# ICEOS 2014

## *The Interdependent Relationship between the Thorax and Lung: The Impact of Thoracic Deformity on Respiratory Function During Growth*

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# Disclosures

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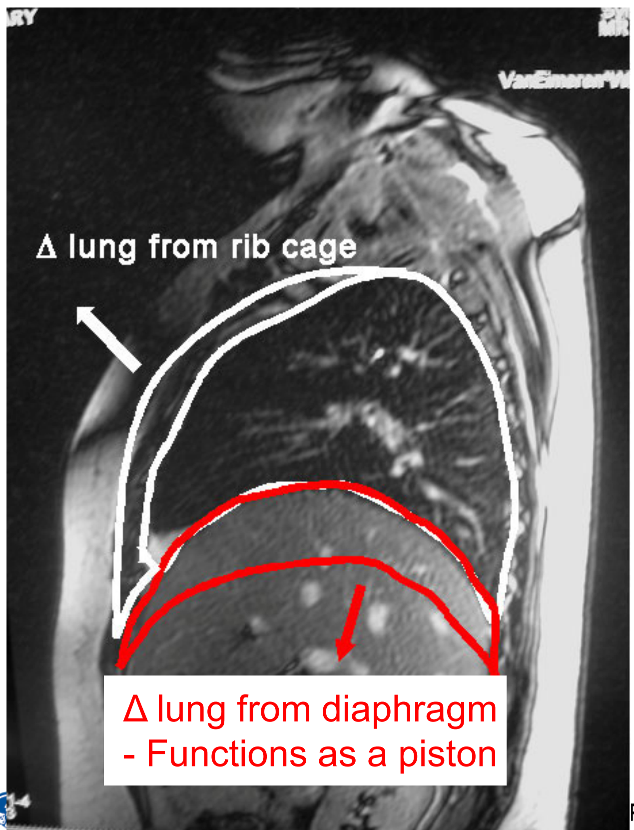
✓Chest Wall and Spinal Deformity Study Group

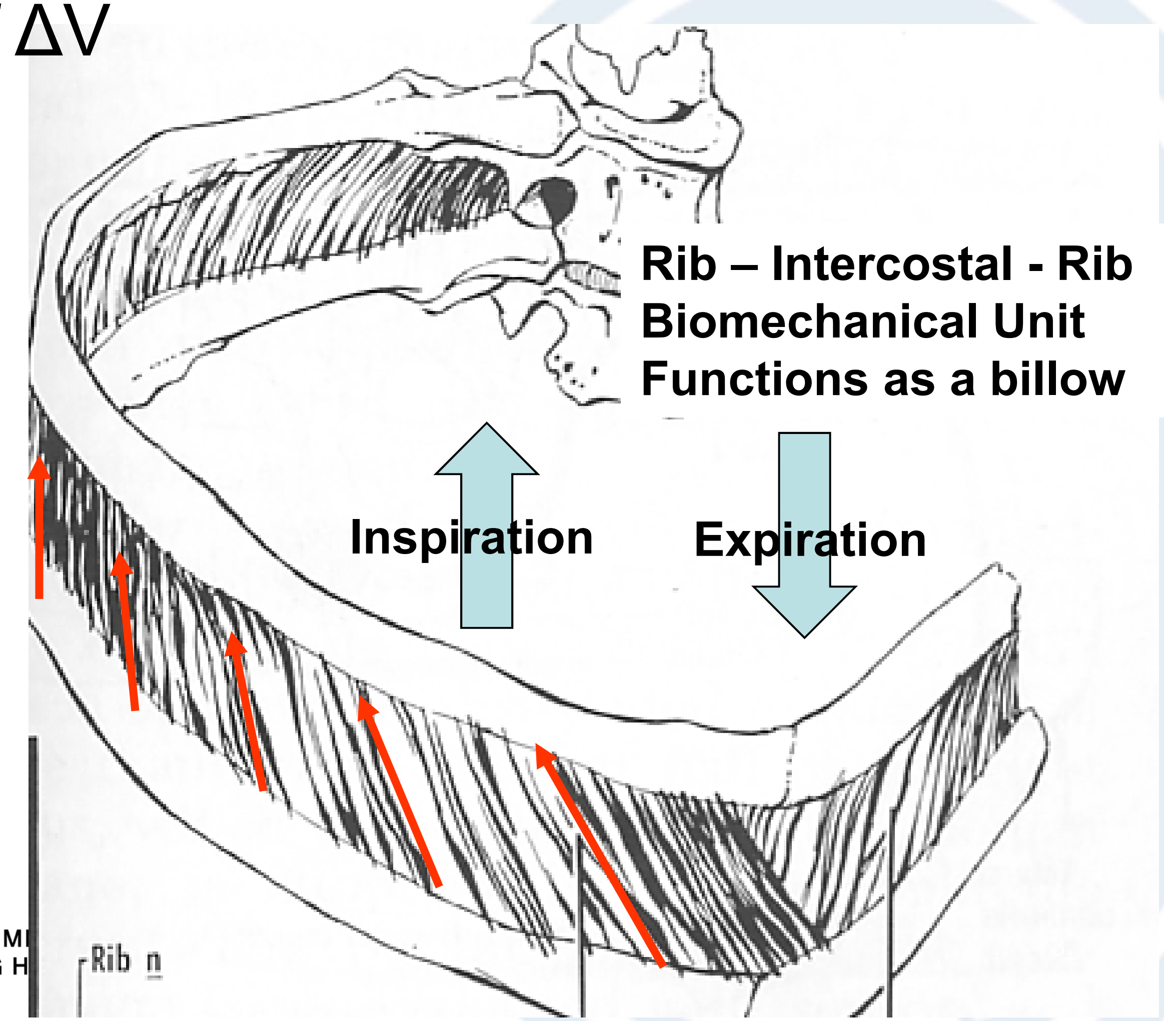
✓Synthes Spine, North America

✓NIH R21

# Respiration

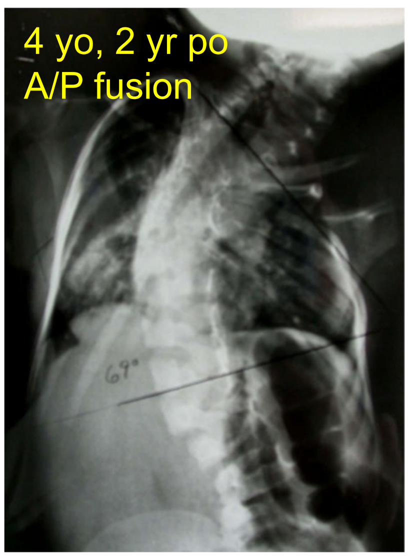
- Normal Mechanics
- Ventilation - thoracic/abdominal excursion
- Diaphragm 85% of ΔV

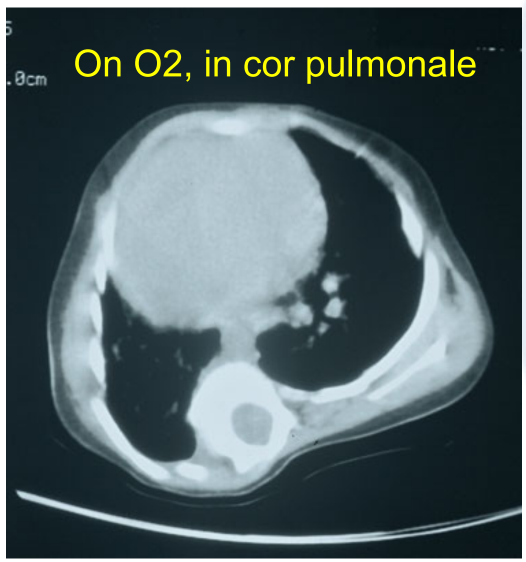


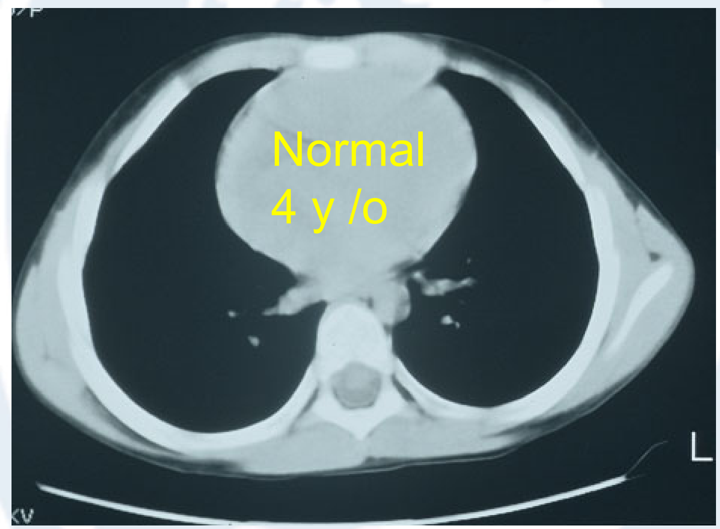



# The Growing Thorax

- **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**



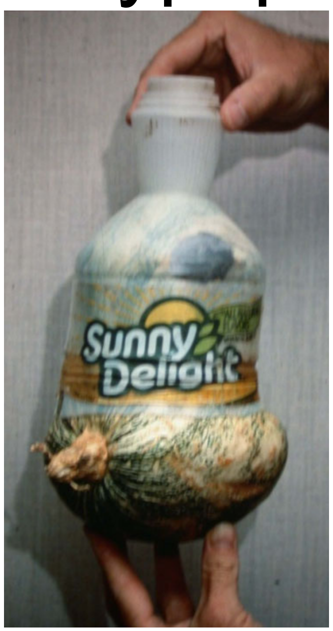



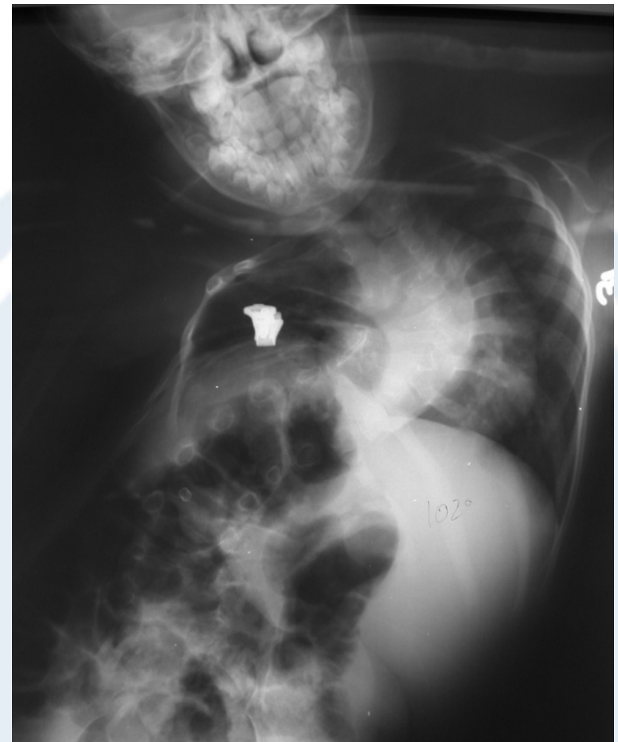
Clinical Problem

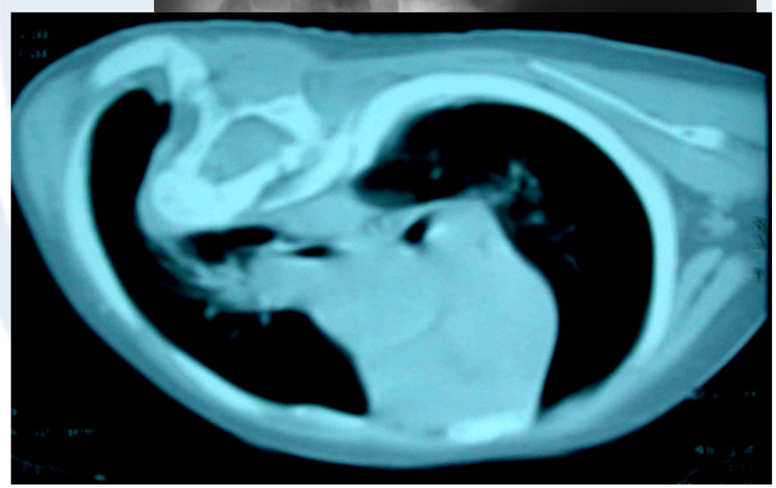
# Thoracic Insufficiency Syndrome

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




Thoracic Insufficiency is *Extrinsic*, restrictive lung disease





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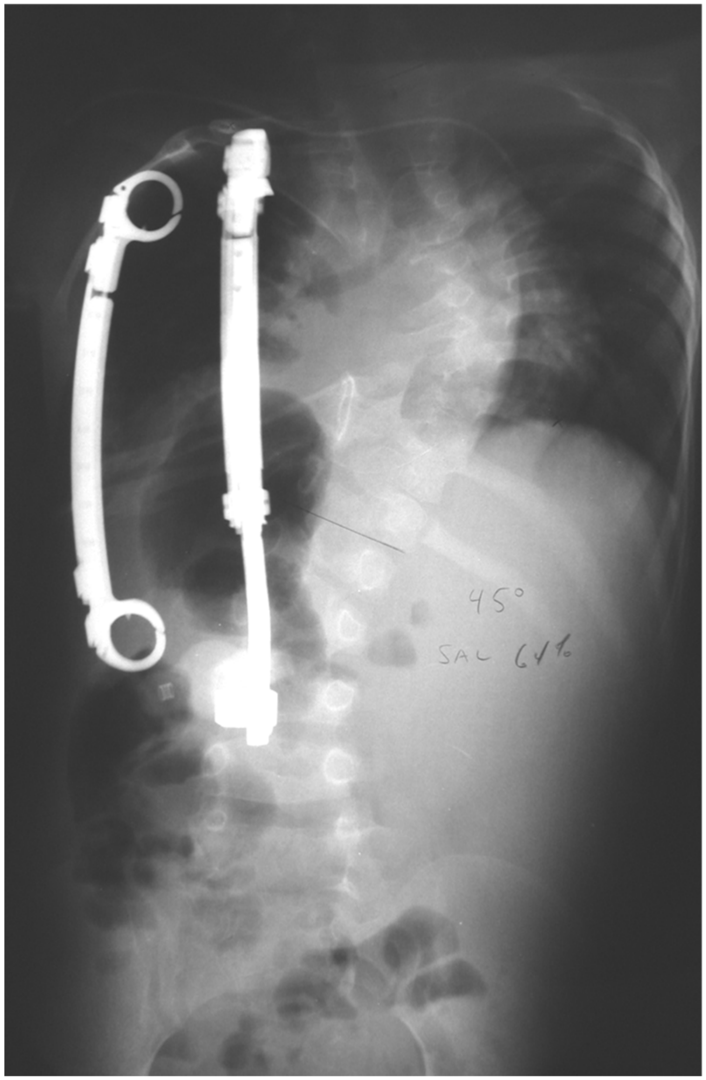
Clinical Problem

# Expansion Thoracoplasty




*Optimizing treatment depends on understanding relationship between growth of thorax and growth/development of the lung*

# Aims

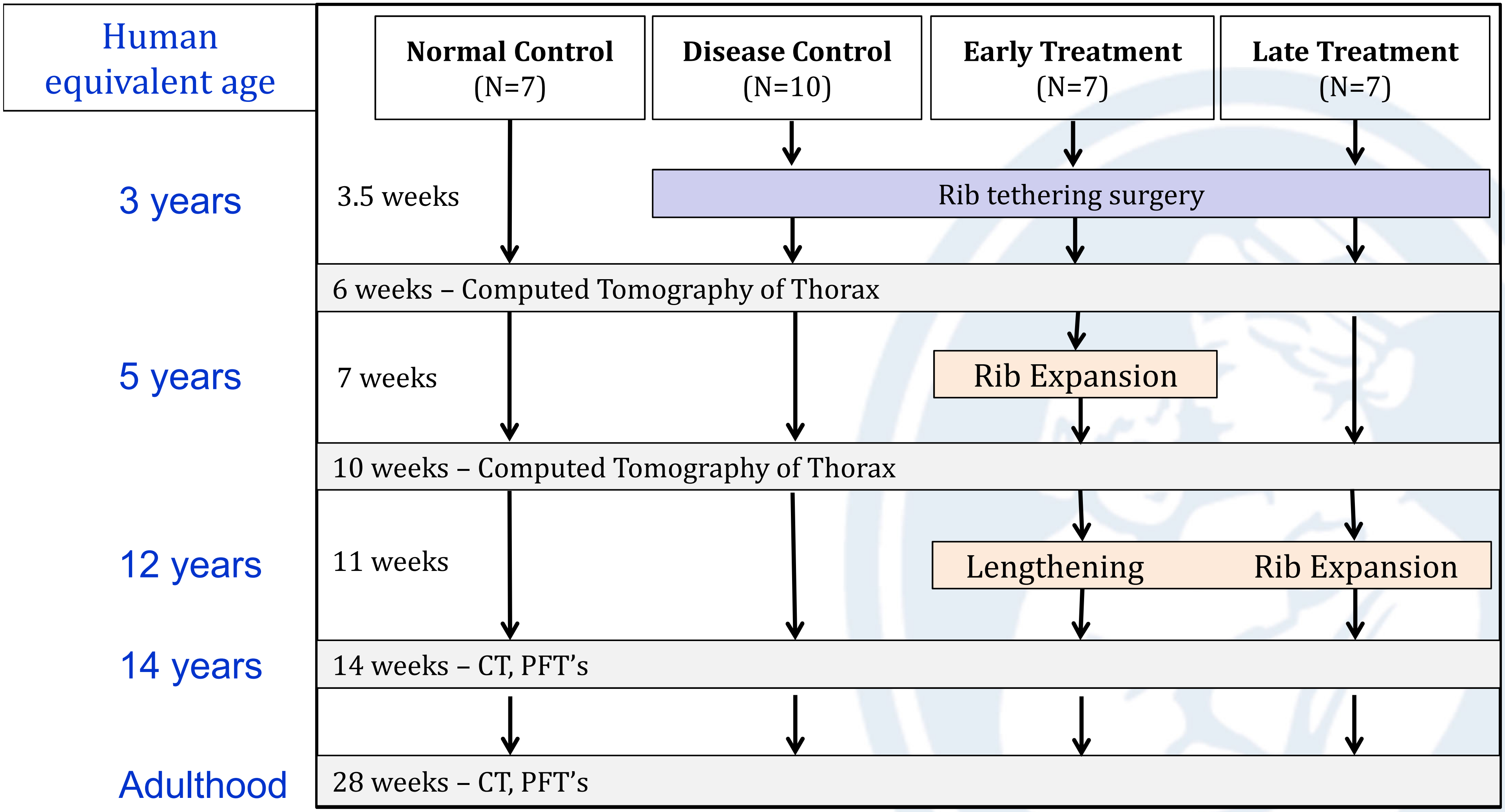
1. **Create rabbit model for early onset scoliosis that develops pulmonary hypoplasia.**
   a) Characterize the relationships between thoracic deformity vs. pulmonary growth & respiratory function

2) **Use model to evaluate effect of expansion thoracoplasty on thoracic growth, pulmonary development and respiratory function.**

# Hypotheses

1. Prolonged inhibition of thoracic growth will induce pulmonary hypoplasia and respiratory insufficiency
2. The extent of thoracic deformity in young growing rabbit influences lung growth and respiratory function in the adult rabbit
3. Expansion thoracoplasty will promote growth of the lungs and thorax in proportion to remaining growth potential

# Experimental Design

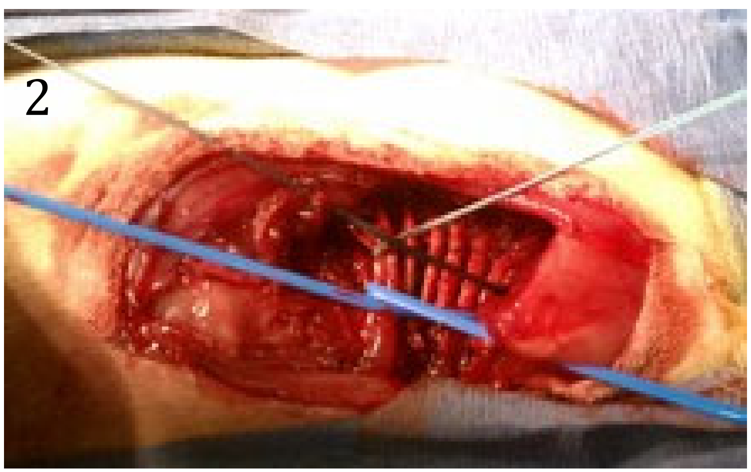



Rabbits skeletally mature by 28 weeks, growth decreases exponentially after 14 wks. Pulmonary development continues in healthy rabbits

Methods: Deformity Model

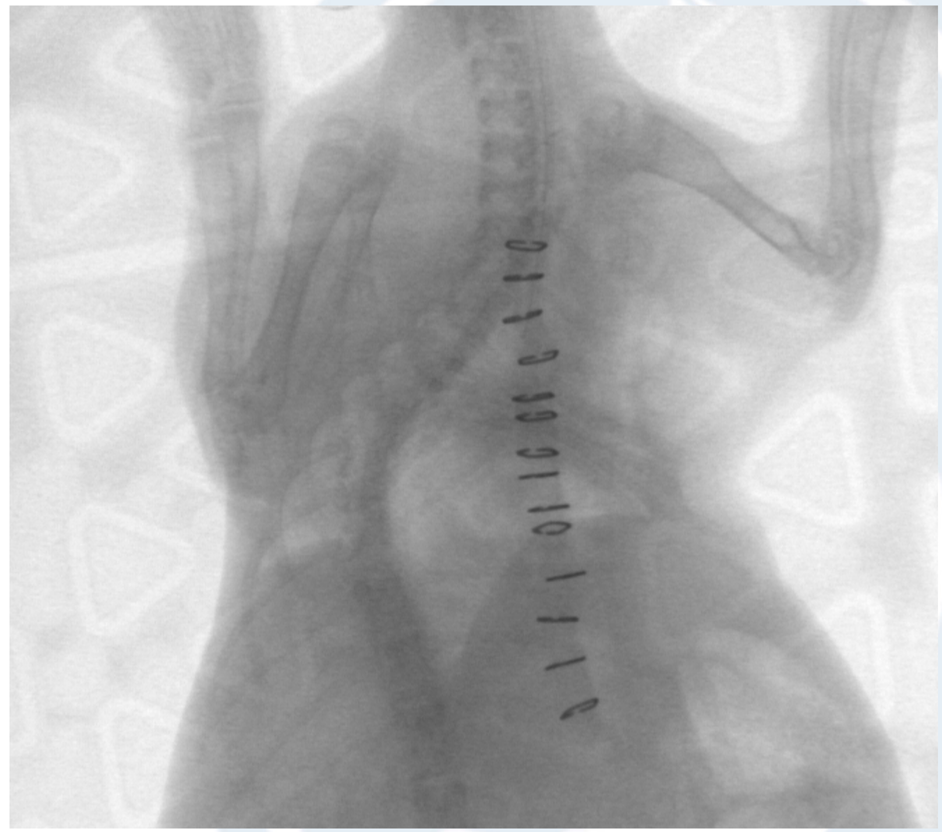
# Rib Tethering – 3 ½ wks old


Exposed right thorax




Tethered right ribs 3-9

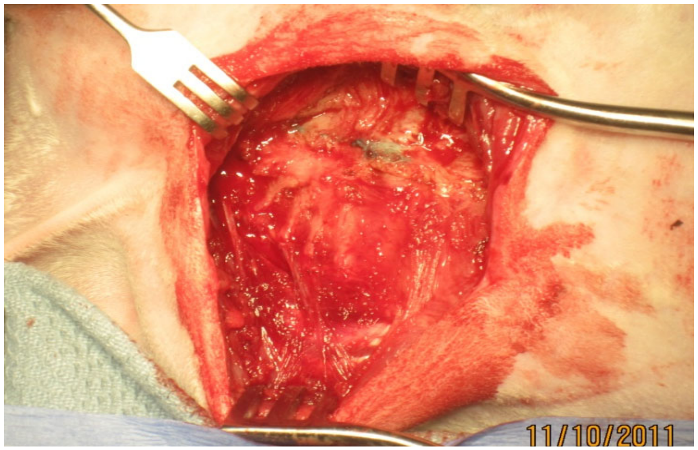
3



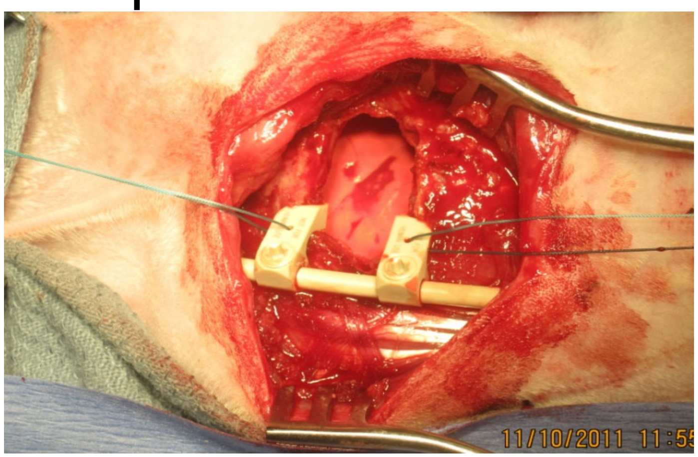
Post-Op AP X-ray

Methods - Treatment

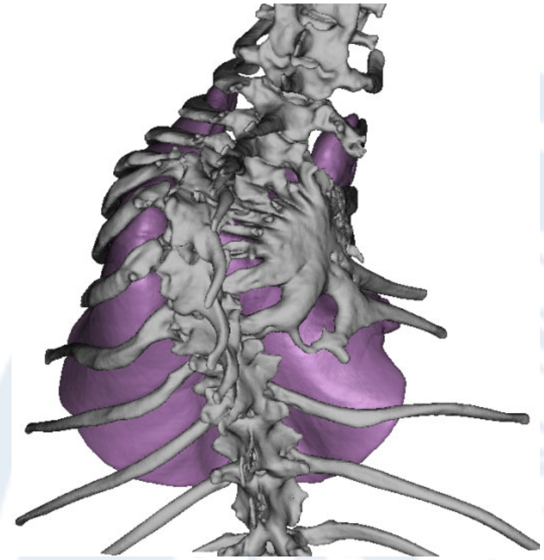
# Expansion Thoracoplasty: age 7 and/or 11 wks



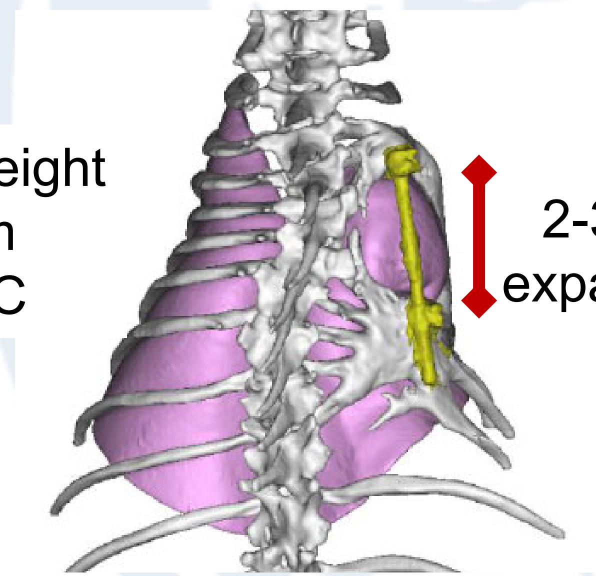

Exposed Rib mass




Rib Expansion/Lengthening



Thorax height
~9 cm
@ TLC



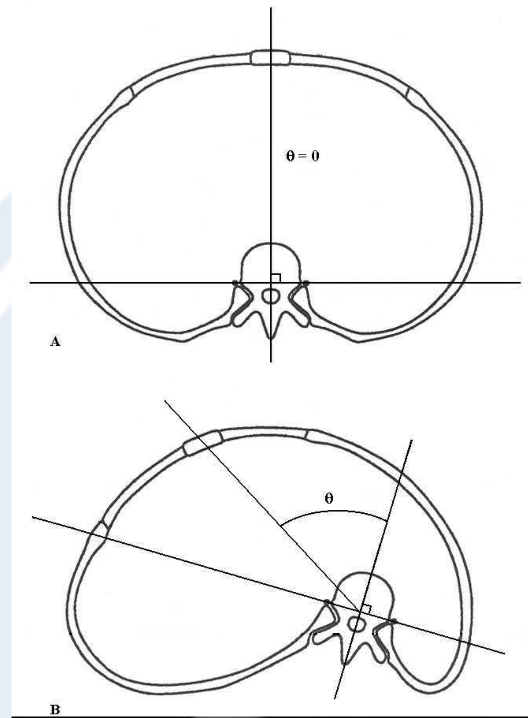
2-3 cm
expansion

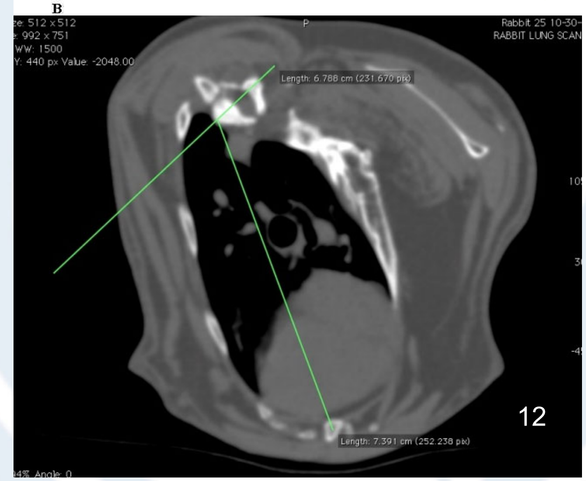
# Metrics of Thoracic Deformity

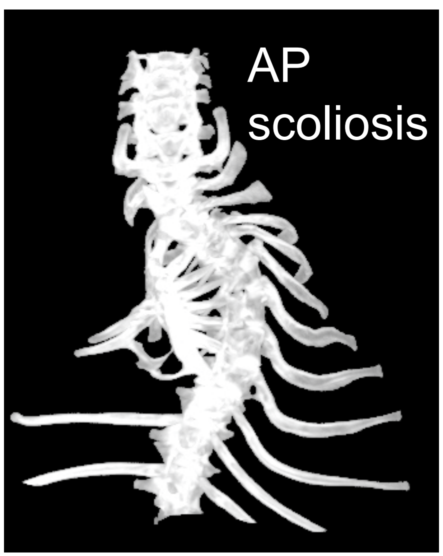
- Scoliosis, (AP projection), $\theta_S$
- Kyphosis, (lateral projection), $\theta_K$
- Thoracic Rotation (Transverse slice)

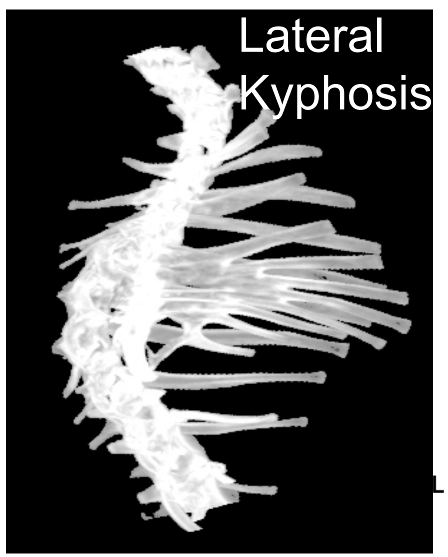
➢ Maximal deformity angle

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



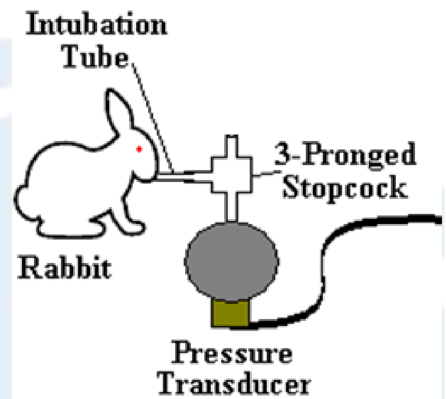


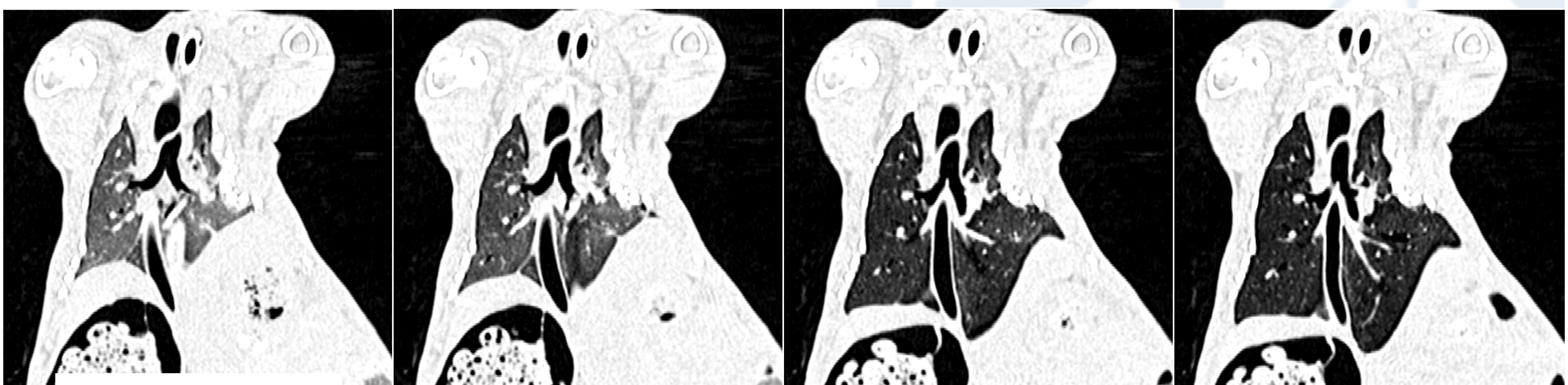



# Breath-hold CT imaging

- 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 $cmH_2O$



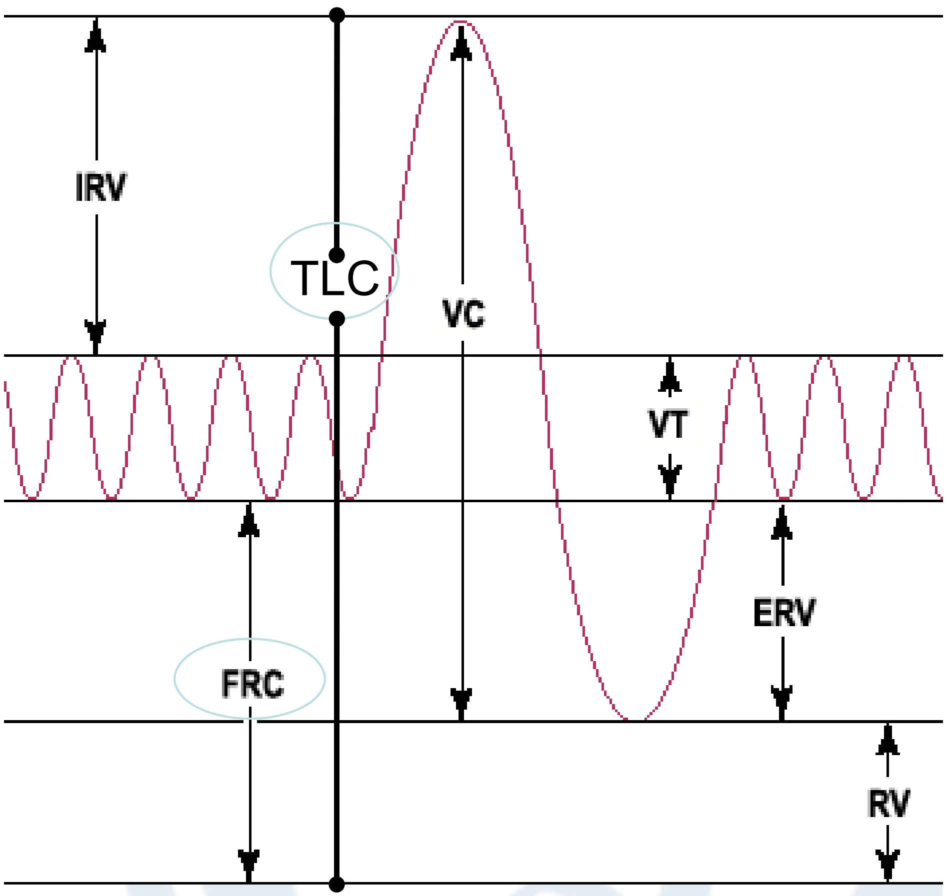



FRC 0 cm $H_2O$ | 5 cm | 15 cm | TLC 25 cm $H_2O$

# Lung Volume Measures

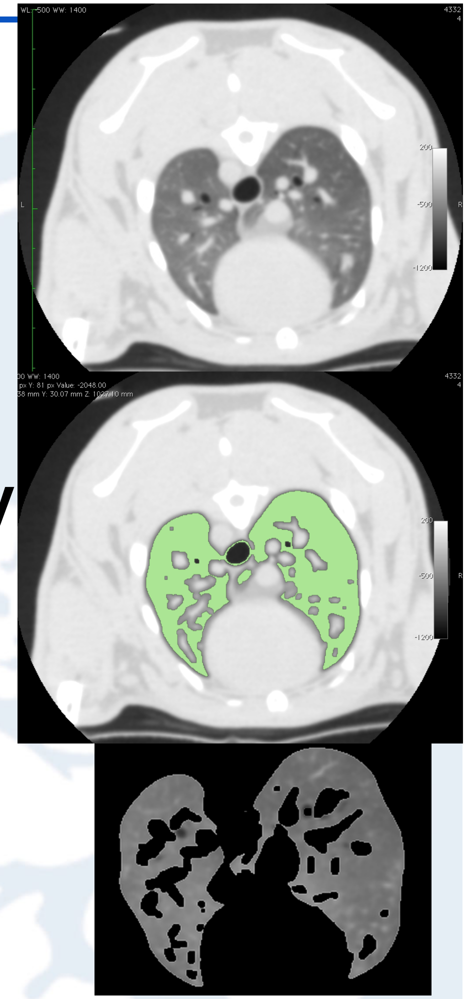
## CT based measures

- <u>TLC</u> : Aerated lung volume @ 25 $cmH_20$ static ETT press.
- <u>FRC</u> : Aerated lung volume @ 0 $cmH_2O$ static ETT press.




Respiratory Volumes

# 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 $cmH_2O$
  - Separate left and right lungs
- **Hounsfield unit(HU)linearly related to density**
  - HU = 0 equivalent to $H_2O$
  - HU = -1000 equivalent to air
  - Lung tissue density equivalent water ~1g/mL Air density negligible ~0g/mL
  - $\rho_{voxel} = 1 + (HU/1000)$
- **Calculations:**

$$V_{air} = \sum_{n=1}^{N} (-HU/1000) \cdot V_{pixel} \qquad M_{lungs} = \sum_{n=1}^{N} ((1 + HU/1000)) \cdot V_{pixel}$$

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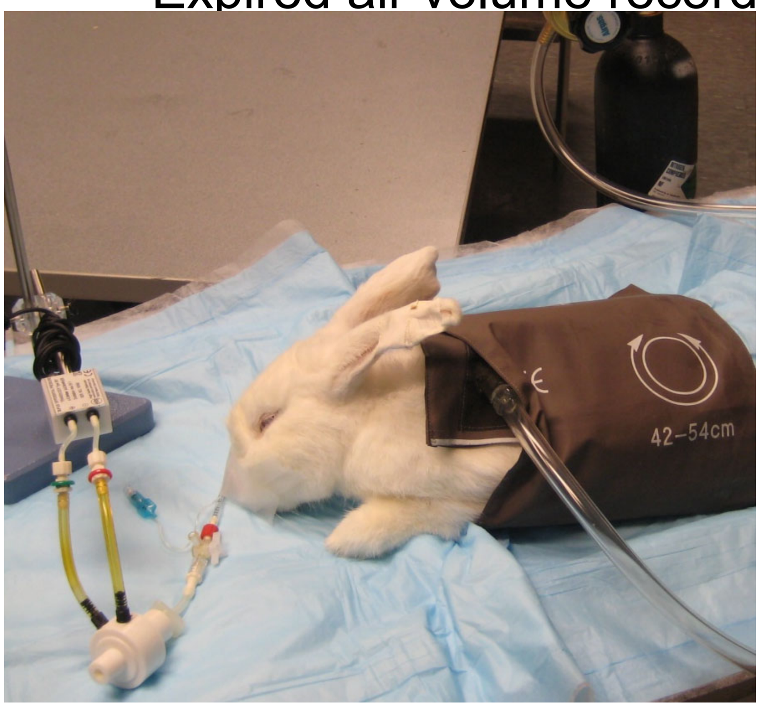
# PFT's – Vital Capacity

- **Raised Volume Rapid Thoracoabdominal Compression (RVRTC)**
  - Protocol for Infant PFT's
  - Lungs forcefully deflated from TLC to RV
- **<u>Protocol</u>: Anesthetized/Ventilated rabbit**
  - Lungs inflated to 25 $cmH_2O$ (TLC)
  - Thoracoabdominal air bladder rapidly raised to 60 $cmH_2O$
  - Expired air volume recorded (VC)

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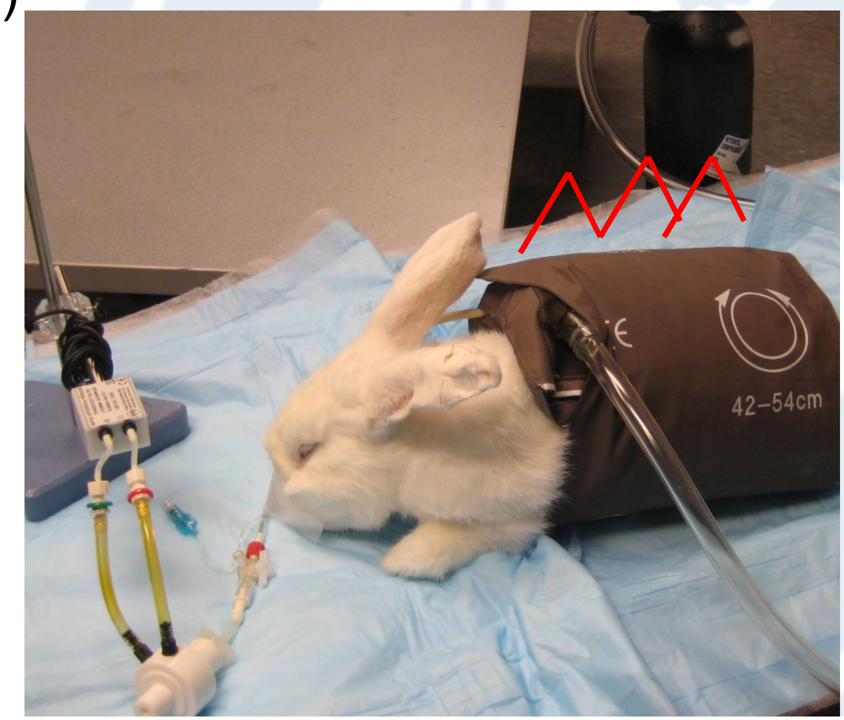
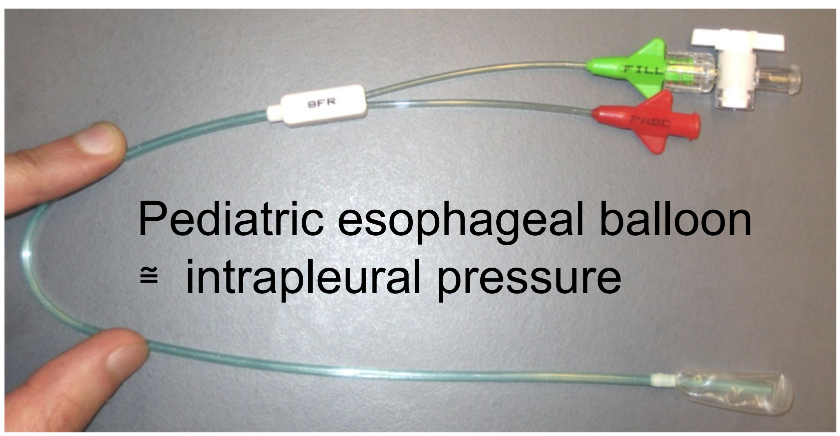
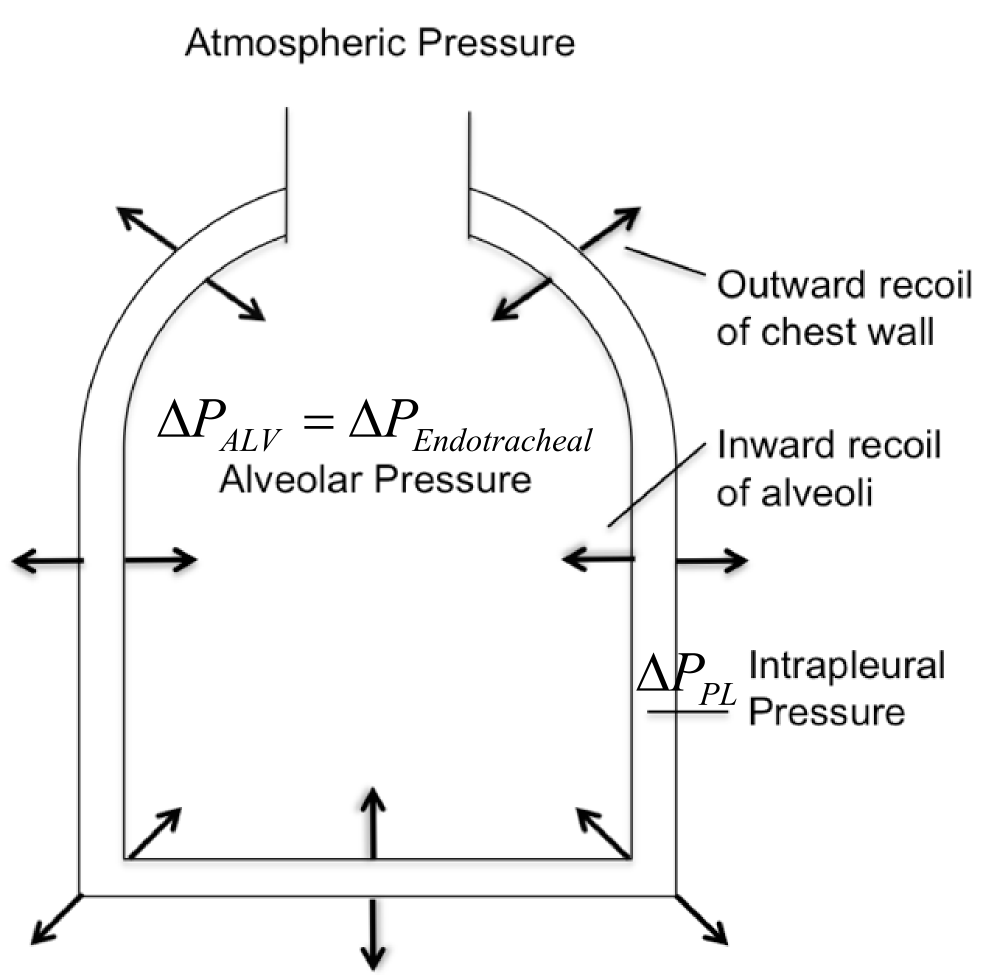


Methods

# Partitioned Compliance/Elastance

- **Chest wall** $C_{CW} = \dfrac{\Delta V_L}{\Delta P_{PL}}$
- **Lung** $C_L = \dfrac{\Delta V_L}{\Delta P_{ALV} - \Delta P_{PL}}$
- **Total Resp.** $C_R = \dfrac{\Delta V_L}{\Delta P_{ALV}}$

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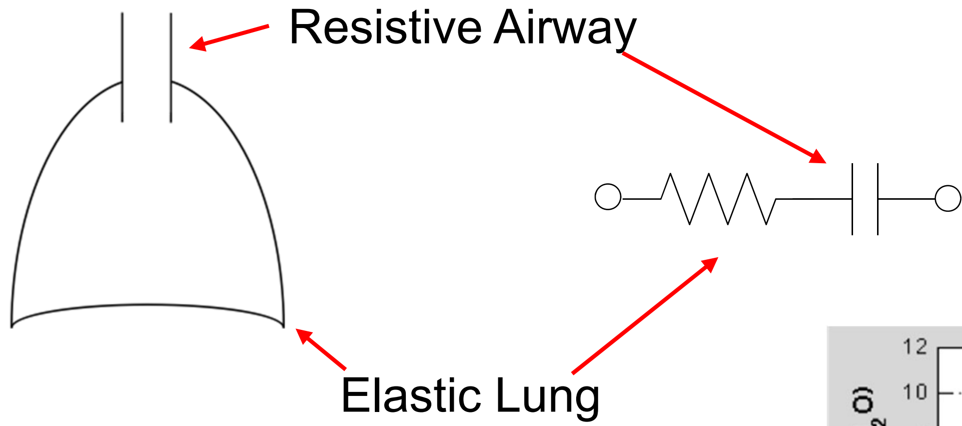
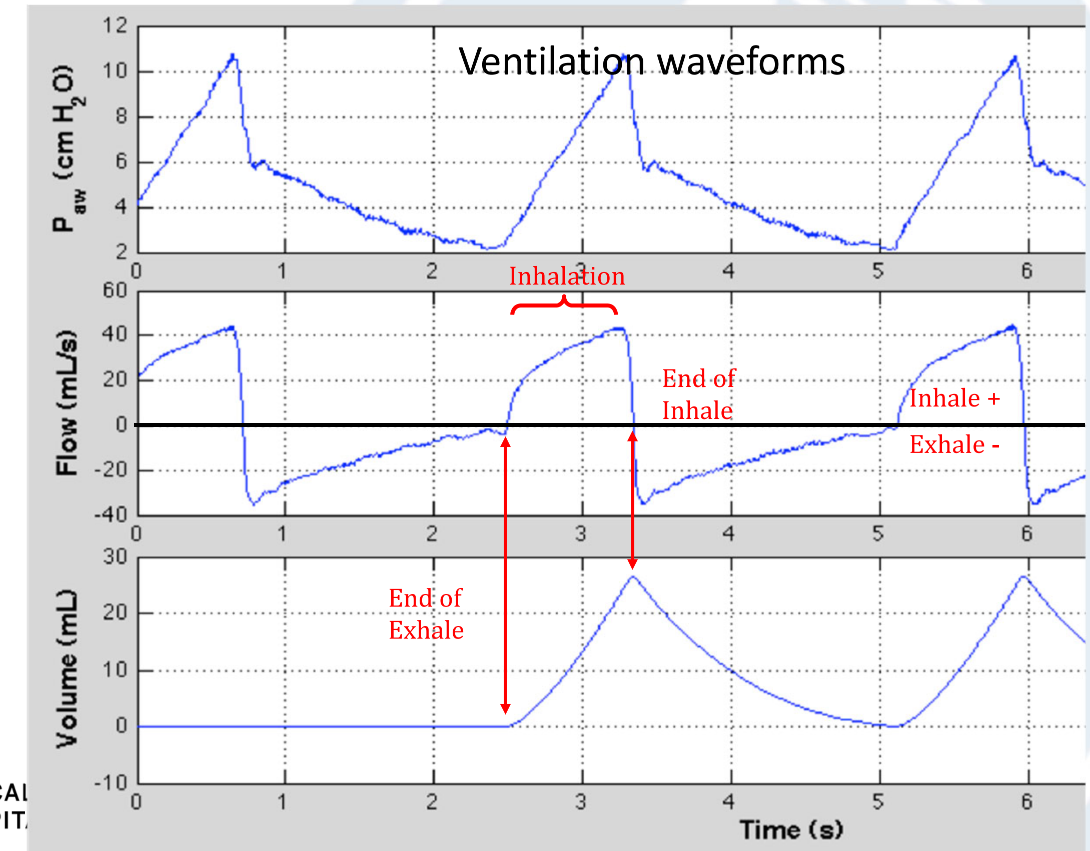
Methods

# PFT's – Single Compartment Model




$$P_{aw} = R * \dot{V} + E * V + P_0$$

Pressure ($P_{aw}$), Resistance ($R$), Flow ($\dot{V}$), Elastance ($E$), Volume ($V$), PEEP ($P_0$)




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

**Ref**: Lauzon AM, JAP 1991

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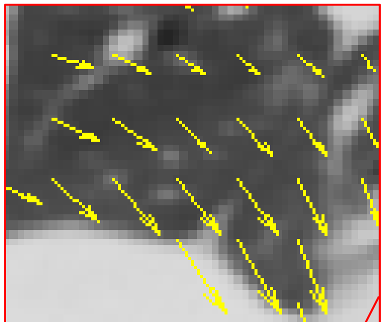
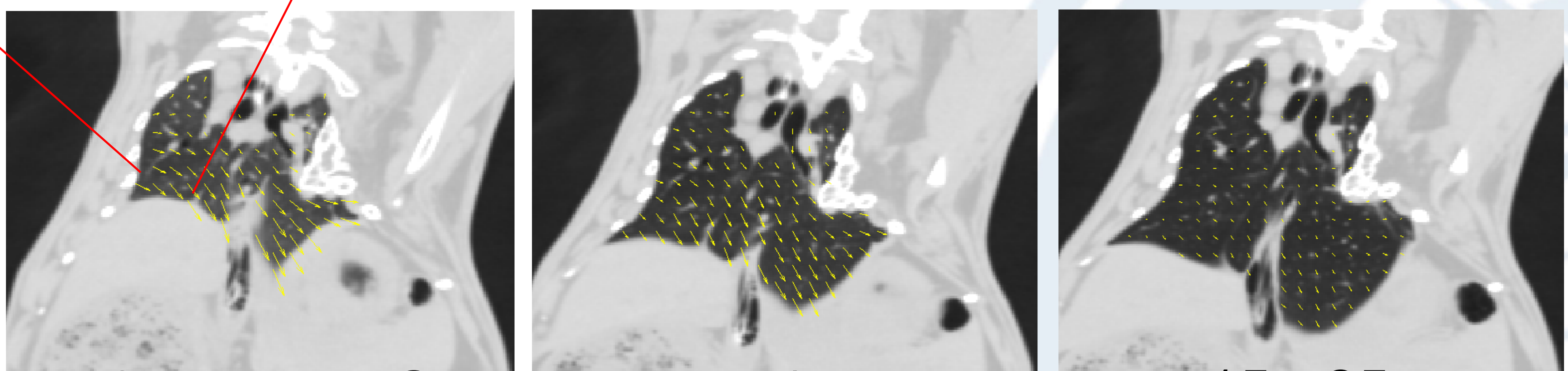
# CT Deformable Image Registration (CT-DIR)

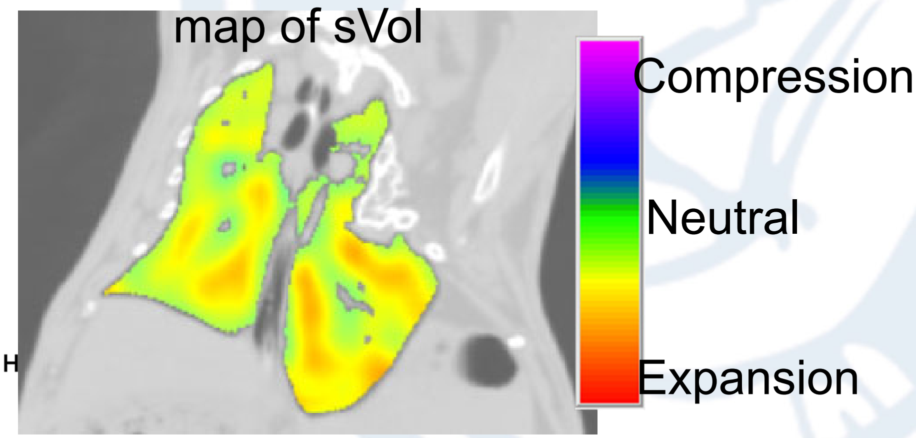


- **Voxel-by-voxel trajectory of lung parenchyma mapped during inflation on each sequential set of CT images[1]**



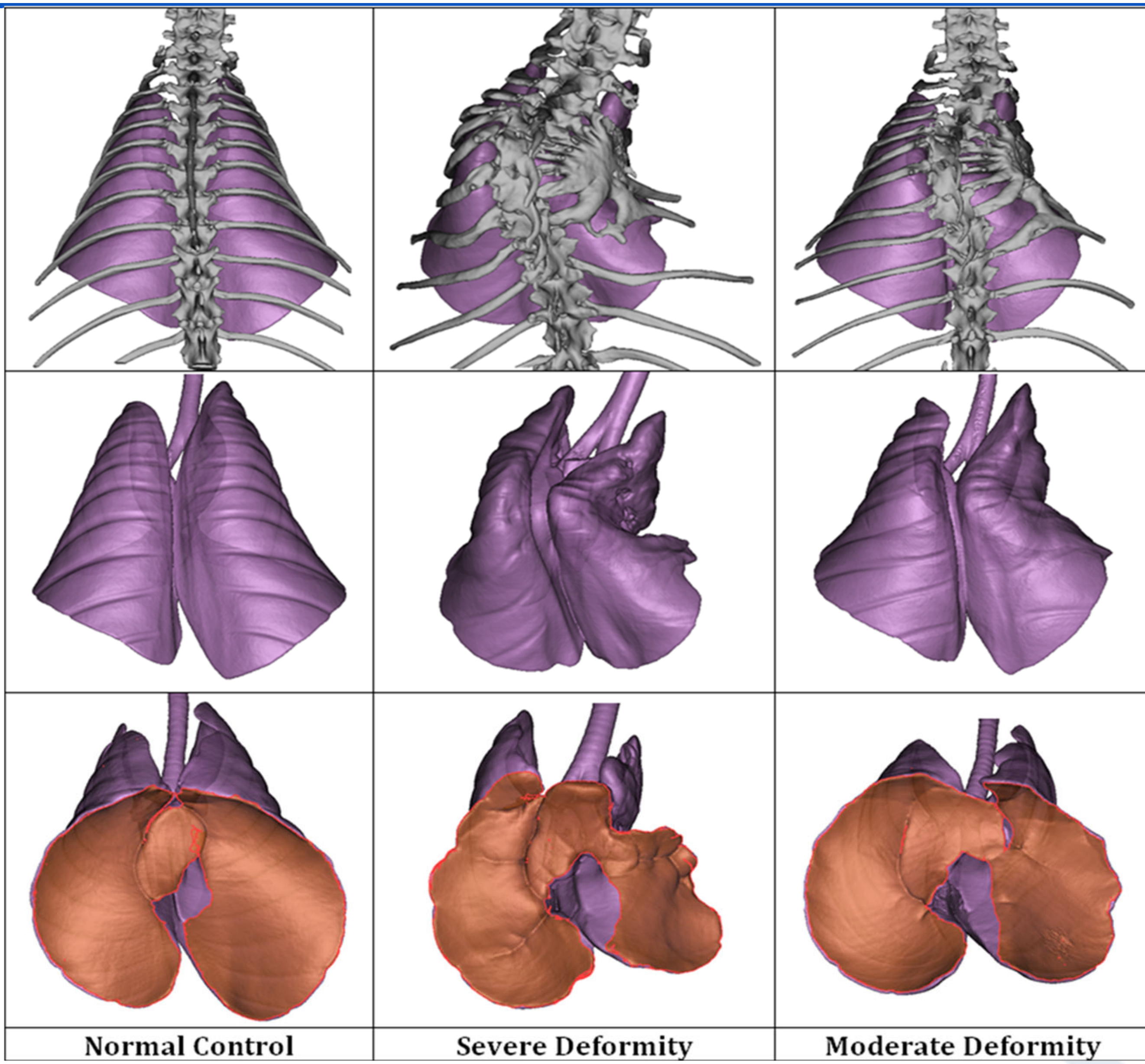
0->5cm$H_2O$ 5->15 15->25

- Local specific volume (sVol = $\Delta V / V_O$) ~ strain
- Jacobian determinant of deformation field




**Ref**: [1]Yin Y, et al.; Med. Physics **2009**

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

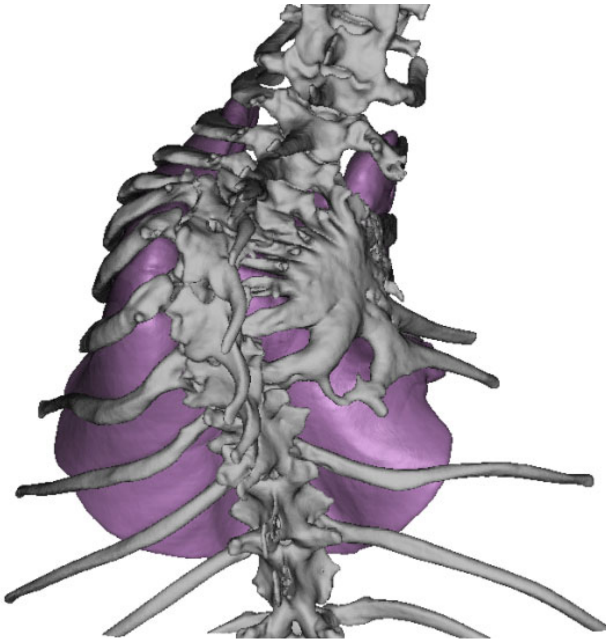


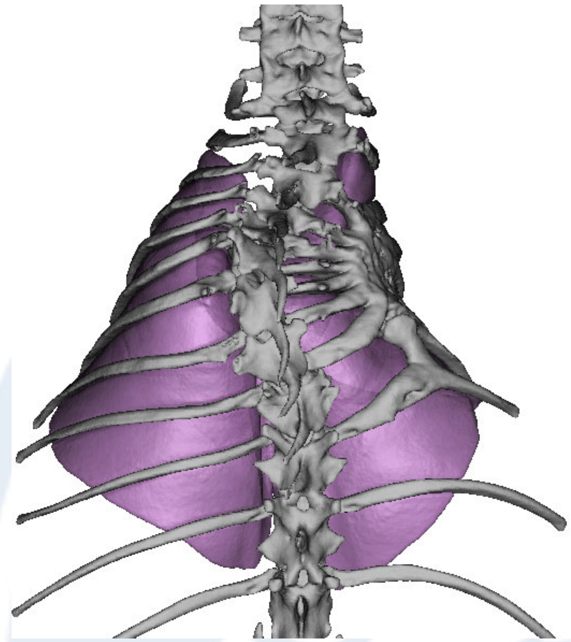

Thoracic Volume

Aerated Lung Volume and Mass

Diaphragmatic Surface Area

# Induced Deformity



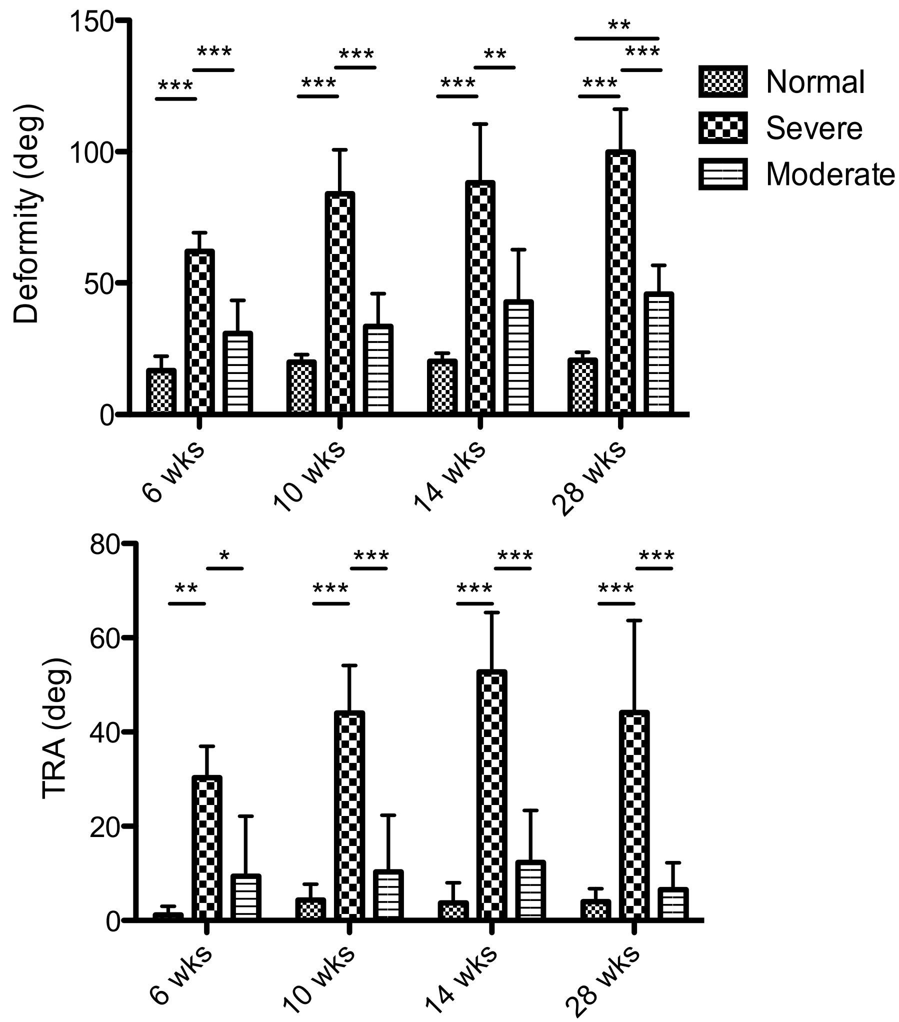


**SEVERE** ( $\theta_M$ >50° , N=5) **MODERATE** ( $\theta_M$ <50° , N=5)

- **All rabbits with tethered ribs developed thoracic deformity**
- **Variable expression:**
  - Deformity, $\theta_M$, ranged 20° to 71° @ age 6 wks
  - Distinction between rabbits with deformity > 50° vs < 50°

Aim1 – Results

# Unilateral Tethering induced Thoracic Deformity




- **Severe group - spine deformity and TRA progressed significantly during growth**
- **Moderate group - achieved significant spine deformity only @ 28 weeks.**

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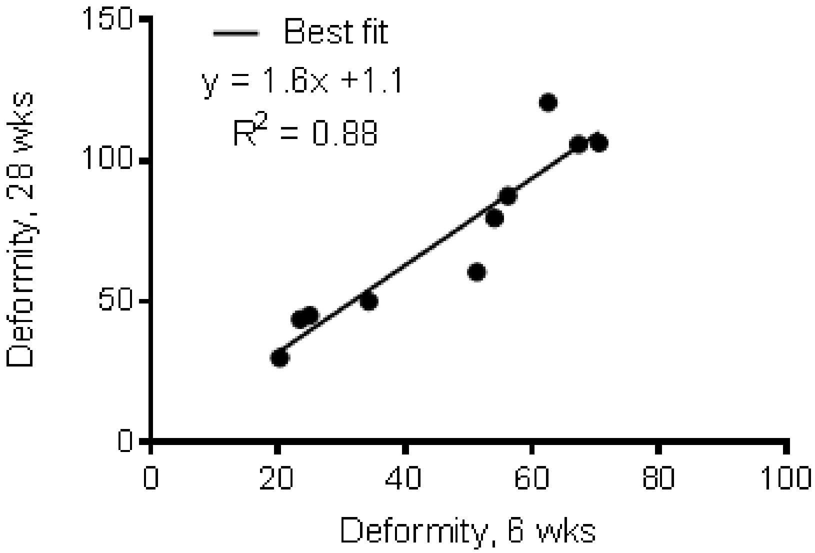
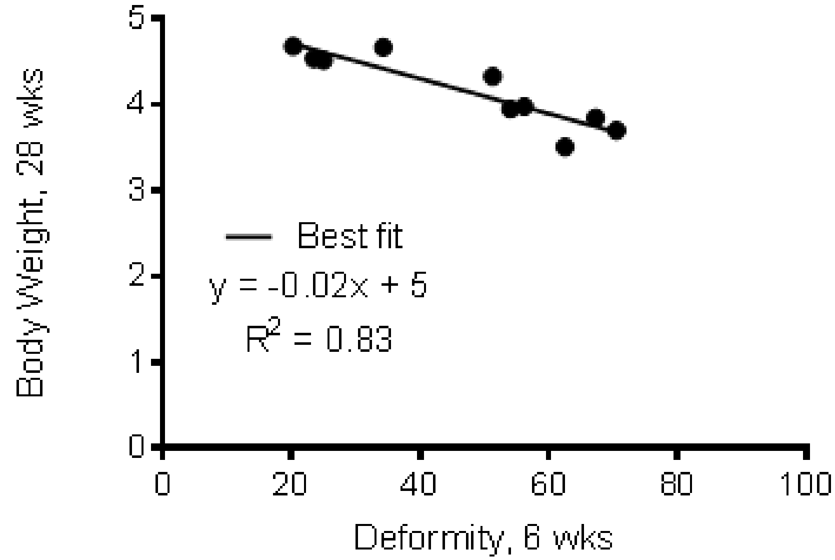
Aim1 Results

# Spinal Deformity in Young Rabbit (6 wks) Predicts: Spine Deformity and Body Weight @ Adulthood

- **Spine deformity @ age 6 wks accounted for:**
  - ↑spine deformity ($R^2 = 0.91$, $p<0.001$) @ 28 weeks
  - ↓ body mass ($R^2 = 0.83$, $p<0.001$) @ 28 weeks

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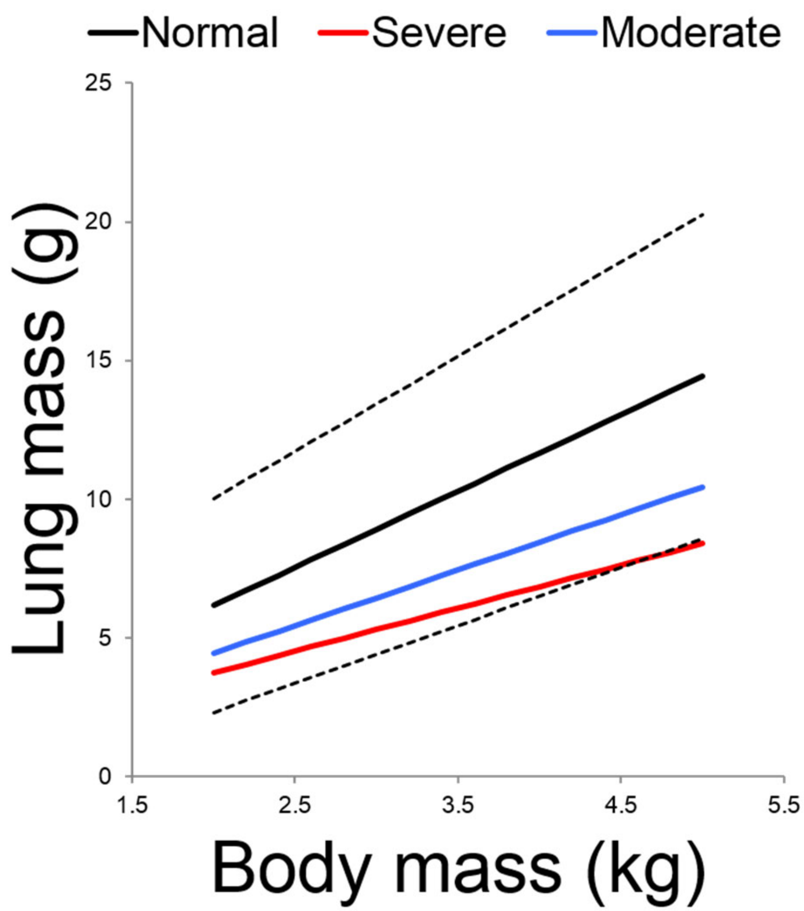
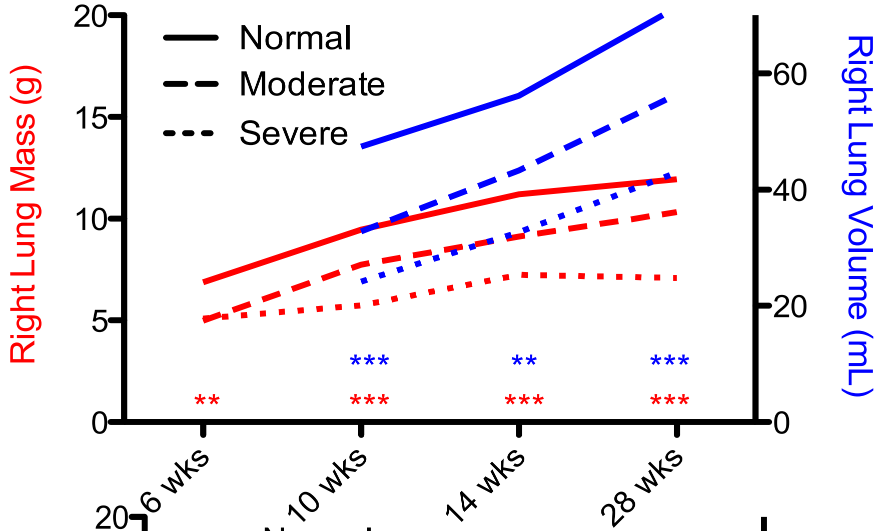
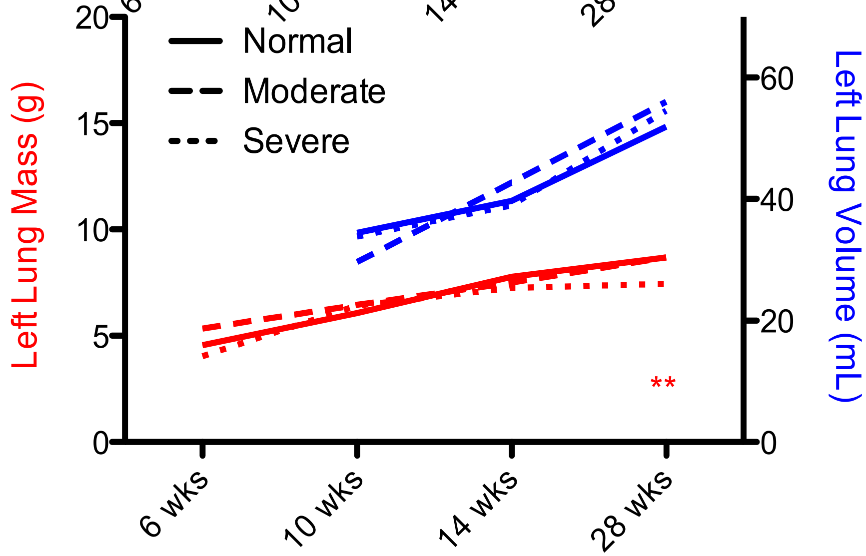
# Lung growth inhibited by spine deformity




- **Lung growth relative to Somatic growth (measured by mass)**
- **Lung growth significantly depressed (p<0.01) for rabbits with severe spine deformity**

# Right vs Left Lung Growth Through Adulthood




## By age 28 weeks

- **Severe Deformity:**
  - Constricted right lung
    - Mass 59% of normal
    - Volume 60% of normal
  - Left lung less affected
    - Mass 86% of normal
    - Volume 105% of normal
- **Moderate Deformity**
  - Right lung less than normal
  - Hypertrophy of left lung

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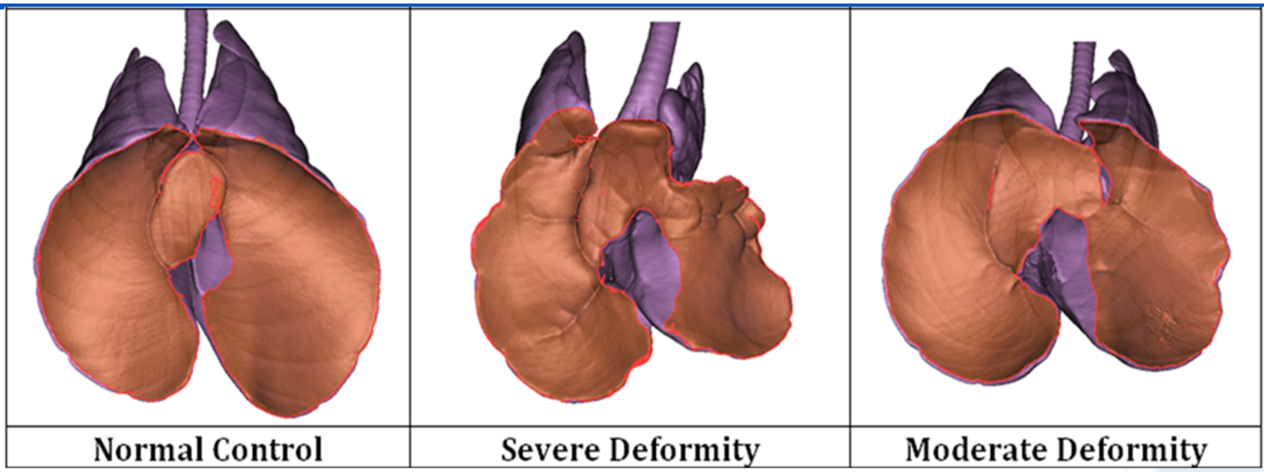
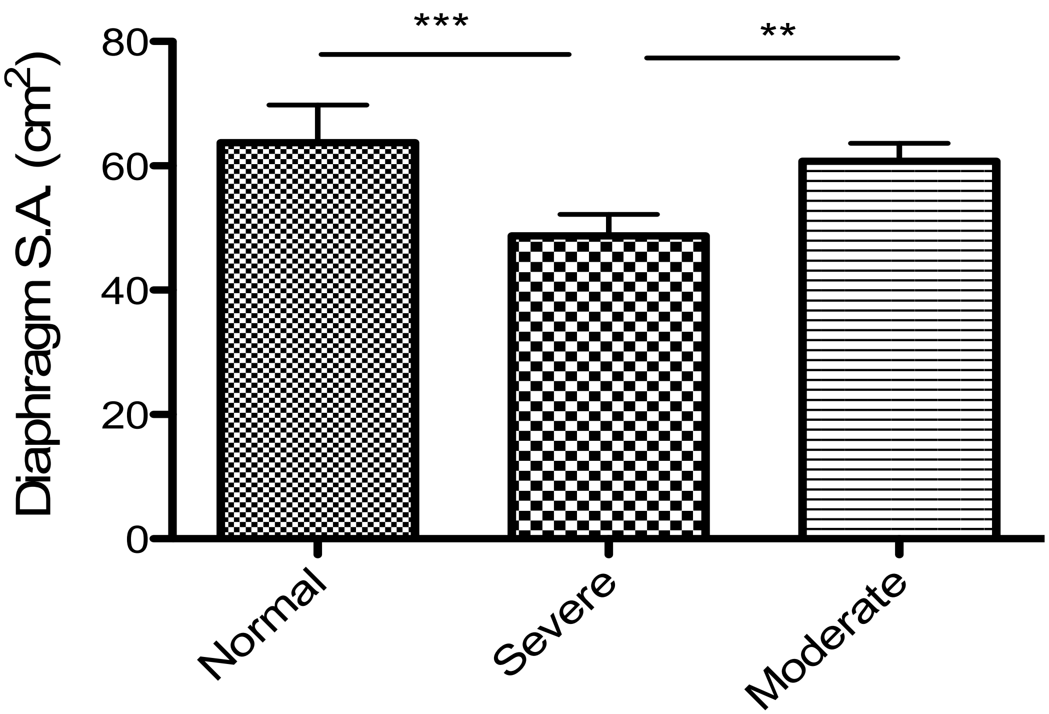
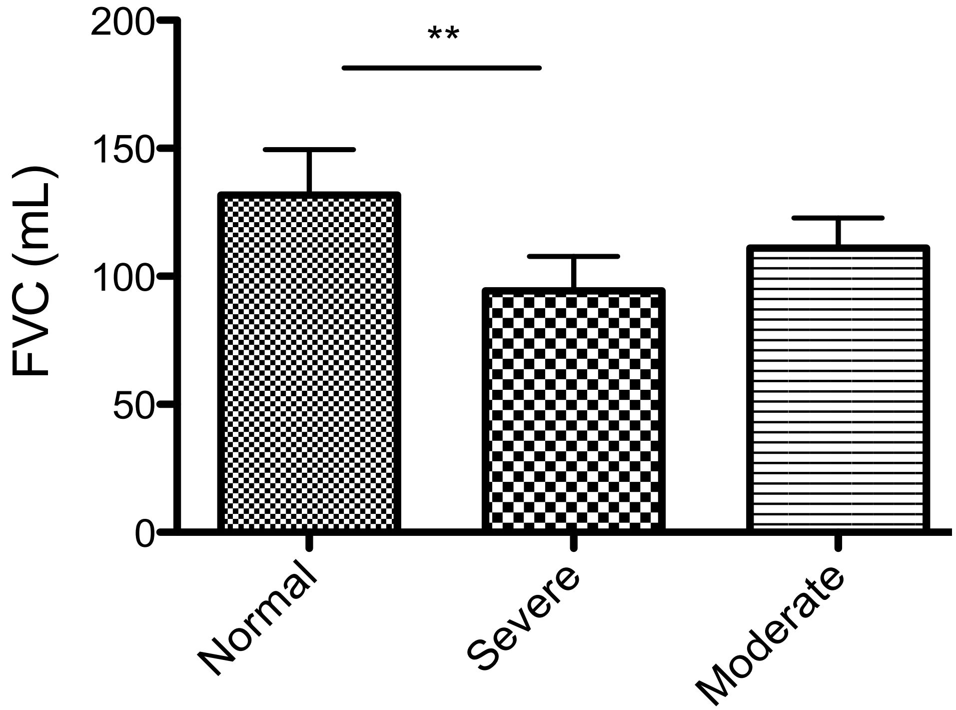
# Diaphragm surface area



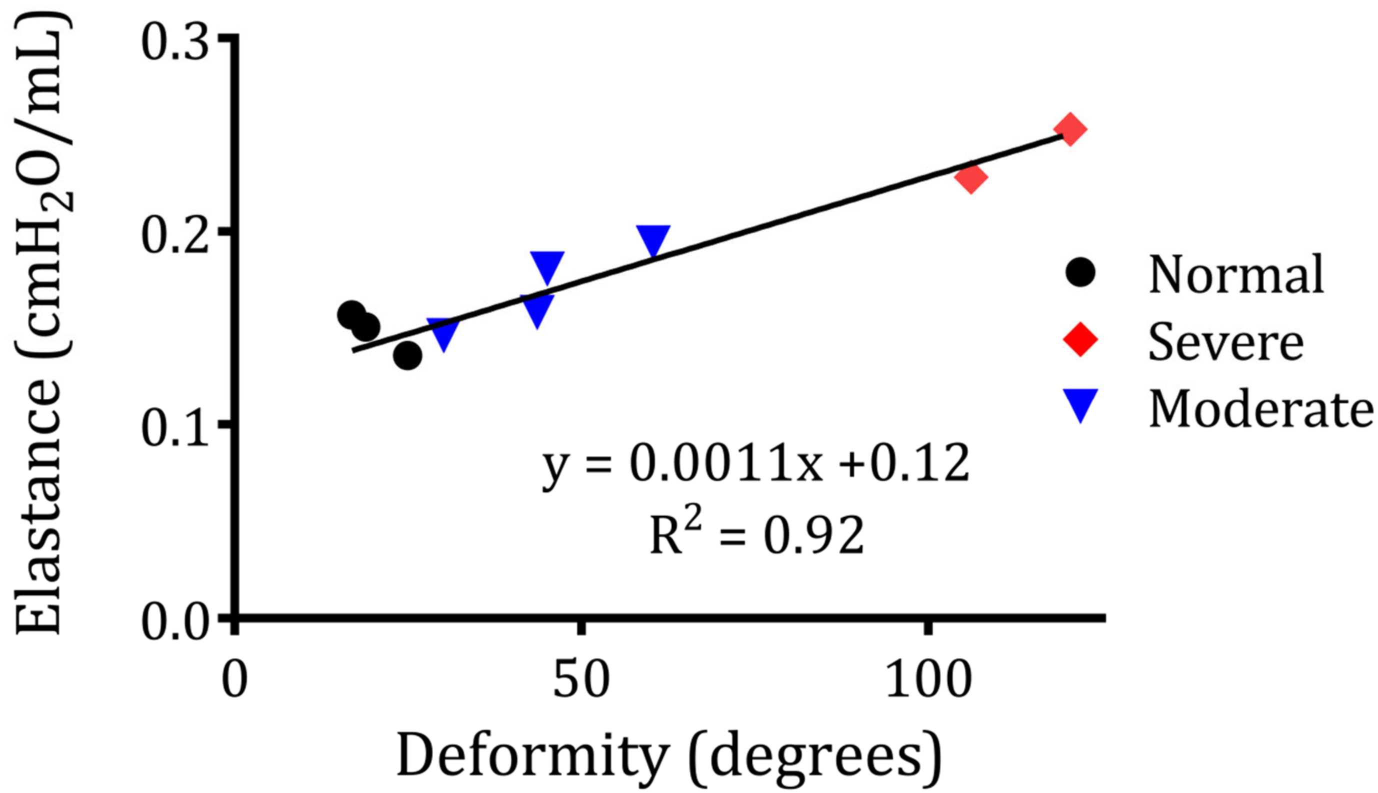

- Diaphragm is primary driver (piston) for mass transfer air in/out lung
- Surface area of diaphragm rabbits with severe deformity 76% of normal

# Forced Vital Capacity



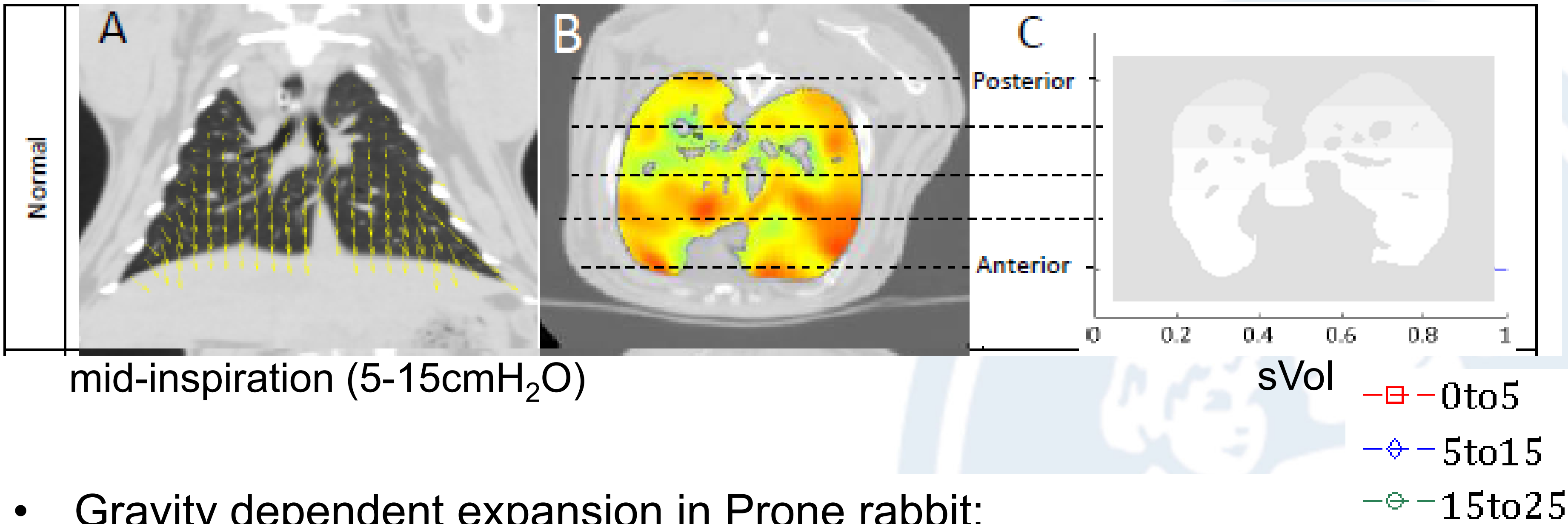

- **FVC in rabbits with severe thoracic deformity 71% normal rabbits ($p<0.01$)**

# Elastance




**Spine deformity @ 6 weeks effected the elastance of the lung parenchyma at maturity**

# Specific Volume (volumetric strain) varies with gravity dependent height

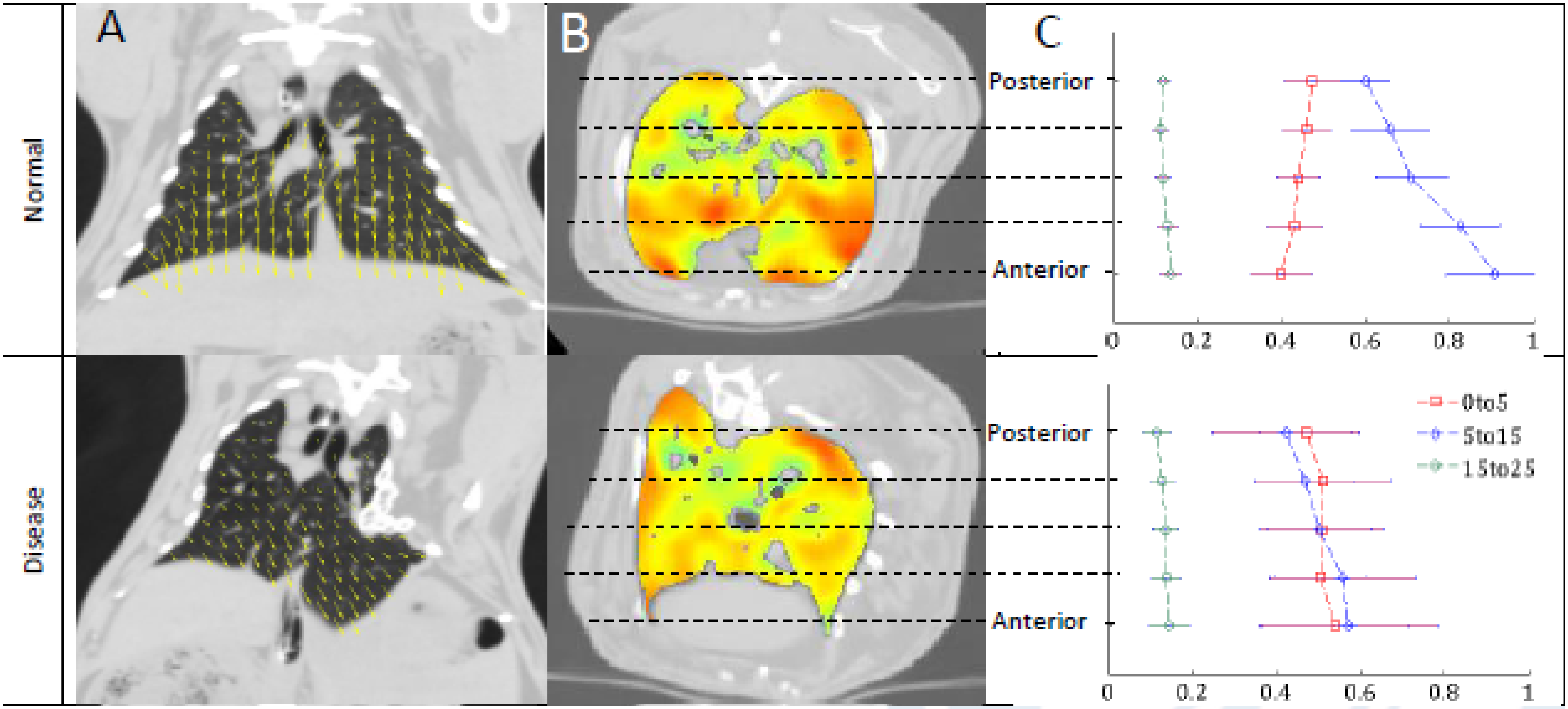



mid-inspiration (5-15cm$H_2O$)

- Gravity dependent expansion in Prone rabbit:
  - initial-inspiration (0-5cm$H_2O$) - sVol posterior > anterior
  - mid-inspiration (5-15cm$H_2O$) - 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*

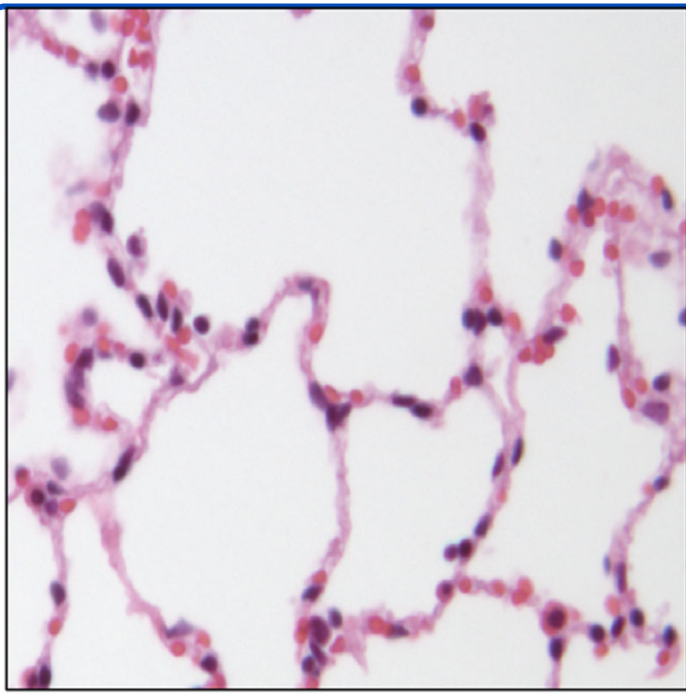
Aim 1 Results

# Comparison of sVol Normal vs. TIS

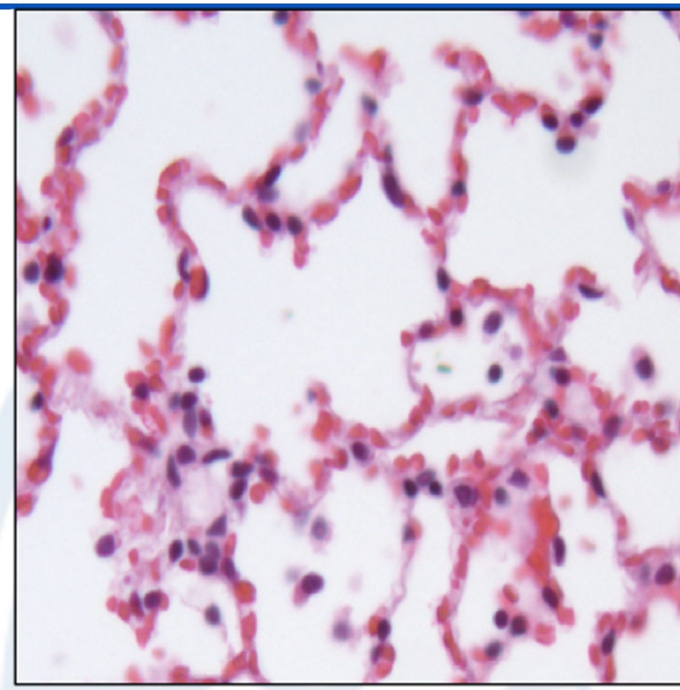



- Thoracic Deformity affects Gravity dependent expansion Right and Left lung
- Dependent portion of lung contributes more to pulmonary reserve capacity
- **This reserve capacity is diminished by thoracic deformity**

# Histology



Disease



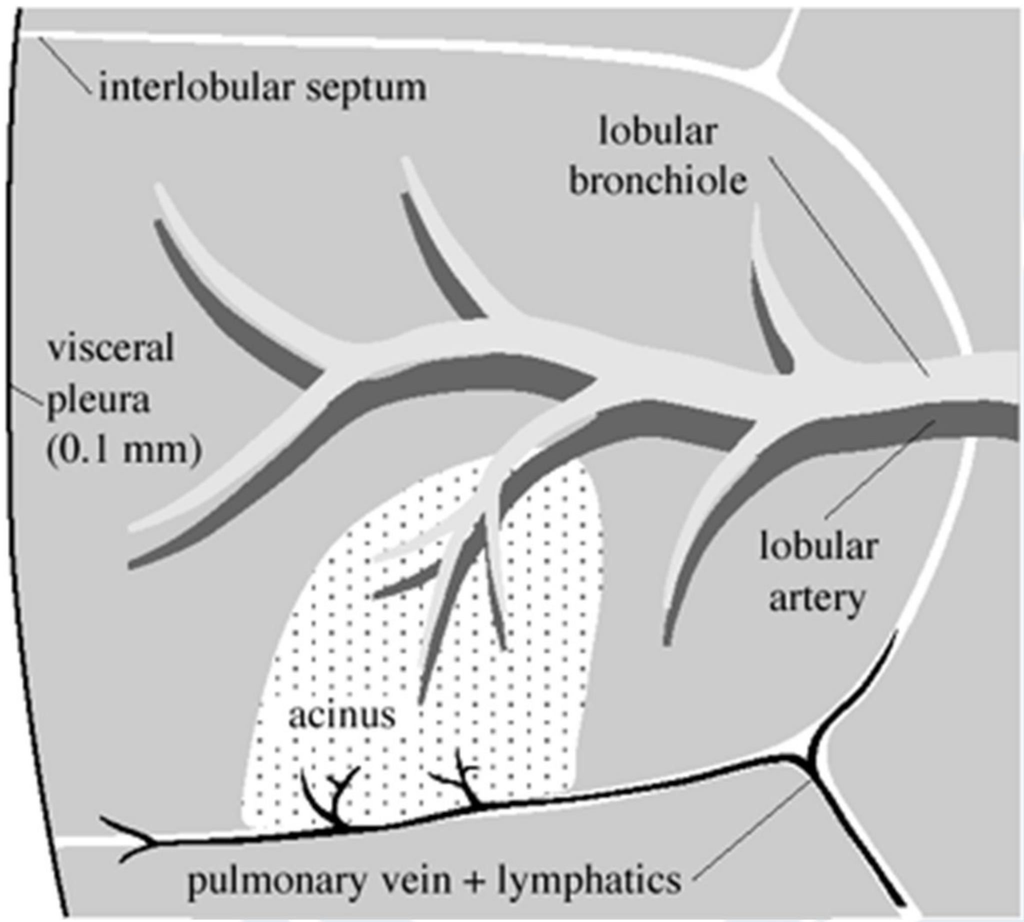
Normal

**Diseased lung**: thinned alveolar walls, significantly greater airspace fraction (emphysema), poor RBC perfusion (indicated by bright pink cells without nuclei.)

# Histo-morphometry
# Parenchymal Structure

The *bronchiolar epithelium* (airway) terminates at center of an *acinus* within a *pulmonary lobule*.

- The distance from a *respiratory bronchiole* and closest edge of *acinus* is constant.




Pulmonary Lobule

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# Histo-morphometry
# Radial Alveolar Count

- RAC: # of Alveoli between respiratory bronchiole and edge of acinus
  - Indicates acinar complexity & pulmonary hypoplasia
  - Decreased RAC is indicative of hypoplasia

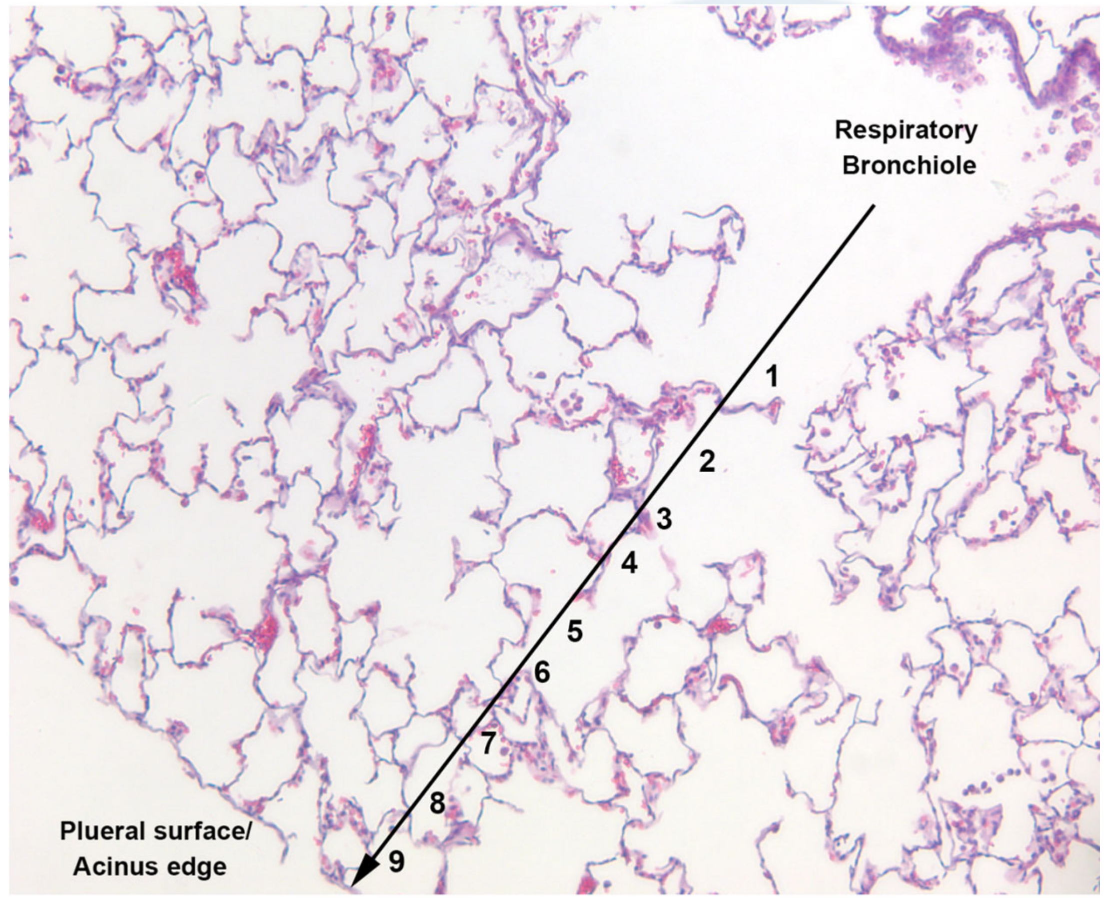



Image: Histology (H&E) rabbit acinus with respiratory bronchiole

# Histo-morphometry – RAC

| | Left Lung | Right Lung |
|---|---|---|
| Normal | 12.5 (2.0) | 12.1 (1.7) |
| Moderate | 12.0 (1.2) | 12.0 (1.9) |
| Severe | **7.7 (1.8)**** | **8.3 (1.4)**** |

** - ANOVA P<0.01 compared to Normal and Moderate groups

- Significant decrease RAC occurs in both lungs of rabbits with SEVERE deformity (curve > 50° )

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

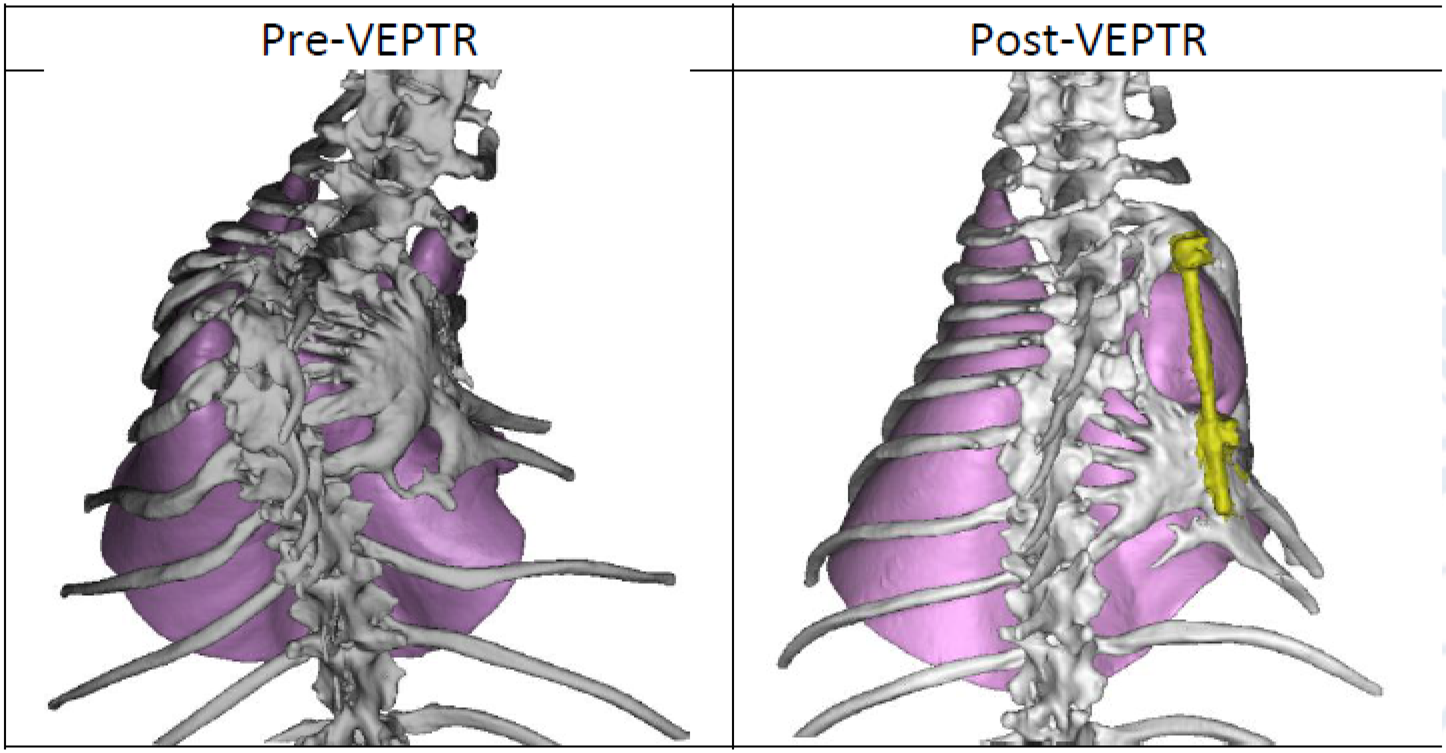
| Deformity (6 wks) vs. | | |
|---|---|---|
| Outcomes (28 wks) | r | $R^2$ |
| Lung Mass<br>- Right lung<br>- Left lung | **-0.87**<br>**-0.89**<br>**-0.78** | **0.76****<br>**0.80*****<br>**0.61**** |
| Total Lung Capacity<br>- Right lung<br>- Left lung | **-0.70**<br>**-0.80**<br>-0.33 | **0.50***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

significance
*-p<0.05, **-p<0.01, ***-p<0.001

**Spine Deformity young growing rabbit highly and inversely correlated with metrics of pulmonary performance in adult:**

- **Lung Mass**
- **TLC**
- **Resp. Elastance**
- **FVC**
- **Diaphragm S.A.**

# RESULTS: *Aim 2* Expansion Thoracoplasty

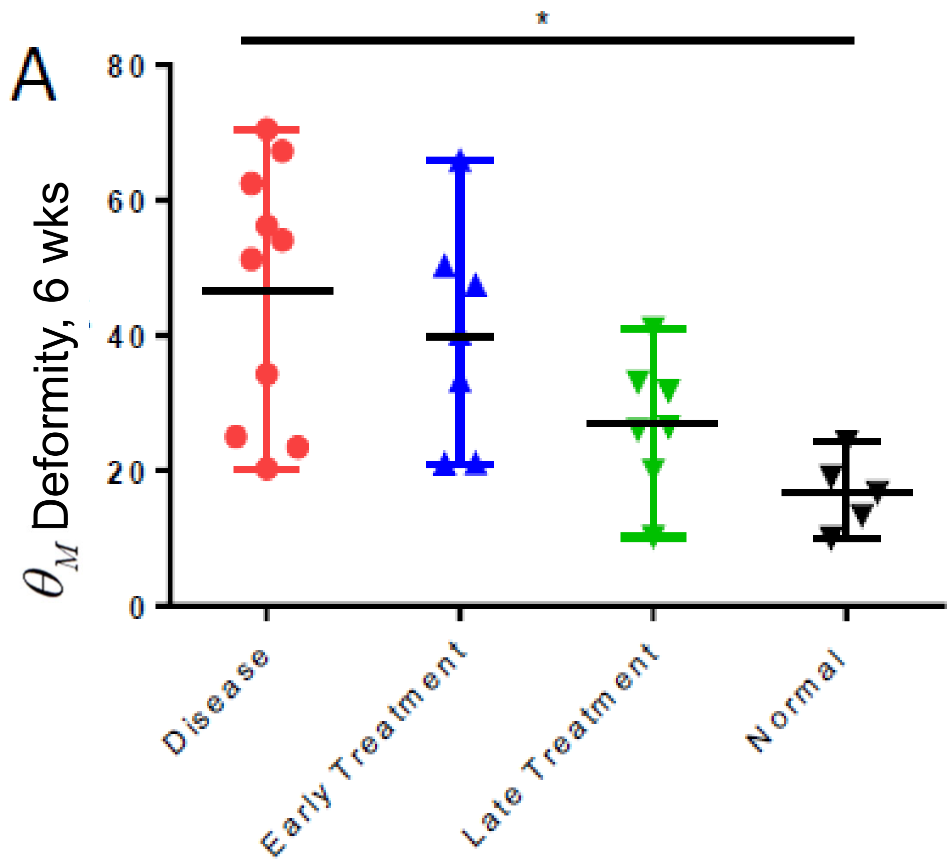



Total rib expansion

Early treatment [2.7 cm] > Late [2.0 cm] ($p<0.001$)

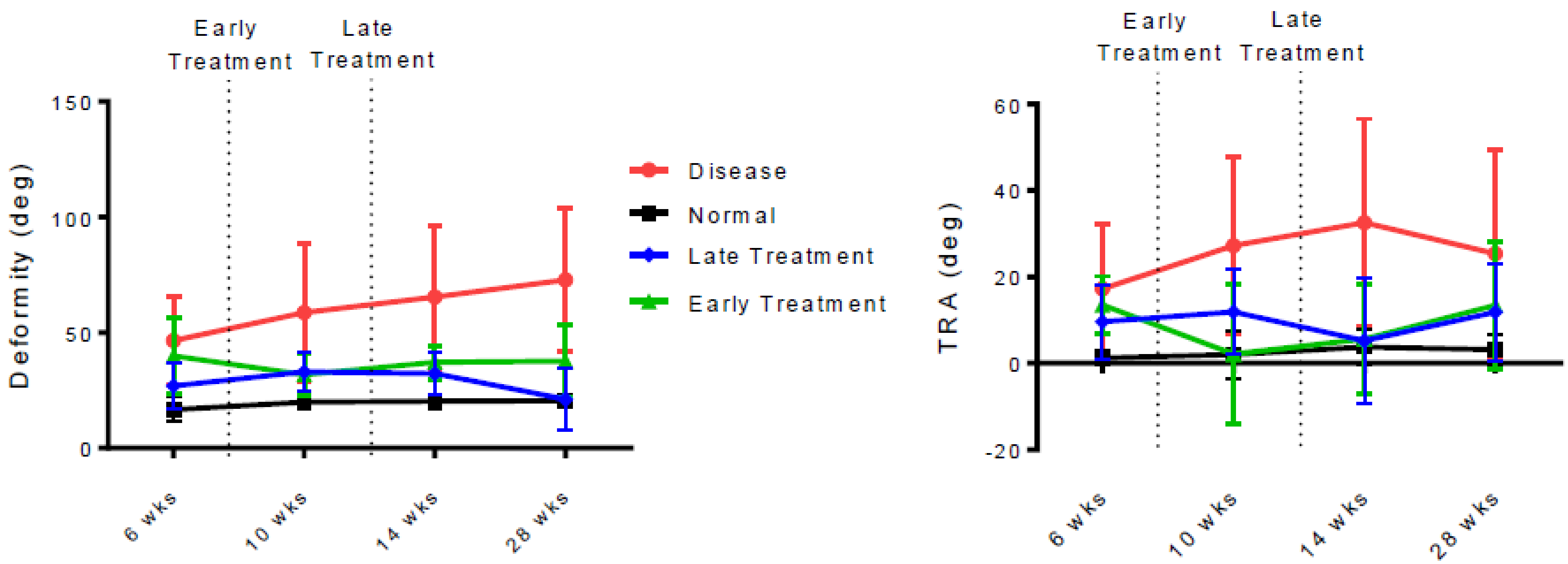
Aim2 – Results

# Baseline Deformity Among Groups




- **Spine deformity @ initiation treatment inconsistent among groups**
  - Late treatment less deformity than Early or Disease
- **Analysis of Covariance performed to compensate**
  - Controls for initial differences in deformity among groups

# Progression of spine deformity and TRA during growth




- Thoracic deformity Early and Late Treatment groups lower than Disease control ($p<0.01$) by completion of growth
- Spine deformity Disease control > Normal throughout growth ($p<0.01$)
- TRA Normal & Treatment groups < Disease control @ age10 & 14 wks

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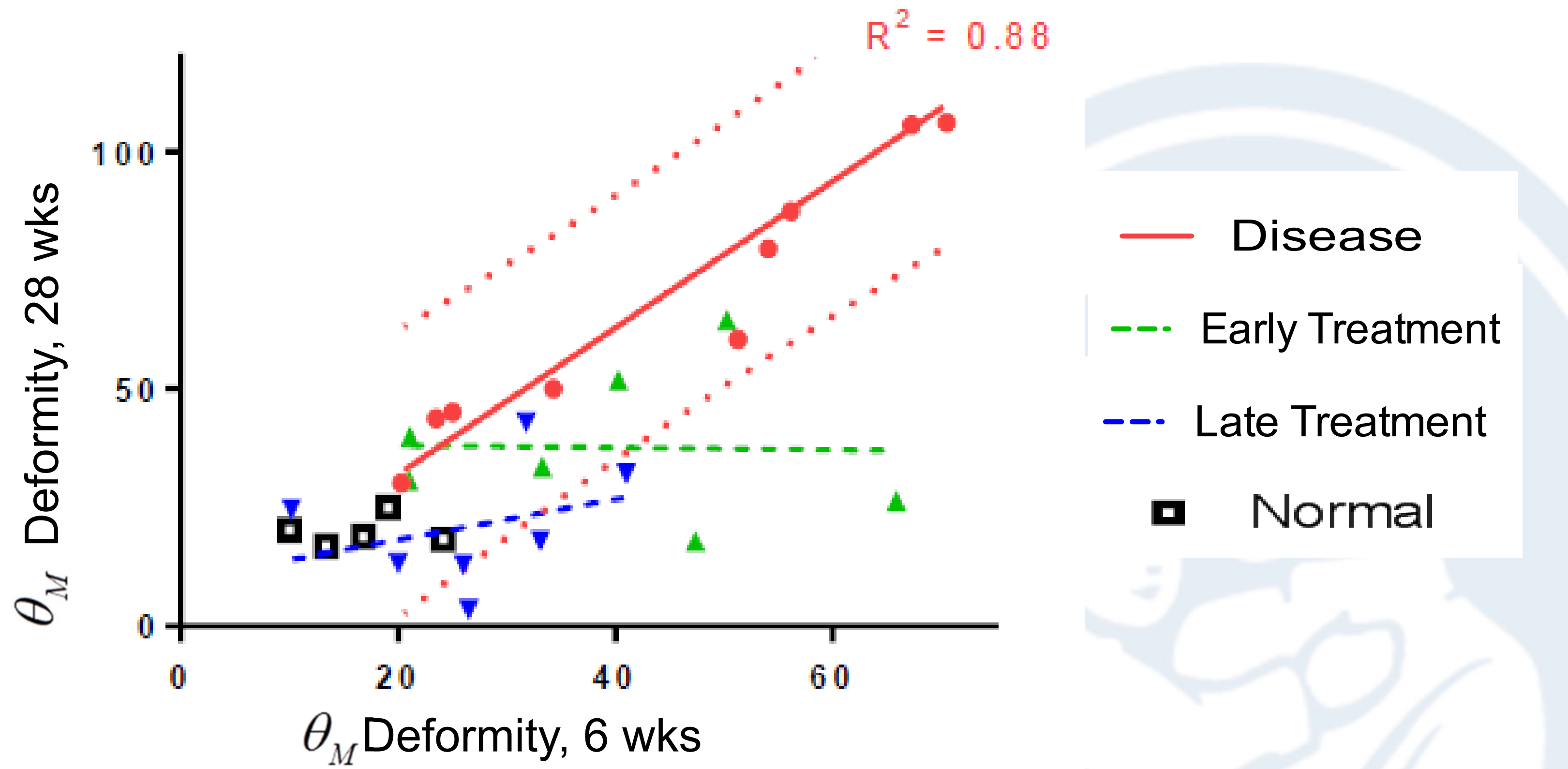
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Aim2 – Results

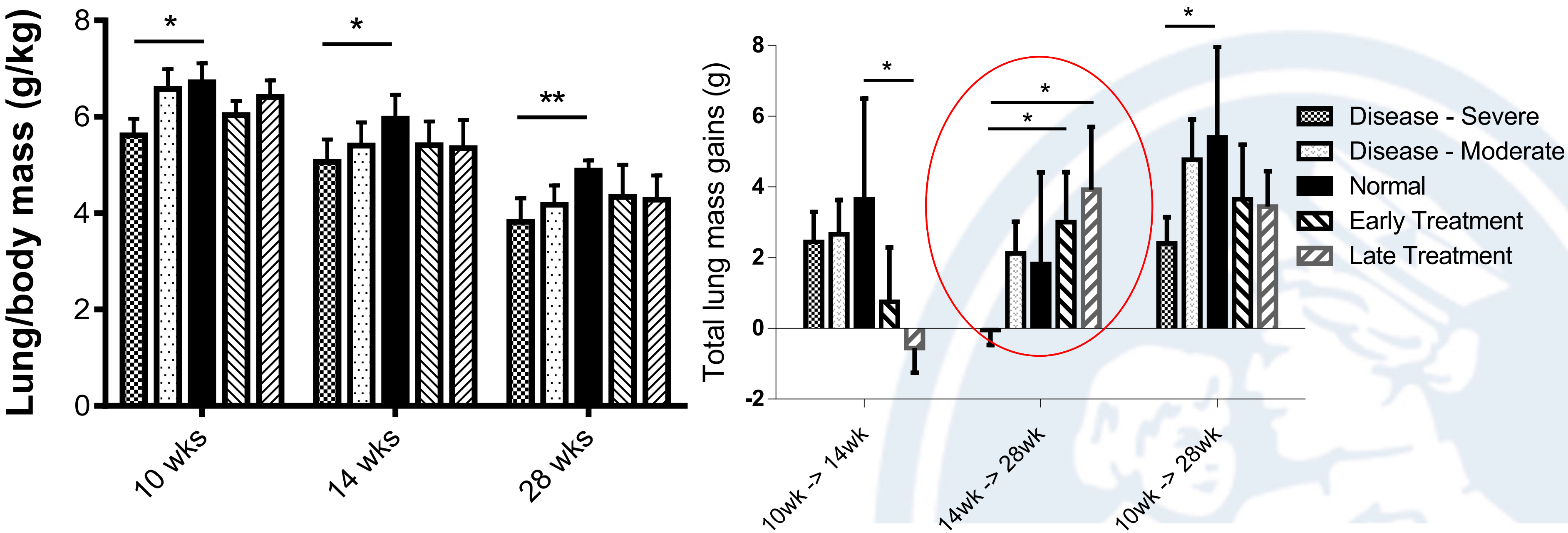
# Progression Spine Deformity: Disease vs. Treatment




- Expansion thoracoplasty ameliorates expected spine deformity in untreated rabbits at maturity

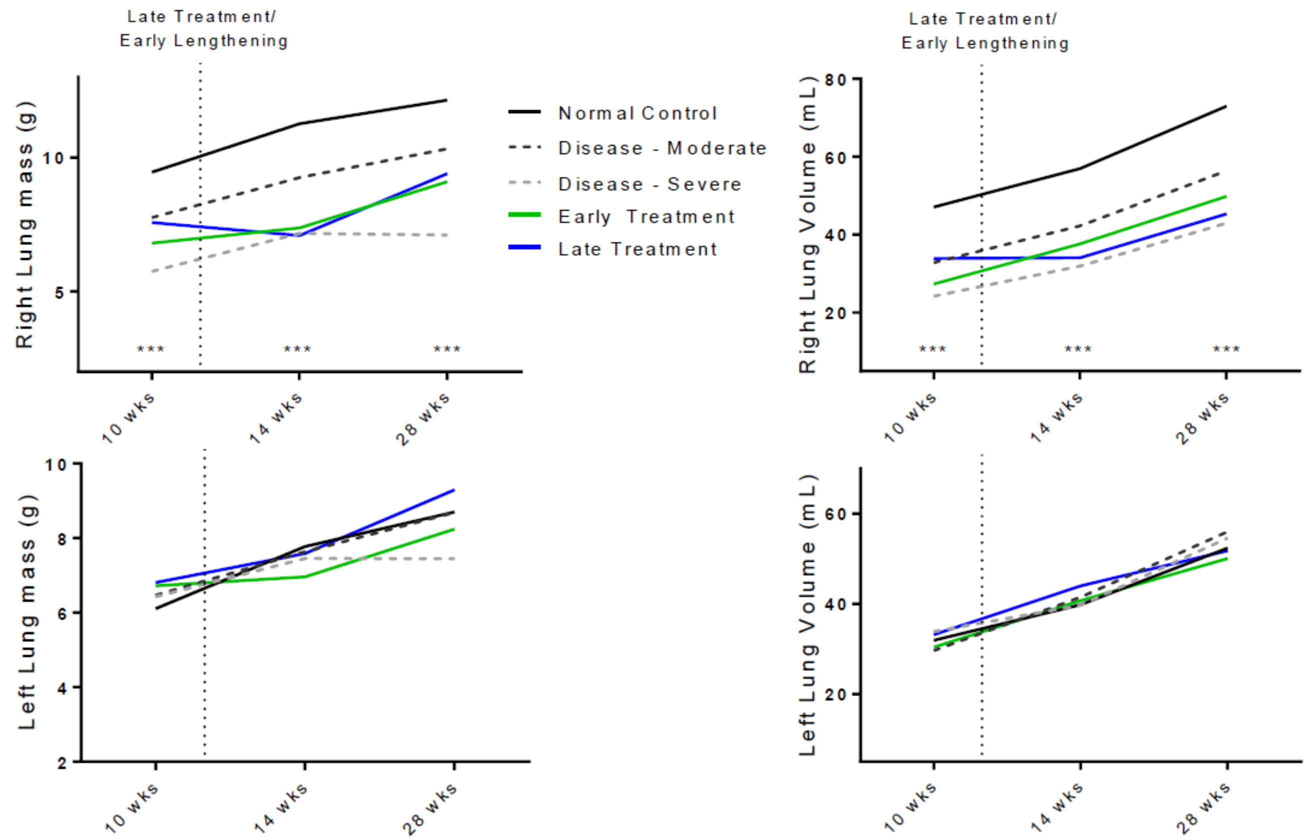
➢ Slopes fit lines for Treatment groups different from Disease ($p<0.01$)

# 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 between10-14 wks. may reflect ill affects of surgical insult

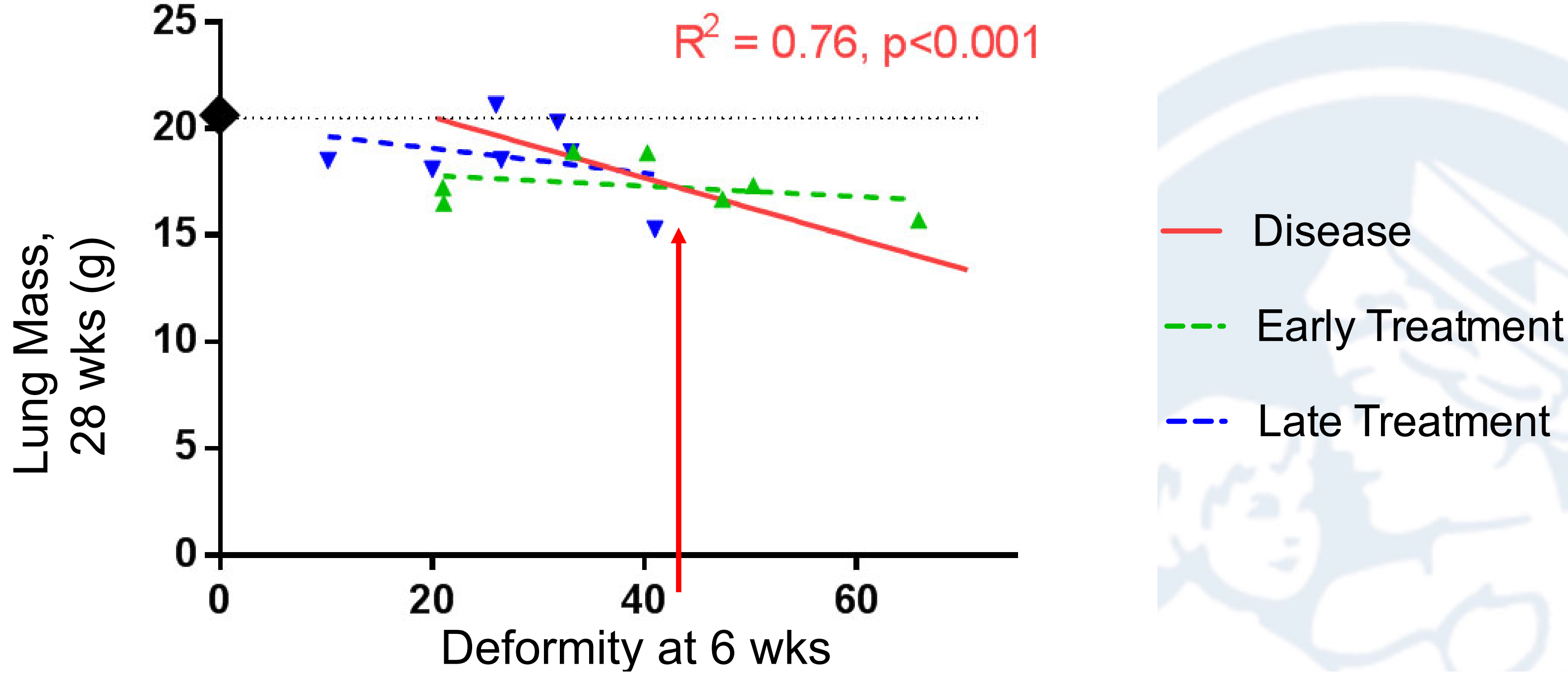
# Mass and volume of segmented left and right lung during growth for treatment and disease groups




- @ 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**

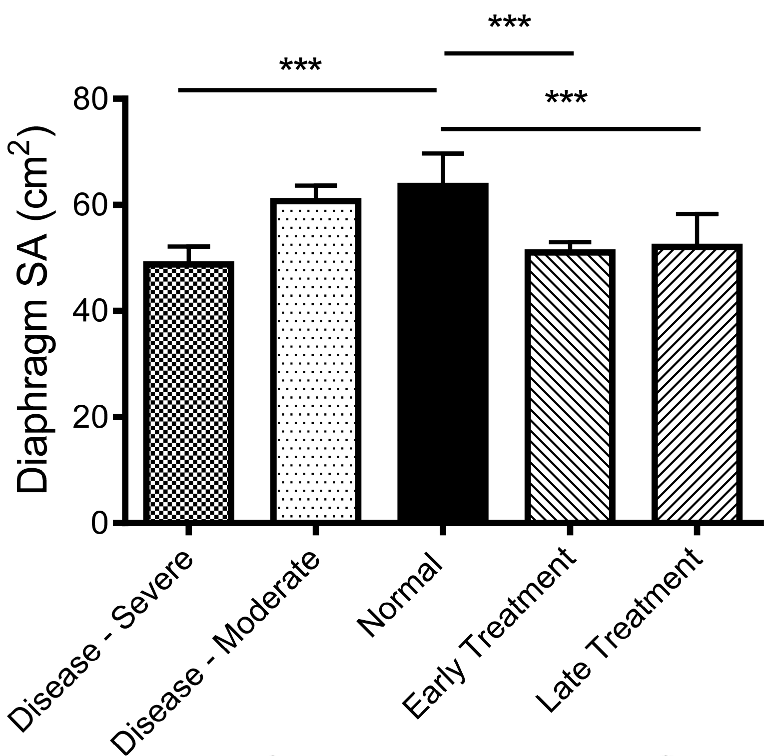
Aim2 – Results

# Treatment stabilized expected decline in lung growth

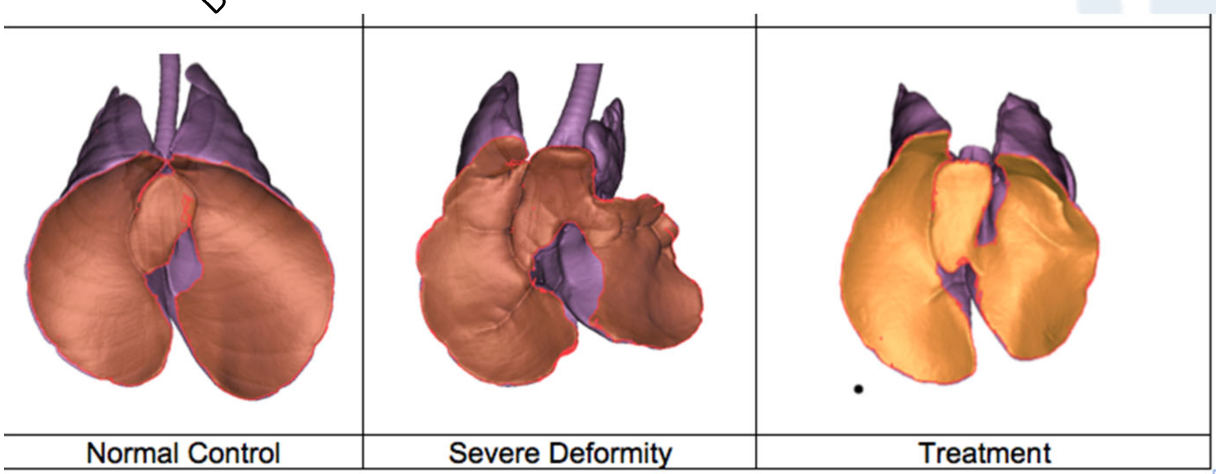



- Slope of relationship lung mass @ maturity as function of thoracic deformity in growing rabbit altered by Early Treatment i.e. Slope early tx less neg. than disease control (ANCOVA $p<0.05$)
- Tipping point only for $\theta_M > 45^o$ did early treatment allow for greater lung growth (mass) than expected relative to disease control

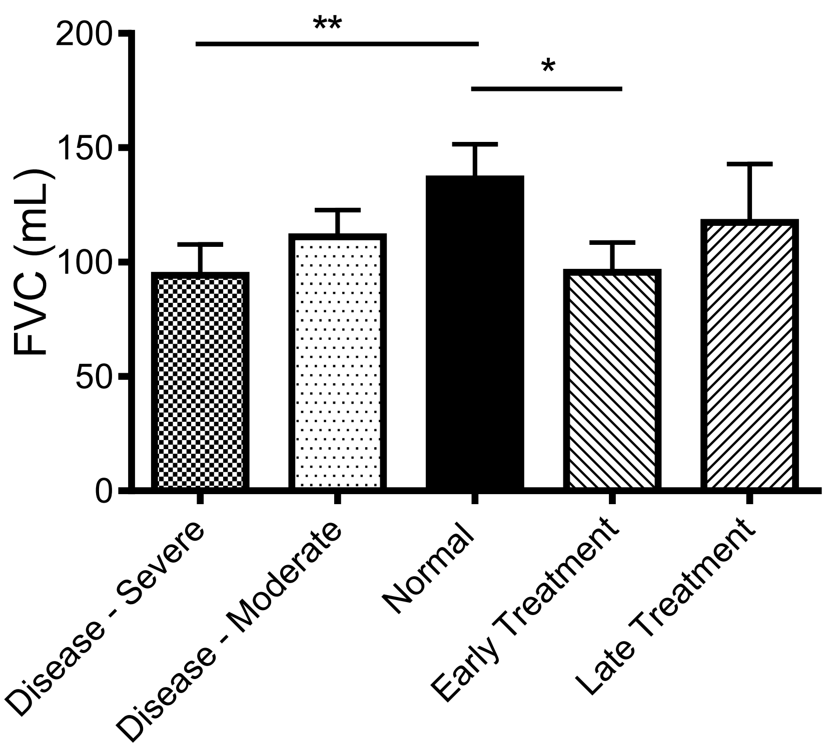
# Surface Area of Diaphragm




- **Expansion Thoracoplasty had little effect on surface area of diaphragm**
- Surface area diaphragm in Early and Late Treatment rabbits 80% of Normal ($p<0.001$)
- Untreated Disease Control rabbits 77% Normal ($p<0.001$)



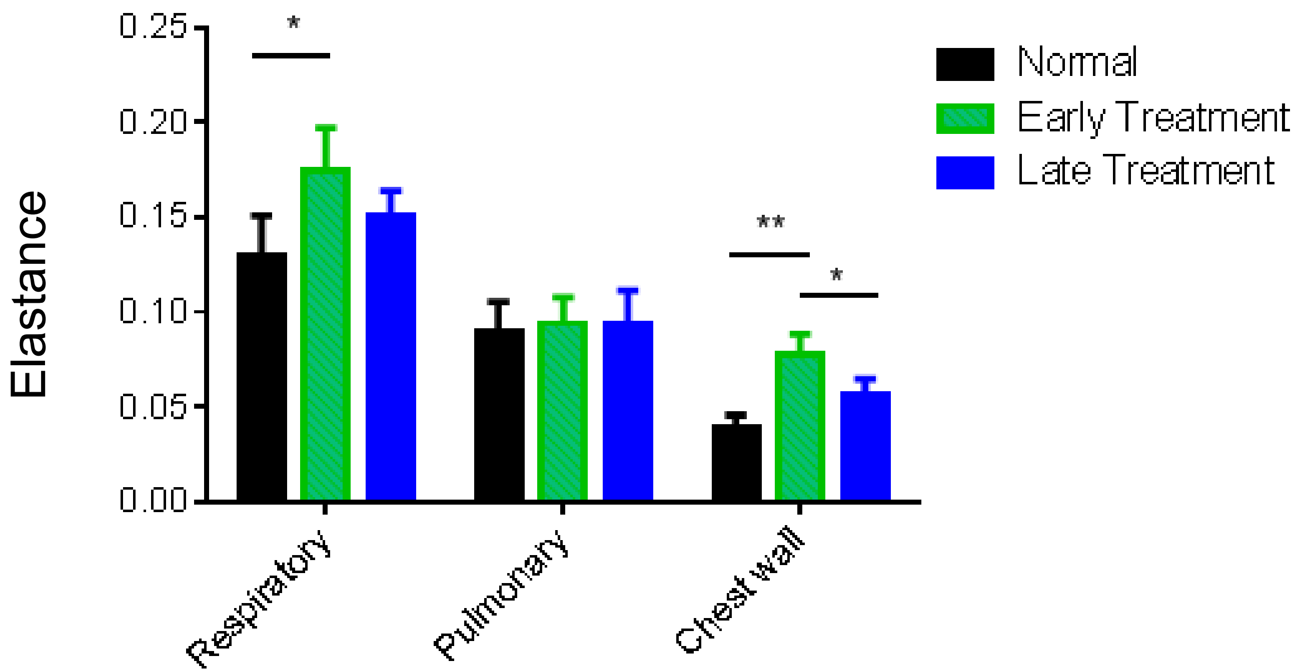
# Forced Vital Capacity




- **Expansion Thoracoplasty did not improve FVC**
- Mean FVC Early Tx rabbits 70% Normal ($p<0.05$), while Late Treatment rabbits 86% Normal.
- Disease Control rabbits 69% Normal ($p<0.01$)

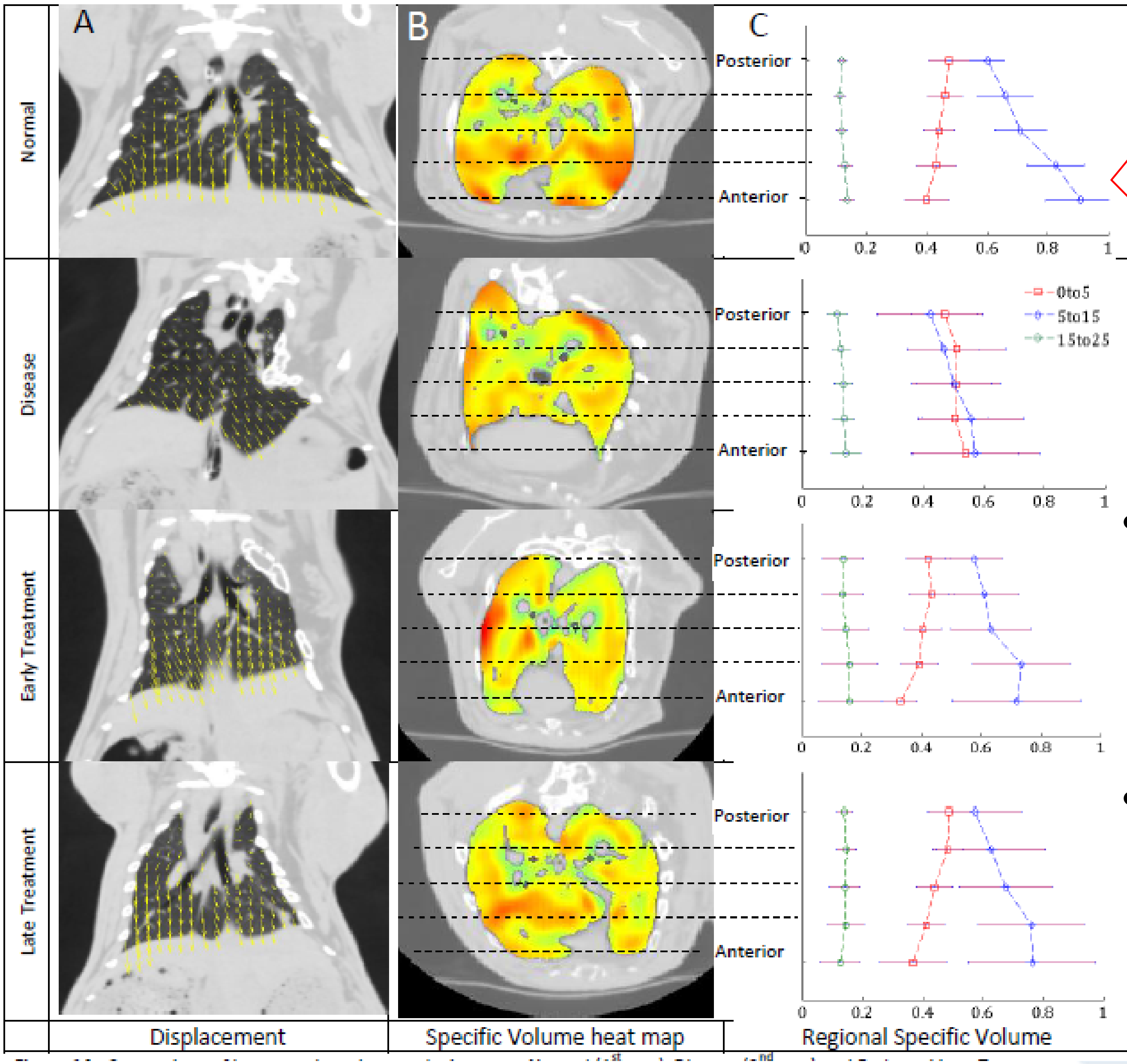
Aim2 – Results

# Partitioned Elastance



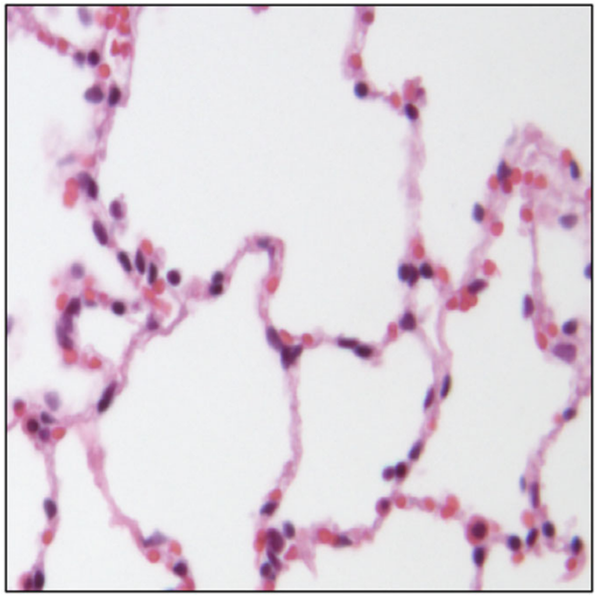

- ↑ **elastance after expansion thoracoplasty reflects persistent stiffness of the chest wall**

# Regional Pulmonary Volumetric strain
# ($\Delta V$ normalized by initial aerated lung volume, $V_0$)

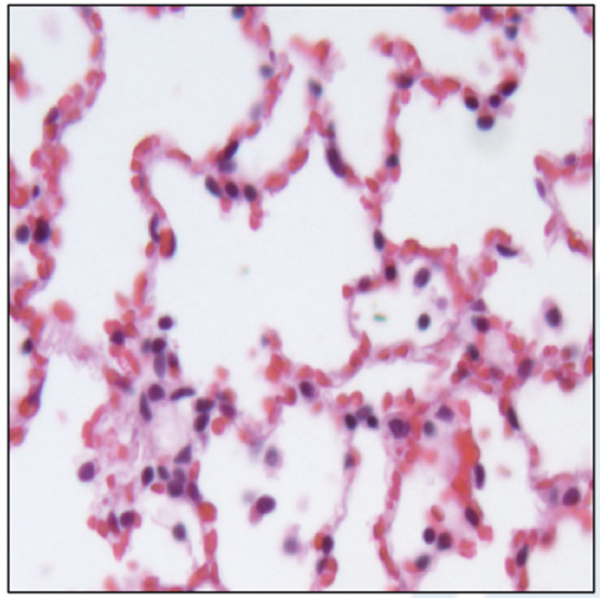



- Treatment normalized regional strain pattern
- Restores reserve capacity that was diminished by the thoracic deformity

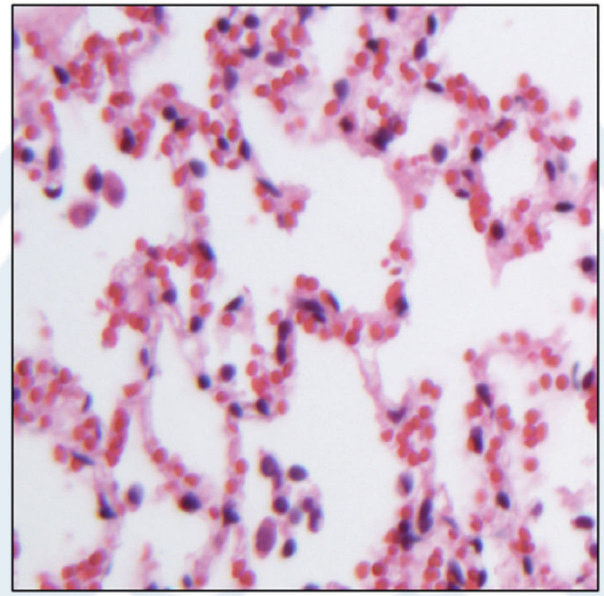
# Histomorphonetry Treated lungs approach Normal



Disease



Normal

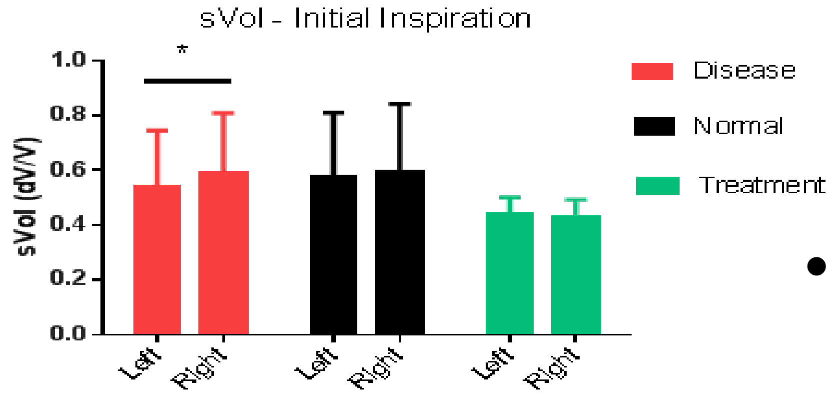


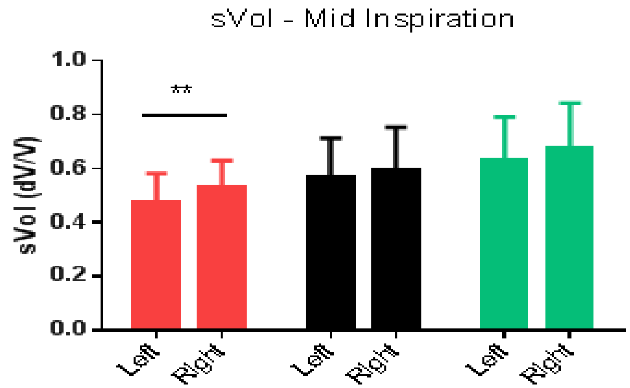
Expansion Thoracoplasty

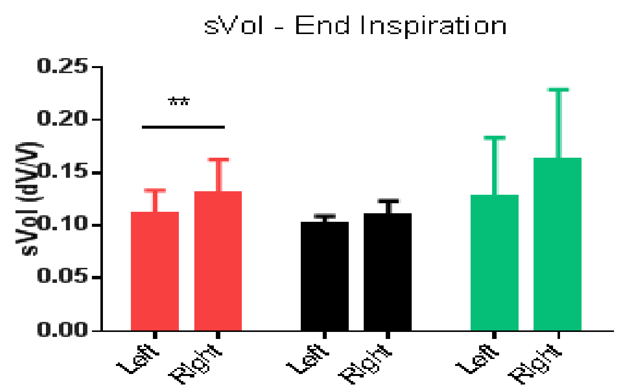
**Treated Group**: Alveolar air space fraction approaches normal, Capillaries adjacent to alveoli prominent

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

| | Residual Volume (% Predicted) | Vital Capacity (% Predicted) | Cobb Angle (degrees) | Left:Right lung (diff. normal) |
|---|---|---|---|---|
| TIS Patients | 139 +/-40.3 | 78.3 +/- 29.6 | 55 +/- 16.4 | 0.46 +/- 0.41 |
| TIS Rabbits | 303 +/-301 | 73.6 +/- 12.9 | 41 +/- 11.1 | 0.36 +/- 0.20 |
| Reference: Emans (2005) Spine; OH Mayer MD, personal communication | | | | |

# 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 [1]
  - 3 yr post-op: ↑ TLC (↑ % RV, but ↔ %VC)[2,3]

**Ref**: [1]Mayer J. Ped. Ortho. 2008,
[2]Motoyama Spine 2006,
[3]Gollogly J. Ped. Ortho.

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# Thank you