Pulmonary Hypoplasia and Postnatal Lung Growth

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Pulmonary Hypoplasia

CDH

Lung Lesion (CPAM)
PHP Enrollment by Diagnosis

<table>
<thead>
<tr>
<th>DX</th>
<th>Number Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH</td>
<td>433</td>
</tr>
<tr>
<td>CDH/GO</td>
<td>7</td>
</tr>
<tr>
<td>CDH/LL</td>
<td>23</td>
</tr>
<tr>
<td>GO</td>
<td>90</td>
</tr>
<tr>
<td>LL/GO</td>
<td>2</td>
</tr>
<tr>
<td>Lung Lesion</td>
<td>125</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>687</strong></td>
</tr>
</tbody>
</table>
Congenital Diaphragmatic Hernia

- 1:2500 – 4000 live births
- 3.3 – 3.8/10,000 total births
- 4 types
  - Posterolateral
    - ~90% of all
    - 70-90% left-sided
  - Anterolateral
  - Pars sternalis
  - Morgagni
Pulmonary Abnormalities in CDH

- Lungs physically smaller
- Fewer airway branches
- Fewer terminal units
- Decreased surfactant
- Smaller and fewer arterioles
  - Excessive smooth muscle
  - Abnormal response to $O_2$

Hislop A and Reid L. Thorax 31:450; 1976
Normal lung, 6 months

CDH, 7 months

Alveolar surface Density (cm⁻¹)
CDH: A Heterogeneous Condition

- Location of hernia
- Degree of pulmonary hypoplasia
- Other organ involvement
  - Cardiac
  - Skeletal
  - Gastrointestinal
- Associated genetic mutations
  - Chromosomal abnormalities
  - Animal models

From Kardon G et al. Dis Model Mech 10:955;2017
### Selected Genetic Mouse Models of Abnormal Diaphragm Development

<table>
<thead>
<tr>
<th>Model</th>
<th>Diaphragm Defect</th>
<th>Human Correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Met</td>
<td>Amuscular</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>COUP-TFII (Nkx 3.2 conditional model)</strong></td>
<td>Posterior hernia (no sac)</td>
<td>Cytogenetic hotspot 15q26.1-26.2 (D1H1, OMIM #142340) (syndromic)</td>
</tr>
<tr>
<td>Fog2 (Zfpm2&lt;sup&gt;III/III&lt;/sup&gt;)</td>
<td>Posterior hernia (sac), muscle patterning defect</td>
<td>de novo mutation (non-syndromic)</td>
</tr>
<tr>
<td>Gab 1</td>
<td>Amuscular</td>
<td>Unknown</td>
</tr>
<tr>
<td>*<em>Gata4 <em>/-</em></em></td>
<td>Central hernia (sac)</td>
<td>Suspected, cytogenetic hotspot 8p23.1</td>
</tr>
<tr>
<td>LOX</td>
<td>Central rupture</td>
<td>Unknown</td>
</tr>
<tr>
<td>MyoD</td>
<td>Thin, not functional</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mogen</td>
<td>Amuscular</td>
<td>Unknown</td>
</tr>
<tr>
<td>MyoR/Capsulin</td>
<td>Posterior hernia (?sac)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pax3 (Splotch)</td>
<td>Amuscular</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>RARα/RARβ2 (retinoic acid receptors)</strong></td>
<td>Compound receptor nulls have posterior hernias</td>
<td>Unknown, suspected</td>
</tr>
<tr>
<td>Slit3</td>
<td>Central midline hernia (sac)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Wt1</td>
<td>Posterior hernia</td>
<td>Syndromic</td>
</tr>
</tbody>
</table>

Morbidity at Discharge and Defect Size

Pulmonary Hypoplasia in CDH: A Two-Hit Hypothesis

• Space occupying lesion
• Embryopathy
• Combination
• ?Accelerated (catch-up) growth?
Giant Omphalocele

- Omphalocele 1 in 6,000 live births
  - Small, giant, ruptured
  - Giant contains most of liver
  - High incidence of respiratory insufficiency
# Chest Shape in Newborns with Abdominal Wall Defects

<table>
<thead>
<tr>
<th></th>
<th>Gastrochisis</th>
<th>Small Omphalocele</th>
<th>Giant Omphalocele</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (g)</td>
<td>2515 ± 573</td>
<td>3393 ± 949†</td>
<td>2863 ± 566</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>37.4 ± 3.1</td>
<td>38.9 ± 3.8</td>
<td>38.3 ± 2.6</td>
</tr>
<tr>
<td>W1/T</td>
<td>1.12 ± 0.08</td>
<td>1.13 ± 0.06</td>
<td>0.97 ± 0.07†</td>
</tr>
<tr>
<td>W2/T</td>
<td>0.71 ± 0.06</td>
<td>0.71 ± 0.07</td>
<td>0.65 ± 0.06†</td>
</tr>
<tr>
<td>((H1+H2)/2T)</td>
<td>0.68 ± 0.09</td>
<td>0.69 ± 0.06</td>
<td>0.74 ± 0.08</td>
</tr>
<tr>
<td>((Ac – Ah)/T)</td>
<td>2.55 ± 0.61</td>
<td>2.70 ± 0.51</td>
<td>2.07 ± 0.26‡</td>
</tr>
</tbody>
</table>

†P < 0.001
‡P < 0.05

**Purported Mechanism of Pulmonary Hypoplasia in GO**

Deformation Sequence:
- Intraabdominal pressure
- Absence of molding by liver
- Lateral displacement of abdominal musculature

- Narrowed chest
- Abnormal Diaphragm Development

**Impaired thoracic cage movement *in utero***

**Pulmonary Hypoplasia**
Pulmonary Hypertension in GO

• N = 54
  - 34 without PH
  - 20 with PH
    • 9 required long term therapy (sildenafil)

• PH associated with
  - Duration of mechanical ventilation
  - Requirement for tracheostomy
  - Need for bronchodilators
  - Supplemental $O_2$ at time of NICU discharge

Postnatal Alveolar Development

Reid LM. Br J Dis Chest 78:12; 1984
Pulmonary Outcomes at 1 Yr vs Support at 30d

- Any Inhaler
- ICS
- Diuretics
- O₂
- Severe V/Q Mismatch


*p<0.001
**p<0.002
Pulmonary Outcomes at 5 Yr vs Support at 30d

Standard Lung Function Testing

Flow

PEFR

FEF_{25-75}

Time

Volume

RV

Flow

Time

FEF_{25-75}

Volume

FRC

RV

TLC

VT

FVC
CDH Study Population

• n = 98 (56 males)
• 11 days – 44 months
  - 24 <37 wk GA (17 35-36 6/7 wks)
• Support
  - 2 no mechanical ventilation
  - 3 prolonged: 22.2, 25.7 and 52.8 mo
  - In remaining 93, MV 22 + 19 d
  - 53 iNO or sildenafil
  - 20 ECMO

• FVC and forced flows were lower than normal
• FEV\textsubscript{0.5}/FVC slightly reduced – 23 with FEV\textsubscript{0.5}/FVC < -1.645 Z scores

Lung Volumes


**Z scores**

| Fractional lung volumes | First study  
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>(n = 98)</td>
</tr>
<tr>
<td>TLC</td>
<td>0.439 ± 1.685*</td>
</tr>
<tr>
<td>FRC</td>
<td>3.901 ± 3.087***</td>
</tr>
<tr>
<td>RV</td>
<td>2.350 ± 2.521***</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>0.780 ± 2.336**</td>
</tr>
</tbody>
</table>

|                         | Second study  
<table>
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<tbody>
<tr>
<td></td>
<td>(n = 43)</td>
</tr>
<tr>
<td>TLC</td>
<td>0.154 ± 2.657</td>
</tr>
<tr>
<td>FRC</td>
<td>6.381 ± 4.337***</td>
</tr>
<tr>
<td>RV</td>
<td>4.523 ± 4.150***</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>1.611 ± 2.180***</td>
</tr>
</tbody>
</table>

Change in Z score from 1st to 2nd study (P-value)

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>TLC</td>
<td>−0.427 ± 2.445 (0.283)</td>
</tr>
<tr>
<td>FRC</td>
<td>2.870 ± 4.344 (&lt;0.001)</td>
</tr>
<tr>
<td>RV</td>
<td>1.922 ± 3.079 (&lt;0.001)</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>−0.190 ± 1.851 (0.525)</td>
</tr>
</tbody>
</table>
Change in Lung Function with Growth

- For every 1.0 ml/cm in healthy controls:
  - FVC increased 0.78 ml/cm
  - FRC increased 1.76 ml/cm
  - RV increased 2.5 ml/cm

Forced Expiratory Flows: GO

Lung Volumes: GO


<table>
<thead>
<tr>
<th>% Predicted</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>63.9 ± 19.6 (38-107)</td>
</tr>
<tr>
<td>FRC</td>
<td>74.1 ± 22.6 (41.0-106)</td>
</tr>
<tr>
<td>RV</td>
<td>81.9 ± 37.0 (35-138)</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>127.1 ± 35.1 (84-200)</td>
</tr>
</tbody>
</table>
Specific Conductance

Subsequent Lung Growth
Expiratory

Inspiratory

R=962 mL
L=792 mL
TLC= 1596 mL (∆=9%)
Long-Term Pulmonary Follow-up

Pulmonary Blood Flow at 2 Years

From: Weis M et al. AJR 206:1315; 2016
“New BPD”: Arrested Alveolar Development


Normal
Thin septae
Uniform fibrosis
Vascular Growth Factors and Alveolarization

Thebaud B and Abman S. Am J Respir Crit Care Med 175:978; 2007
Alveolar Development and Angiogenesis

Jakkula M et al.  
*Am J Physiol Lung Cell Physiol* 279:L600; 2000
Change in FRC and RV Over Time

- \( n = 29 \)
  - 6 persistent PAH
  - 8 PAH first study, normal second study
  - 15 never with PAH

Healy F et al.
Pediatr Pulmonol 50:672; 2015
PAH and Lung Function

- Presence of PAH resulted in
  - Normal TLC but
  - Elevated RV and FRC
  - Elevated RV/TLC and FRC/TLC
  - Lower forced expiratory flows
  - Lower sGrs

- Persistence of PAH correlated with greater changes
Long-Term Follow-up

- 26 CDH (10.2 - 16.9 yrs, X = 13.2 yrs) vs. age- and gender-matched controls

CDH Adult Survivors

How Will New Therapies Change Outcomes?

Fetal Endoluminal Tracheal Occlusion (FETO) for CDH

Next Steps: EIT

1. Healthy lung

Lung imaging: Air content

Lung function imaging: Change of air content
Left CDH, Supine
Summary

- Clinical questions regarding pulmonary parenchymal and vascular remodeling remain
  - Role of initial mutation
  - Function of initial cause of hypoplasia
- Severity of initial impairment predicts long term outcome
- Most survivors do functionally well
  - Bronchospasm/RAD
  - PAH, GERD
- Prenatal and postnatal interventions may be possible to alter the course of disease
## Effect of PAH on Lung Function

<table>
<thead>
<tr>
<th></th>
<th>Adjusted mean in no PH group (SE)</th>
<th>Difference between PH and no PH groups (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung volumes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC z-score</td>
<td>-0.506 (0.327)</td>
<td>1.070 (0.698)</td>
<td>0.1310</td>
</tr>
<tr>
<td>FRC z-score</td>
<td>1.703 (0.465)</td>
<td>3.672 (1.052)</td>
<td>0.0009</td>
</tr>
<tr>
<td>RV z-score</td>
<td>-0.264 (0.414)</td>
<td>3.709 (1.050)</td>
<td>0.0008</td>
</tr>
<tr>
<td>FRC/TLC z-score</td>
<td>1.079 (0.252)</td>
<td>1.534 (0.564)</td>
<td>0.0086</td>
</tr>
<tr>
<td>RV/TLC z-score</td>
<td>-1.790 (0.363)</td>
<td>1.843 (0.731)</td>
<td>0.0145</td>
</tr>
<tr>
<td><strong>Forced flows</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln(FVC) z-score</td>
<td>-0.014 (0.222)</td>
<td>-0.597 (0.493)</td>
<td>0.2306</td>
</tr>
<tr>
<td>ln(FEV0.5) z-score</td>
<td>-0.005 (0.225)</td>
<td>-1.345 (0.506)</td>
<td>0.0101</td>
</tr>
<tr>
<td>ln(FEV0.5/FVC) z-score</td>
<td>0.052 (0.238)</td>
<td>-1.369 (0.601)</td>
<td>0.0265</td>
</tr>
<tr>
<td>ln(FEF25–75) z-score</td>
<td>0.307 (0.277)</td>
<td>-2.046 (0.619)</td>
<td>0.0016</td>
</tr>
<tr>
<td><strong>Tidal mechanics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln(sCrsl) (ln(1/cm H2O))</td>
<td>-2.876 (0.074)</td>
<td>-0.360 (0.203)</td>
<td>0.0827</td>
</tr>
<tr>
<td>Crs/kg (ml/(cm H2O,kg))</td>
<td>1.369 (0.056)</td>
<td>-0.050 (0.172)</td>
<td>0.7730</td>
</tr>
<tr>
<td>ln(sGrsl) (ln[1/(cmH2O,sec)])</td>
<td>-1.791 (0.057)</td>
<td>-0.513 (0.170)</td>
<td>0.0042</td>
</tr>
</tbody>
</table>

SE, standard error of mean.

1 Adjusted for gender, ECMO use in the neonatal period and age at time of IPFT.