Rabbit Model of Thoracic Insufficiency Syndrome

Lessons learned

Clinical Implications

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Background

Respiration

- Normal Mechanics
- Ventilation - thoracic/abdominal excursion
- Diaphragm 85% of $\Delta V$
Normal Growth of Lung and Thorax

- Lung + Thoracic Growth Interdependent
- **Birth - age 8 years:** *Alveolarization*
  - New growth largely ceases > age 8 yrs
- **8 years - maturity:** *Alveolar hypertrophy*
  - Lung volume increases with growth of thorax until maturity

Ref: Campbell RM JBJS 20
The Growing Thorax

- Must enlarge for lung growth
  - Rib cage provides width and depth
  - Thoracic spine provides height
- Failure of thorax to grow causes extrinsic, restrictive lung disease

4 yo, 2 yr po
A/P fusion

On O2, in cor pulmonale

Normal 4 yo /o
Thoracic Insufficiency Syndrome

- Inability of thorax to support normal respiration or lung growth
- Results in post-natal pulmonary hypoplasia

Thoracic Insufficiency is *Extrinsic*, restrictive lung disease
Optimizing treatment depends on understanding the relationship between growth of the thorax and growth/development of the lung.
Aims

1. Create rabbit model for early onset scoliosis that develops pulmonary hypoplasia.
   a) Characterize the relationships between thoracic deformity vs. pulmonary growth & respiratory function

2) Use model to evaluate affect of expansion thoracoplasty on thoracic growth, pulmonary growth, and respiratory function.
Hypotheses

1. Prolonged inhibition of thoracic growth will induce pulmonary hypoplasia and respiratory insufficiency

2. Spine/chest wall deformity @ 6 wks (growing rabbit) influences lung growth and respiratory function @ 28 wks (adult rabbit)

3. Expansion thoracoplasty will promote growth of the lungs and thorax in proportion to remaining growth potential
Approach

**Compare Disease, Treatment, and Normal rabbits**

1) Anatomy of spine and thorax
2) Lung growth
3) Respiratory function
3) Regional mechanics during respiration through CT-Deformable Image Registration (CT-DIR)
### Experimental Design

<table>
<thead>
<tr>
<th>Human equivalent age</th>
<th>Normal Control (N=7)</th>
<th>Disease Control (N=10)</th>
<th>Early Treatment (N=7)</th>
<th>Late Treatment (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>3.5 weeks</td>
<td></td>
<td></td>
<td>Rib tethering surgery</td>
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<tr>
<td>6 weeks – CT, PFT’s</td>
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<tr>
<td>6 years – Computed Tomography of Thorax</td>
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<tr>
<td>5 years</td>
<td>7 weeks</td>
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<td>Rib Expansion</td>
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<td>10 weeks – CT, PFT’s</td>
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<tr>
<td>12 years</td>
<td>11 weeks</td>
<td></td>
<td>Lengthening</td>
<td>Rib Expansion</td>
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<tr>
<td>14 weeks</td>
<td>14 weeks – CT, PFT’s</td>
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<tr>
<td>Adulthood</td>
<td>28 weeks – CT, PFT’s</td>
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Rabbits skeletally mature by 28 weeks, growth decreases exponentially after 14 wks. Pulmonary development continues in healthy rabbits.
Methods: Deformity Model

Rib Tethering – 3 ½ wks old

1. Exposed right thorax

2. Tethered right ribs 3-9

3. Post-Op AP flouroscopy
Methods - Treatment

Expansion Thoracoplasty @ age 7 or 11 wks

Exposed Rib mass

Rib Expansion/Lengthening

~9 cm @ TLC

2-3 cm
Methods

Measures – Thoracic Structure

• Thoracic Deformity
  – Scoliosis, (AP projection), $\theta_S$
  – Kyphosis, (lateral projection), $\theta_K$
  – Thoracic Rotation (Transverse slice)

  – Estimation of maximal deformity angle

$$\theta_M = 2 \cdot \tan^{-1}\left(\sqrt{\tan^2(\theta_S / 2) + \tan^2(\theta_K / 2)}\right)$$
Methods

Breath-hold CT imaging

- CT scans: 6, 10, 14, & 28 weeks of age
  - Rabbits anesthetized, mechanically ventilated
  - Hyperventilated to induce apnea
  - “Breath-hold” on 3rd breath
- ETT pressure maintained @ 0, 5, 15, 25 cmH₂O

FRC 0 cm H₂O  5 cm  15 cm  TLC 25 cm H₂O
Lung Volume Measures

CT based measures

- **TLC**: Aerated lung volume @ 25 cmH$_2$O static ETT press.
- **FRC**: Aerated lung volume @ 0 cmH$_2$O static ETT press.
Calculation Lung Mass and Volume

- **Segment Lung:**
  - Based on tissue density threshold
  - Manually remove esophagus and trachea
  - Obtain total lung volume @ sequential “breath hold” pressures 0-25 cmH₂O
  - Separate left and right lungs

- **Hounsfield unit (HU) linearly related to density**
  - HU = 0 equivalent to H₂O
  - HU = -1000 equivalent to air
  - Lung tissue density equivalent water ~1g/mL Air density negligible ~0g/mL
  - \( \rho_{\text{voxel}} = 1 + (\text{HU}/1000) \)

- **Calculations:**
  - \( V_{\text{air}} = \sum_{n=1}^{N} (-\text{HU}/1000) \cdot V_{\text{pixel}} \)
  - \( M_{\text{lungs}} = \sum_{n=1}^{N} ((1 + \text{HU}/1000)) \cdot V_{\text{pixel}} \)
Methods

PFT’s – Vital Capacity

• Raised Volume Rapid Thoracoabdominal Compression (RVRTC)
  – Protocol for Infant PFT’s
  – Lungs forcefully deflated from TLC to RV

• Protocol: Anesthetized/Ventilated rabbit
  – Lungs inflated to 25 cmH₂O (TLC)
  – Thoracoabdominal air bladder rapidly raised to 60 cmH₂O
  – Expired air volume recorded (VC)
Methods

Partitioned Compliance/Elastance

- Chest wall
  \[ C_{CW} = \frac{\Delta V_L}{\Delta P_{PL}} \]

- Lung
  \[ C_L = \frac{\Delta V_L}{\Delta P_{ALV} - \Delta P_{PL}} \]

- Total Resp.
  \[ C_R = \frac{\Delta V_L}{\Delta P_{ALV}} \]

Pediatric esophageal balloon
\( \approx \) intrapleural pressure

\( \Delta P_{ALV} = \Delta P_{Endotracheal} \)

\( \Delta P_{PL} \)

Intrapleural Pressure

Atmospheric Pressure

Outward recoil of chest wall

Inward recoil of alveoli

Boston Children's Hospital Orthopedic Center

HARVARD MEDICAL S TEACHING HOSPITAL
Methods

PFT’s – Single Compartment Model

- Least squares fit in time-domain
- Pressure and flow measured at airway opening

Ref: Lauzon AM, JAP 1991
CT Deformable Image Registration (CT-DIR)

- Voxel-by-voxel trajectory of lung parenchyma mapped during inflation on each sequential set of CT images\(^1\)

- Local specific volume (\(s\text{Vol} = \frac{\Delta V}{V_0}\)) \(\sim\) strain
- Jacobian determinant of deformation field

Results: **Aim 1- Rabbit model of TIS**

- **Thoracic Volume**
- **Aerated Lung Volume and Mass**
- **Diaphragmatic Surface Area**

<table>
<thead>
<tr>
<th></th>
<th>Normal Control</th>
<th>Severe Deformity</th>
<th>Moderate Deformity</th>
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<tbody>
<tr>
<td>Thoracic Volume</td>
<td></td>
<td></td>
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<tr>
<td>Aerated Lung</td>
<td></td>
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<td></td>
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<tr>
<td>Volume and Mass</td>
<td></td>
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<tr>
<td>Diaphragmatic</td>
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<td></td>
<td></td>
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<tr>
<td>Surface Area</td>
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</table>
Aim 1 – Results

**Induced Deformity**

- Progressive spine deformity for all rib-tether rabbits
- Variability in disease model
  - Deformity, $\theta_M$, ranged from 20° to 71° by 6 wks
  - Distinction between rabbits with deformity > 50°
Unilateral Tethering induced Thoracic Deformity

Aim1 – Results

- Severe group had significant spinal deformity and increased TRA that progressed with growth
- Moderate group achieved significant spine deformity only @ 28 weeks.
Aim 1 – Results

Spinal Deformity @ 6wks Predicts: Deformity and Body Weight @ adulthood

- Spine deformity @ age 6 wks highly correlated with:
  - spine deformity ($R^2 = 0.91$, $p<0.001$) at 28 weeks
  - body mass ($R^2 = 0.83$, $p<0.001$) at 28 weeks
Lung growth inhibited by spine deformity

Aim1 – Results

- Rate of lung growth relative to rate of somatic growth (as measured by mass) significantly depressed (p<0.01) for rabbits with severe spine deformity.
Aim 1 – Results

Volume & Mass Right and Left Lung during Growth

By age 28 weeks

• **Severe Deformity:**
  - Constricted right lung
  - Mass 59% of normal
  - Volume 60% of normal
  - Left lung
  - Mass 86% of normal
  - Volume 105% of normal

• **Moderate Deformity**
  - Mass right lung less than normal
  - Hypertrophy of left lung
Aim1 – Results

Diaphragm surface area

- Surface area of diaphragm in rabbits with severe deformity 76% of normal
- Diaphragm is primary driver (piston) for mass transfer air in/out lung
Forced Vital Capacity

- FVC in rabbits with severe thoracic deformity 71% normal rabbits (p<0.01)
Partitioned Compliance

Aim 1 – Results

- V-P curves fit to exponential function:

\[ V = A - Be^{-kp} \]

- Severe deformity plateaus early = rigid thorax
- But coefficients Salazar-Knowles model not significantly different for respiratory, pulmonary, or thoracic compliance among deformity groups (broad range of “NORMAL”)
### Aim 1 – Results

**Spine Deformity @ 6 wks Predicts Pulmonary Outcomes @ 28 wks**

<table>
<thead>
<tr>
<th>Deformity (6 wks) vs.</th>
<th>Outcomes (28 wks)</th>
<th>r</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung Mass</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Right lung</td>
<td></td>
<td>-0.87</td>
<td>0.76**</td>
</tr>
<tr>
<td>- Left lung</td>
<td></td>
<td>-0.89</td>
<td>0.80***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.78</td>
<td>0.61**</td>
</tr>
<tr>
<td><strong>Total Lung Capacity</strong></td>
<td></td>
<td>-0.70</td>
<td>0.50*</td>
</tr>
<tr>
<td>- Right lung</td>
<td></td>
<td>-0.80</td>
<td>0.64**</td>
</tr>
<tr>
<td>- Left lung</td>
<td></td>
<td>-0.33</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Resp. Elastance</strong></td>
<td></td>
<td>0.91</td>
<td>0.83***</td>
</tr>
<tr>
<td><strong>FVC</strong></td>
<td></td>
<td>-0.56</td>
<td>0.31*</td>
</tr>
<tr>
<td><strong>Diaphragm S.A.</strong></td>
<td></td>
<td>-0.89</td>
<td>0.80***</td>
</tr>
</tbody>
</table>

Significance:
- *p<0.05
- **p<0.01
- ***p<0.001

Spine Deformity @ 6 wks highly and inversely correlated with pulmonary outcomes @ 28 wks:

- Lung Mass
- TLC
- Resp. Elastance
- FVC
- Diaphragm S.A.
Specific Volume (volumetric strain) varies with gravity dependent height

Gravity dependent expansion in Prone rabbit:
- initial-inspiration (0-5cmH₂O) - sVol posterior > anterior
- mid-inspiration (5-15cmH₂O) - sVol anterior > posterior (p<0.05)

Gravity accounts for 25% variability sVol as a function of height

Intrinsic mechanical properties of lung and thorax passively controls distribution of airflow that accounts for regional variation in lung expansion determined by gravity and inspiratory pressure
Aim 1 Results

**Comparison of sVol Normal vs. TIS**

- Thoracic Deformity affects Gravity dependent expansion Right and Left lung
- Dependent lung contributes more to pulmonary reserve capacity
- **This reserve capacity is diminished by thoracic deformity**
RESULTS: *Aim 2 Expansion Thoracoplasty*

Total rib expansion
Early treatment [2.7 cm] > Late [2.0 cm] (p<0.001)
Baseline Deformity Among Groups

Aim2 – Results

Spine deformity @ 6 wks inconsistent among groups
  - Late treatment less deformity than Early or Disease

Groups evaluated by Analysis of Covariance
  - Controls for initial differences in deformity among groups
Progression of spine deformity and TRA during growth

- Spine deformity of Early and Late Treatment groups was lower than Disease rabbits (p<0.01) by completion of growth.
- Spine deformity Disease rabbits greater than Normal throughout growth (p<0.01).
- TRA Normal & Treatment rabbits less than Disease @ age 10 & 14 wks.
Aim2 – Results

Progression Spine Deformity: Disease vs. Treatment

- Expansion thoracoplasty ameliorates predicted spine deformity @ 28 wks (slopes Tx groups different from Disease, p<0.01)
Changes in Lung Mass Among Groups with Growth

- For Severe-Disease rabbits, Lung mass normalized by body mass was less than Normal rabbits at all time points (p<0.05)
- Overall treatment did not significantly improve normalized lung mass
- BUT Significant gains in lung mass with treatment did occur after 14 wks.
  - Poor gain in lung mass between 10-14 wks. may reflect ill affects of surgical insult
Mass and volume of segmented left and right lung during growth for treatment and disease groups

- @ 28 weeks Early & Late Treatment groups and Severe Disease group had decreased right lung Mass and Volume vs. Normal rabbits (p<0.001)
- After 14 wks, treatment altered the trajectory of right lung growth from that of severe deformity to that of moderate deformity
Aim2 – Results

Treatment stabilized expected decline in lung growth

- Slope of Early Treatment > Disease (ANCOVA, p<0.05)
- **Tipping point** = Deformity > 45°: Lung growth early treatment > than expected for disease group
Surface Area of Diaphragm

- Expansion Thoracoplasty had little effect on surface area of diaphragm.
- Surface area diaphragm in Early and Late Treatment rabbits 80% of Normal (p<0.001).
- Severe rabbits 77% Normal (p<0.001).
Forced Vital Capacity

- Expansion
  Thoracoplasty did not improve FVC
- Mean FVC in Early rabbits was 70% of Normal (p<0.05), while Late Treatment rabbits were 86% of Normal.
- Severe-Disease rabbits 69% of Normal (p<0.01)
Aim2 – Results

Partitioned Elastance

- ↑ elastance after expansion thoracoplasty reflects persistent stiffness of the chest wall
Regional Pulmonary Volumetric strain
($\Delta V$ normalized by initial aerated lung volume, $V_0$)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Displacement</th>
<th>Specific Volume heat map</th>
<th>Regional Specific Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Disease</td>
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<td></td>
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<tr>
<td>Early Treatment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Late Treatment</td>
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</tbody>
</table>

- Treatment normalized regional strain pattern
- Restores reserve capacity that was diminished by the thoracic deformity
Aim 2 Results

sVol, Left vs. Right lung

- In Disease rabbits
  - sVol left < right lung (unexpected result)
  - 15% of variability in sVol
  - Implies mechanics of contralateral left lung are abnormal
  - ↑ residual volume in left lung with ↓ expansion related to globally rigid chest
- In Treatment group
  - sVol left ≈ right
Conclusion

Hypotheses supported:

• Unilateral rib tether induces scoliosis
• Restriction of thorax creates post-natal pulmonary hypoplasia
• Spine/chest wall deformity present @ 6 wks (in growing rabbit) influences lung volume and respiratory function @ 28 wks (in adult rabbit)
• Rabbit model with constricted hemithorax creates TIS equivalent to that seen in growing children

<table>
<thead>
<tr>
<th></th>
<th>Residual Volume (% Predicted)</th>
<th>Vital Capacity (% Predicted)</th>
<th>Cobb Angle (degrees)</th>
<th>Left:Right lung (diff. normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIS Patients</td>
<td>139 +/- 40.3</td>
<td>78.3 +/- 29.6</td>
<td>55 +/- 16.4</td>
<td>0.46 +/- 0.41</td>
</tr>
<tr>
<td>TIS Rabbits</td>
<td>303 +/- 301</td>
<td>73.6 +/- 12.9</td>
<td>41 +/- 11.1</td>
<td>0.36 +/- 0.20</td>
</tr>
</tbody>
</table>

Conclusion

• Kyphoscoliosis was corrected by expansion thoracoplasty performed early or late

• Expansion thoracoplasty performed earlier, followed by subsequent distraction of hemithorax, stabilized the decline in lung growth better than expansion thoracoplasty performed later, but does not normalize function
  – Expanded thorax remains rigid – ↓ respiratory compliance
  – Surface area of diaphragm remains smaller

• Rabbit model similar to clinical studies:
  • Improved Cobb angle
  • 1 yr post-op: ↓ %VC, ↑ % RV
  • 3 yr post-op: ↑ TLC (↑ % RV, but ↔ %VC)

Ref: ¹Mayer J. Ped. Ortho. 2008,
  ²Motoyama Spine 2006,
  ³Gollogly J. Ped. Ortho.
Thank you