AJRCMB 2017.
Neonatal Hyperoxic Lung Injury Favorably Alters Adult Right Ventricular Remodeling Response to Chronic Hypoxia Exposure

Kara N. Goss, Anthony R. Cucci, Amanda Jo Fisher, Marjorie Albrecht, Andrea L Frump, Roziya Tursunova, Yong Gao, Mary Beth Brown, Irina Petrache, Robert S. Tepper, Shawn Kristopher Ahfield, Tim Lahm

American Journal of Physiology - Lung Cellular and Molecular Physiology Published 6 February 2015 Vol. no., DOI: 10.1152/ajplung.00276.2014
Pulmonary Vascular Disease Stabilizes, Bimodal RV Dysfunction

- **Fulton Index**
  - Postnatal Age: 1, 14, 21, 90, 365
  - Values: * (significantly different)

- **RVSP**
  - Postnatal Age: 0, 21, 35, 90, 365
  - Values: * (significantly different)

- **EF**
  - Postnatal Age: 0, 21, 35, 90, 365
  - Values: * (significantly different)

* Normoxia
* Hyperoxia
Pulmonary Vascular Disease Stabilizes, Bimodal RV Dysfunction

**ESPVR**
- **Postnatal Age:** 0, 21, 35, 90, 365
- **ESPVR (mmHg/µl):**
  - 0: 3.0
  - 21: 2.0
  - 35: 1.0
  - 90: 0.5
  - 365: 0.0

**Ea**
- **Postnatal Age:** 0, 21, 35, 90, 365
- **Ea (mmHg/ml):**
  - 0: 2.0
  - 21: 1.5
  - 35: 1.0
  - 90: 0.5
  - 365: 0.0

**RV-PV Coupling**
- **Postnatal Age:** 0, 21, 35, 90, 365
- **Ees/Ea:**
  - 0: 6.0
  - 21: 4.5
  - 35: 3.0
  - 90: 2.5
  - 365: 2.0

*Statistically significant differences.*
RV Dysfunction Due to Mitochondrial Dysfunction

**Graphical Representation:**
- **Respiratory Control Ratio**
  - Different states (State 3/State 4) for respiration under normoxia and hyperoxia conditions.

**Chemical Reactions**
- **Leak:** (Glutamate+Malate)
- **Complex I (ADP Stimulated)**
- **Complex II (Succinate Stimulated)**
- **Complex IV (Asc+TMPD Stimulated)**

**Oxygen Consumption**
- **P21**, **P90**, **P365** conditions are plotted for each complex state and oxygen consumption.

**Legend:**
- **Normoxia**
- **Hyperoxia**

**Stimuliubles:**
- **Leak Resp.**
- **Comp I (ADP Stim)**
- **Comp II (Succ Stim)**
- **Comp IV (ASC-TMPD Stim)**
- **Outer mt membrane**
- **Comp I Inhibitor**
- **Comp II Inhibitor**
- **Uncoupler**
Late RV Mitochondrial Dysfunction Caused by Accumulation of mtDNA Mutations

Goss, AJRCMB 2017.
Accumulation of mtDNA Mutations Follows Increased Mitochondrial Biogenesis

**PGC1α**

**PPARα**

**TFAM**

**Polymerase Gamma**

- **Normoxia**
- **Hyperoxia**
The Barker Hypothesis: Developmental Origins of Heath and Disease

• Key concepts:
  – Predictive adaptive responses of the fetus to environmental cues
    • Mismatch between prenatal and postnatal environments

“To survive in a stressful or nutrient-poor environment, a fetus must make “choices” about how to use scarce resources in a way that maximizes the likelihood of survival in early life, even at the expense of greater susceptibility to chronic illnesses and increased mortality in adulthood.”

Wadhwa, Semin Reprod Med 2009
Summary: Right Ventricular-Pulmonary Vascular Interactions in Adults Born Preterm

• Adults born preterm have elevated resting PAP
  – Increased pulmonary vascular stiffness
  – Decreased pulmonary vascular recruitability

• RV dysfunction out of proportion to pulmonary vascular disease
  – Inability to augment stroke volume
  – RV energetically less efficient, increased work
  – Animal studies suggest impaired mitochondrial function in RV

• Bimodal RV response likely to have implications for screening
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  – Mari Palta, PhD (Newborn Lung Project)
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  – Alan McMillan, PhD (Radiology)
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  – Ruedi Braun, PhD
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