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Rabbit Model of Thoracic Insufficiency Syndrome

Lessons learned

Clinical Implications

Olson JC[1,2]; Glotzbecker MP[3]; Snyder BD[1,3]

[1]Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center;
[2]Dept. of Bioengineering, Boston University School of Engineering;
[3]Dept. of Orthopaedic Surgery, Children's Hospital; Harvard Medical School

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Disclosures

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✓Chest Wall and Spinal Deformity Study Group

✓Synthes Spine, North America

✓NIH R21

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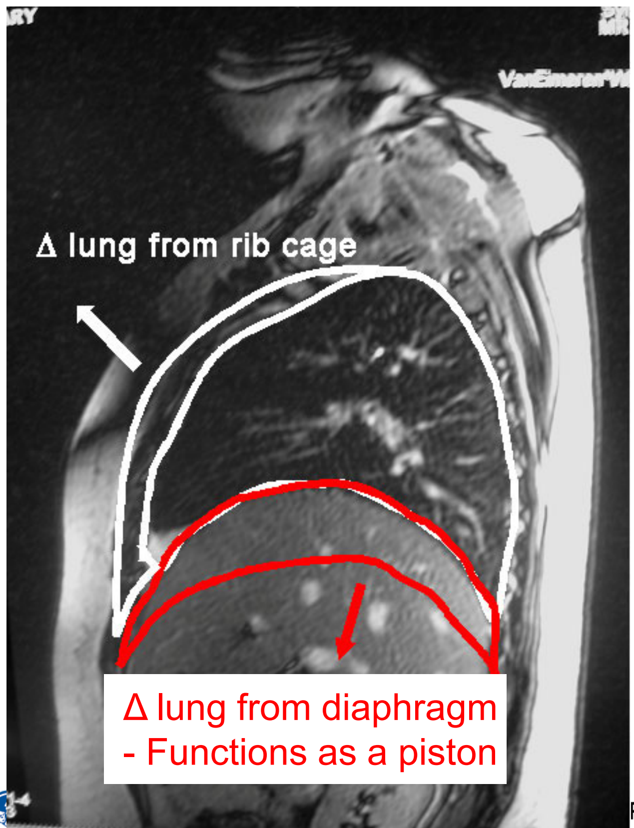
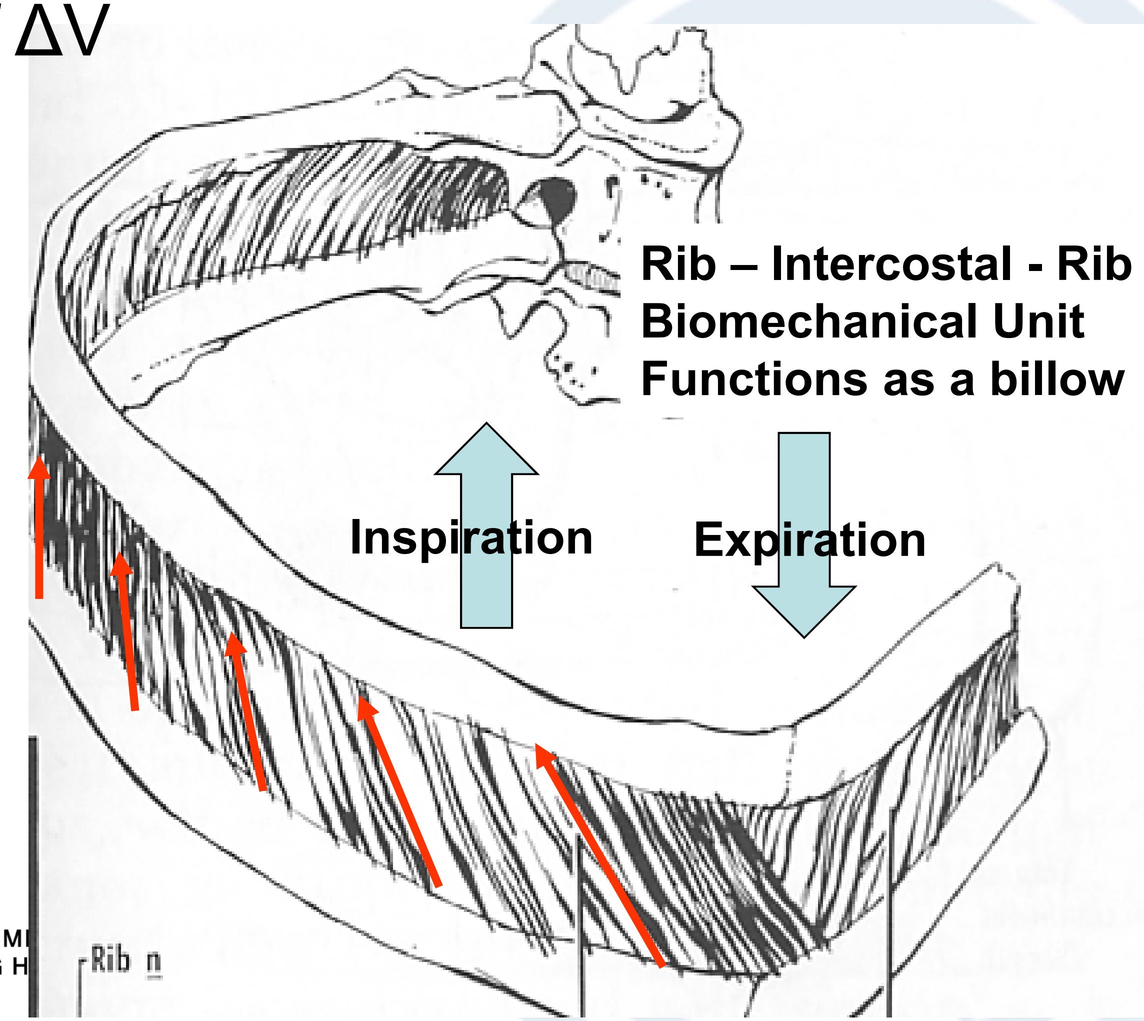
Respiration

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



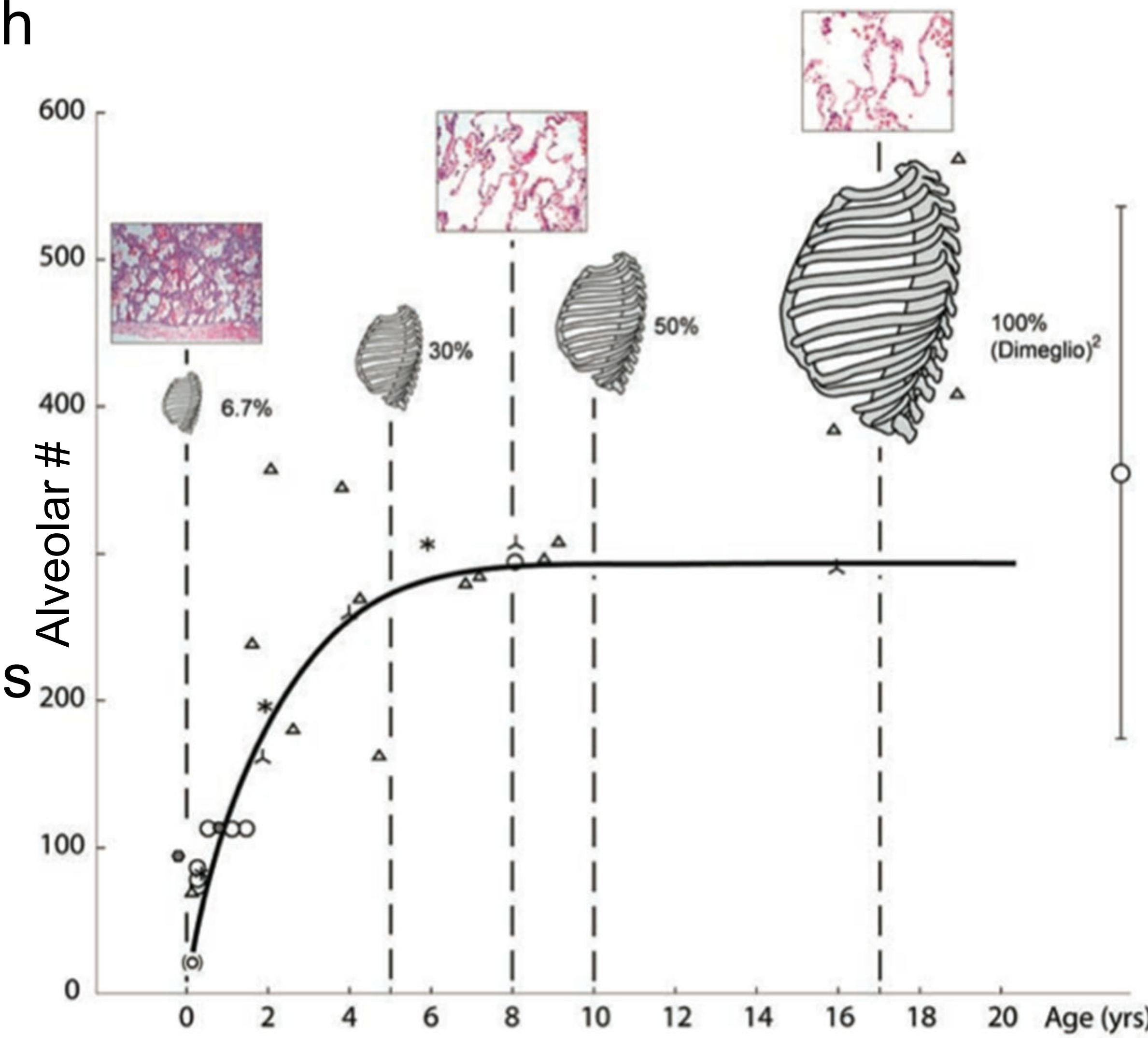


Normal Growth of Lung and Thorax

- Lung + Thoracic Growth Interdependent
- **Birth - age 8 years:** ***Alveolarization***

  New growth largely ceases > age 8 yrs
- **8 years - maturity:** ***Alveolar hypertrophy***

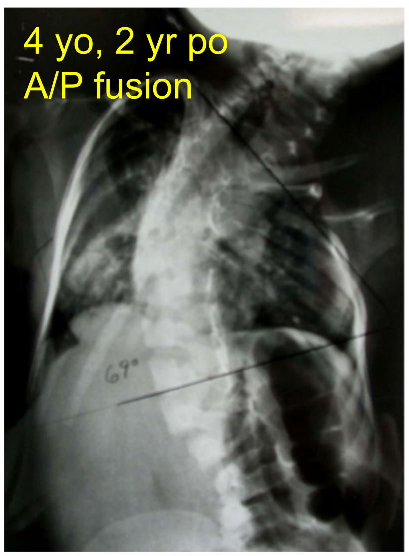
  Lung volume increases with growth of thorax until maturity

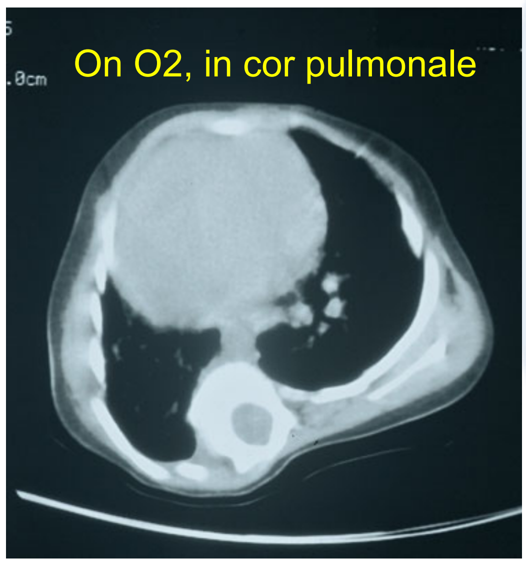


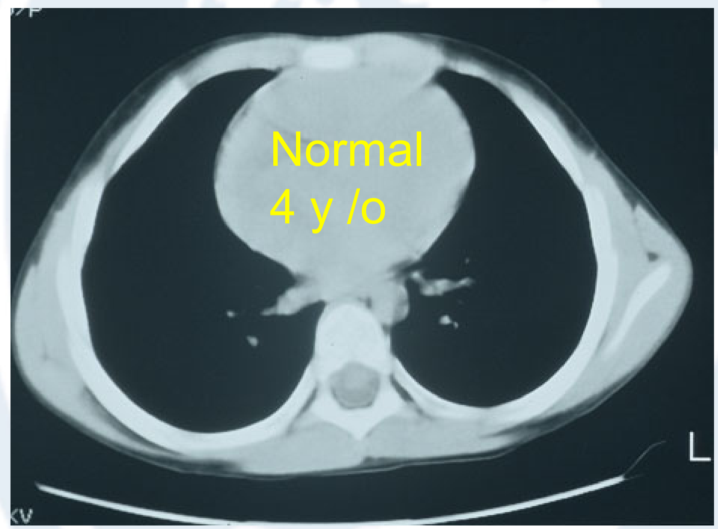
Ref: Campbell RM JBJS **20**

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**



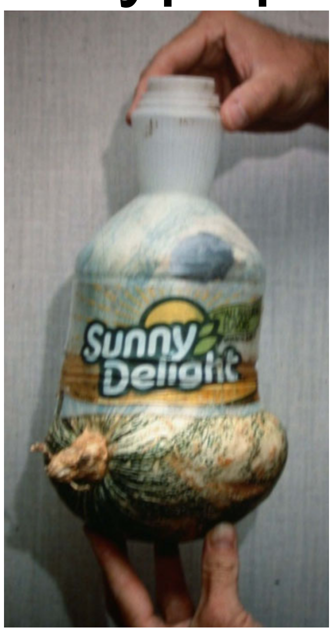




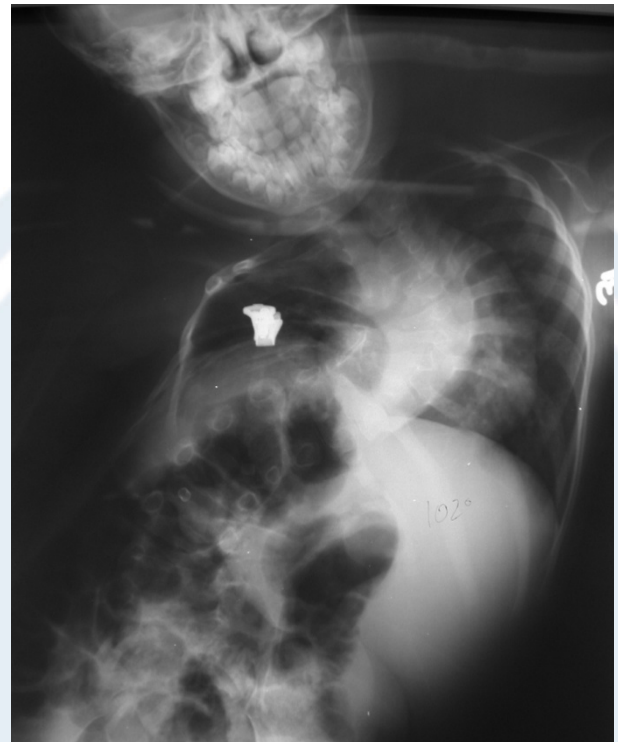
Clinical Problem

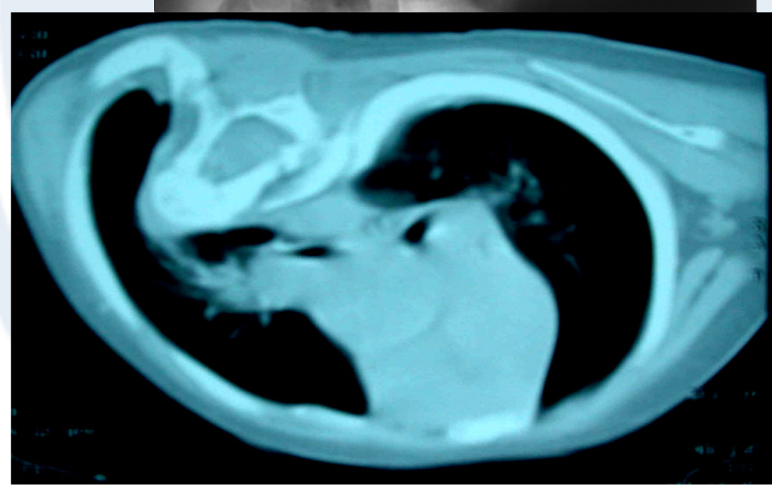
Thoracic Insufficiency Syndrome

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



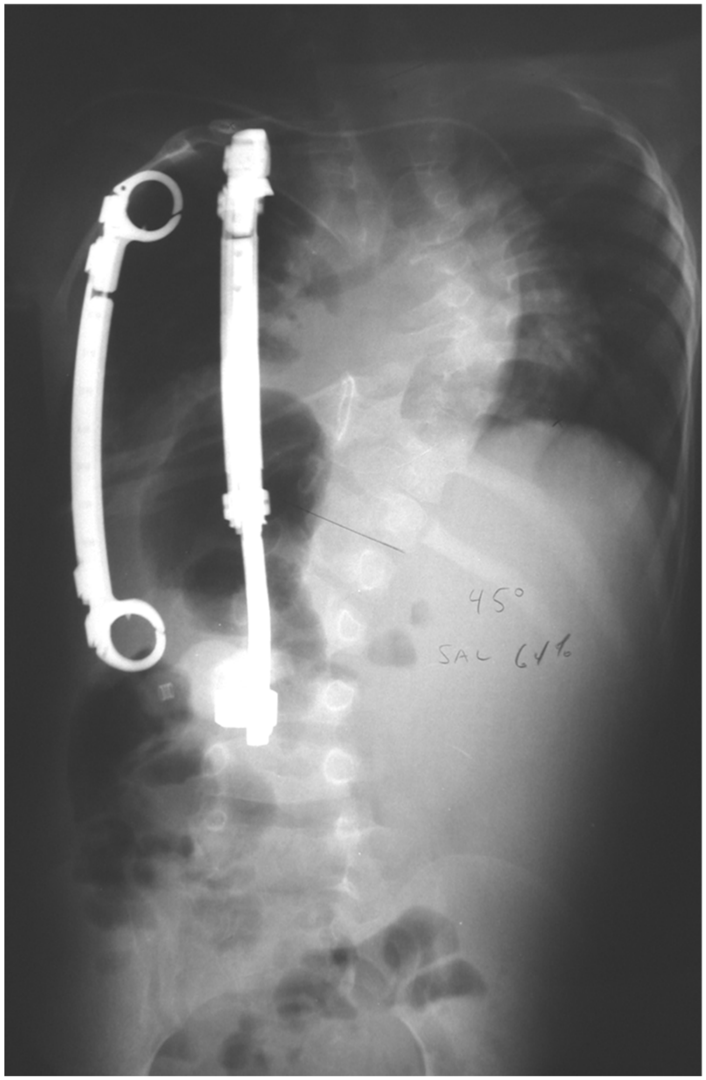
Thoracic Insufficiency is *Extrinsic*, restrictive lung disease





Clinical Problem

Expansion Thoracoplasty



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

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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

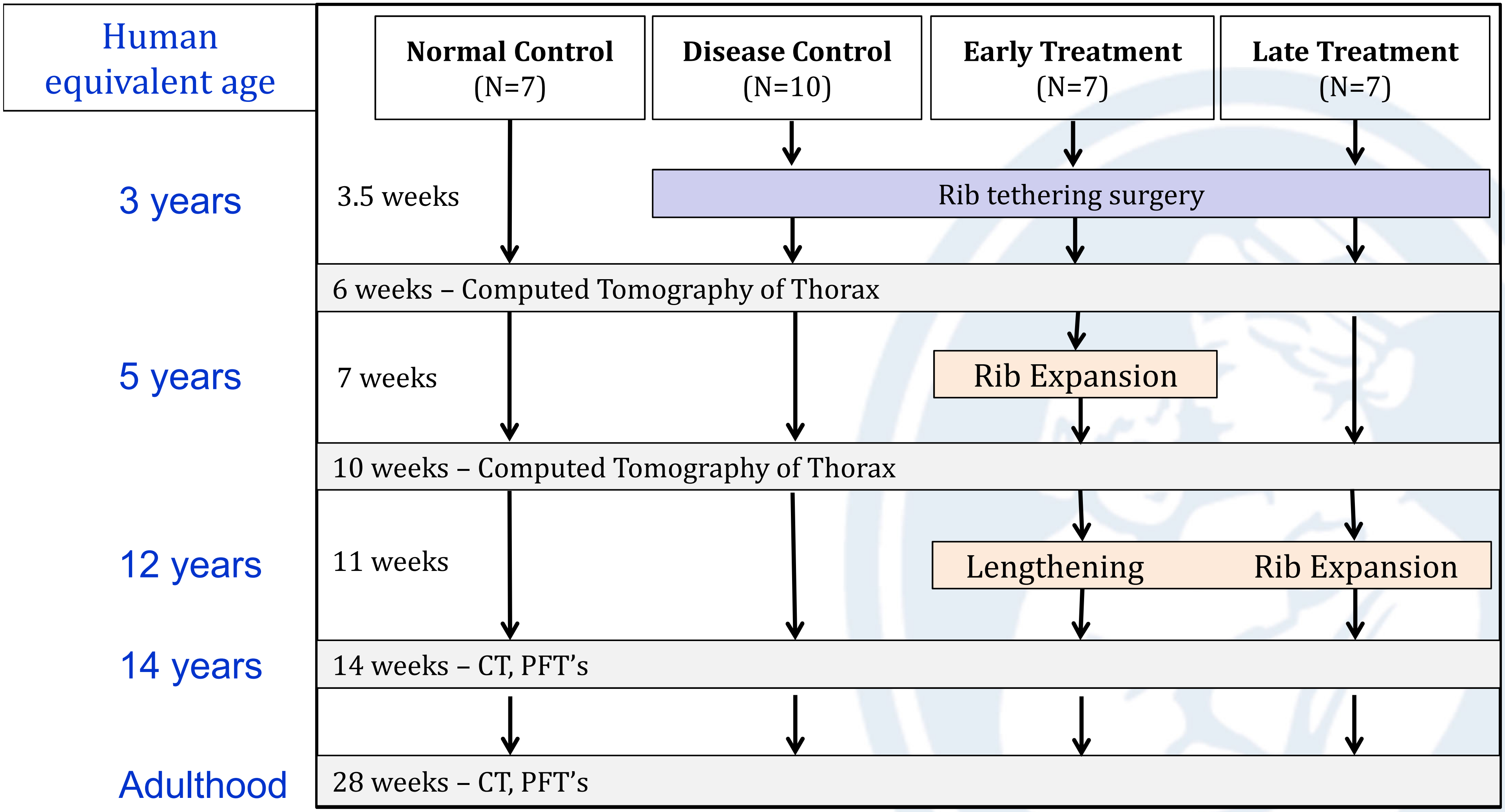
1. Prolonged inhibition of thoracic growth will induce pulmonary hypoplasia and respiratory insufficiency
2. Spine/chest wall deformity @ 6 wks (growing rabbit) influences lung growth and respiratory function @ 28 wks (adult rabbit)
3. Expansion thoracoplasty will promote growth of the lungs and thorax 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

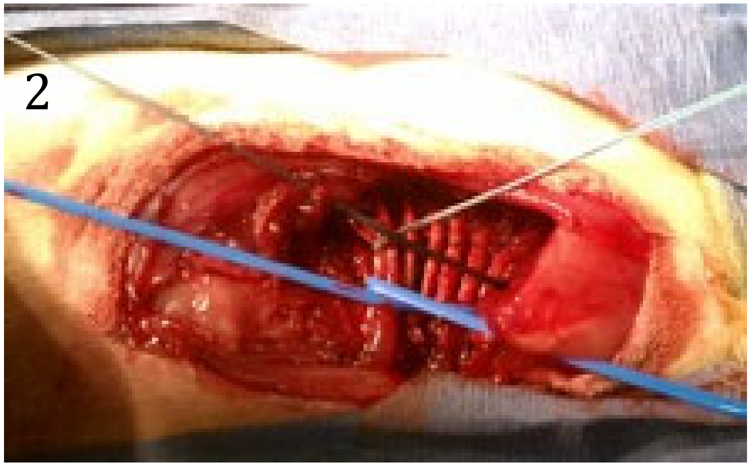


Rabbits skeletally mature by 28 weeks, growth decreases exponentially after 14 wks. Pulmonary development continues in healthy rabbits

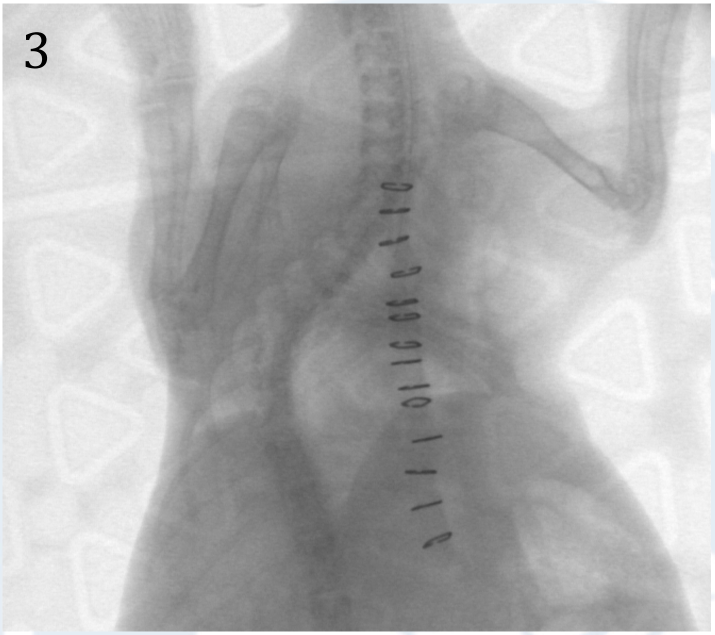
Methods: Deformity Model

Rib Tethering – 3 ½ wks old

Exposed right thorax



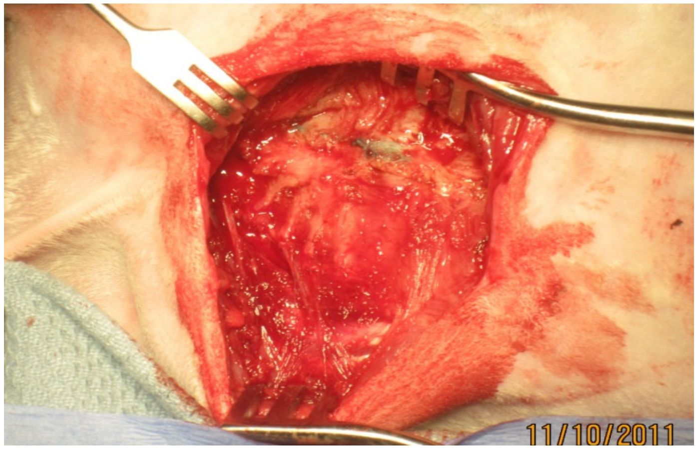
Tethered right ribs 3-9



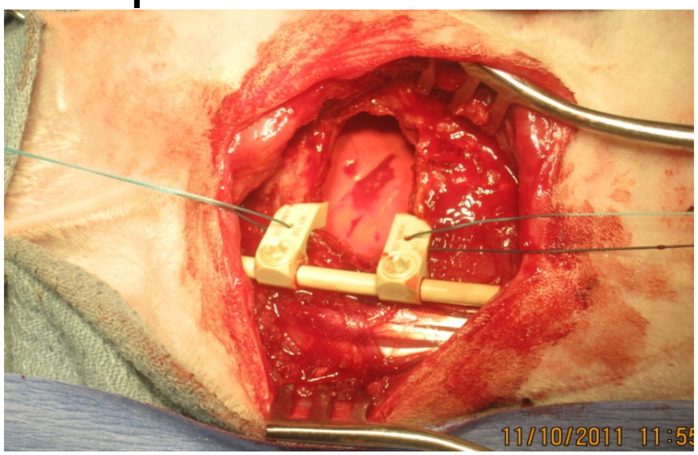
Post-Op AP flouroscope

Methods - Treatment

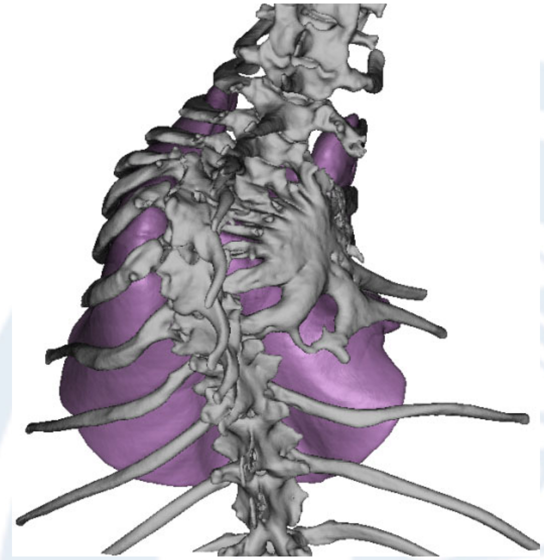
Expansion Thoracoplasty @ age 7 or 11 wks

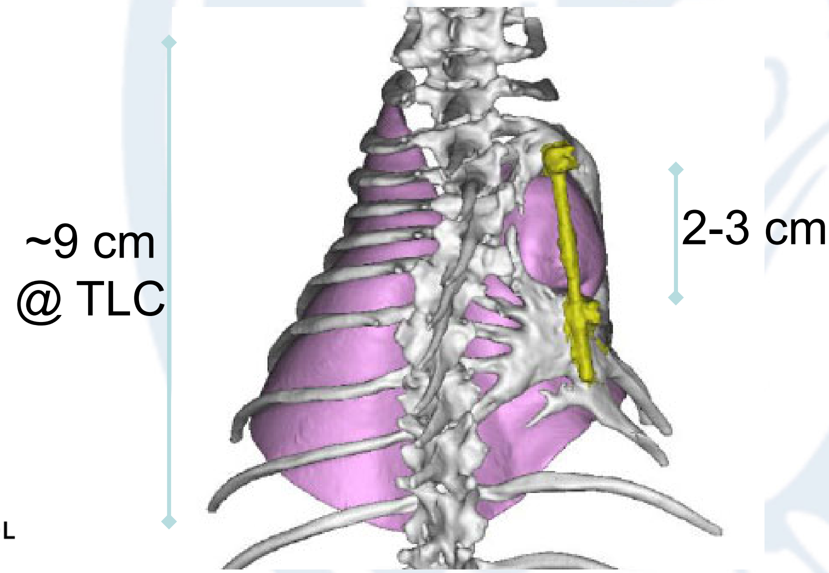


Exposed Rib mass



Rib Expansion/Lengthening



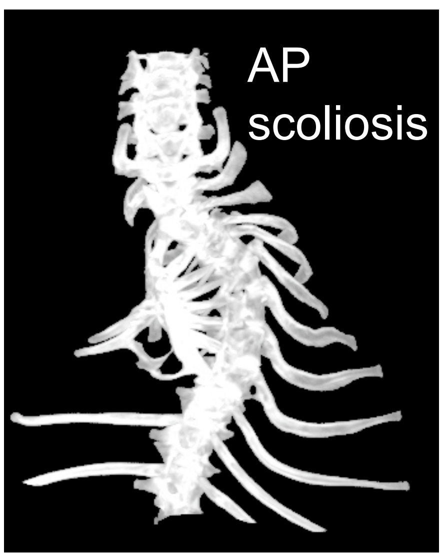


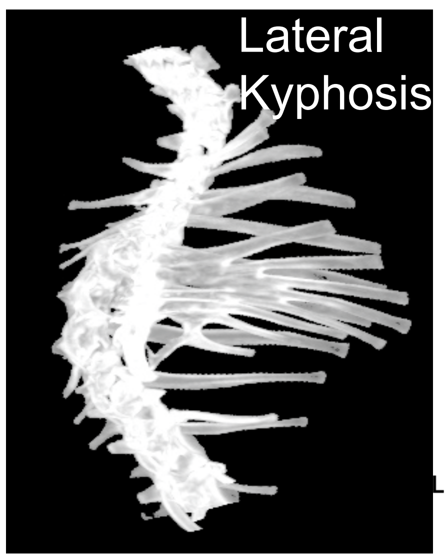
Measures – Thoracic Structure

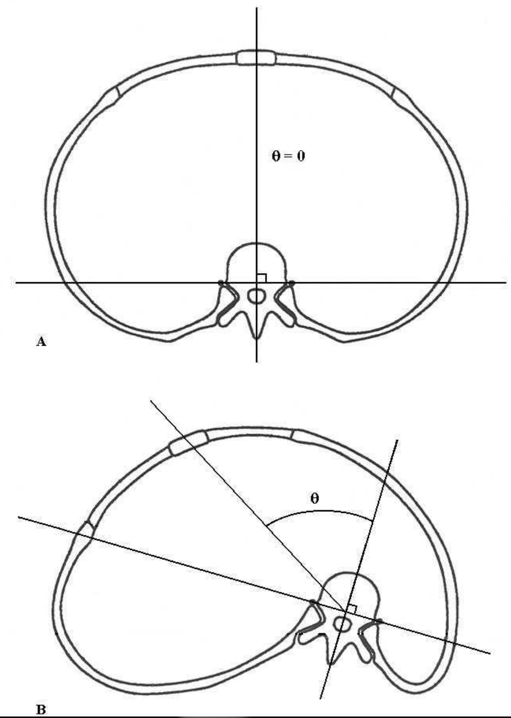
- Thoracic Deformity
  - Scoliosis, (AP projection), θ_S
  - Kyphosis, (lateral projection), θ_K
  - Thoracic Rotation (Transverse slice)

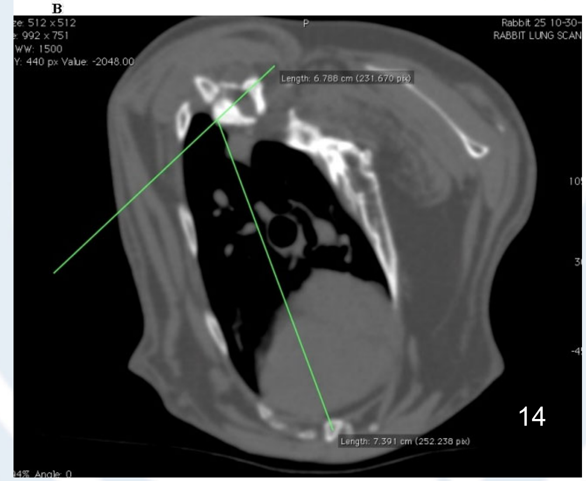
  - Estimation of maximal deformity angle

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





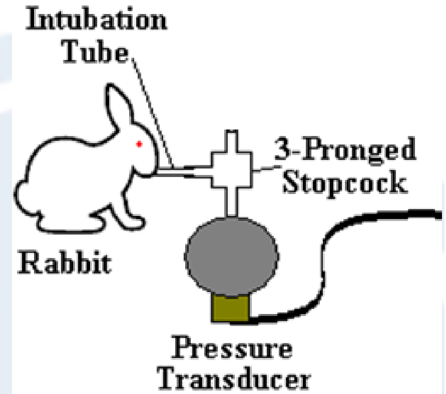


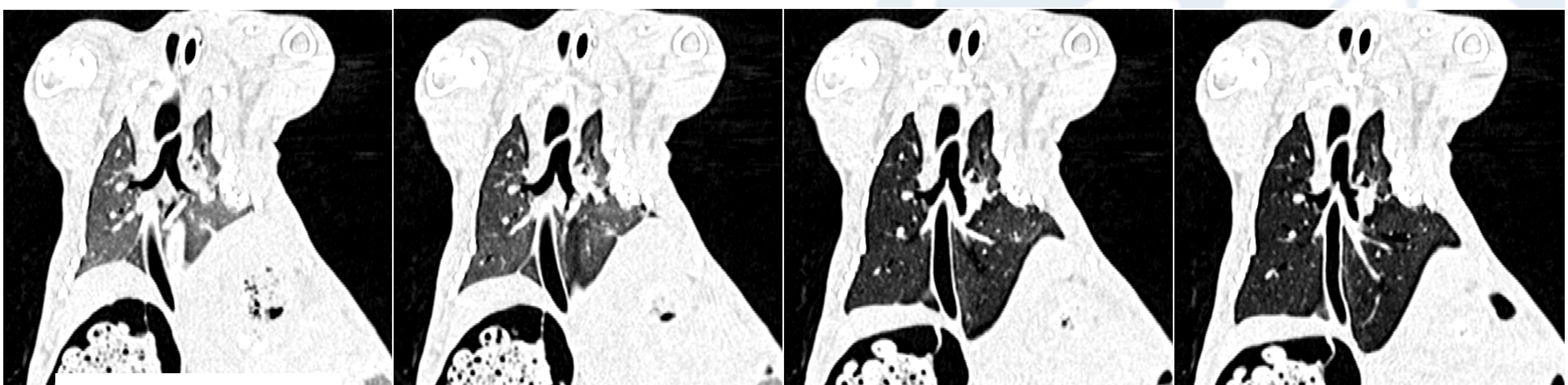


Breath-hold CT imaging

- 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



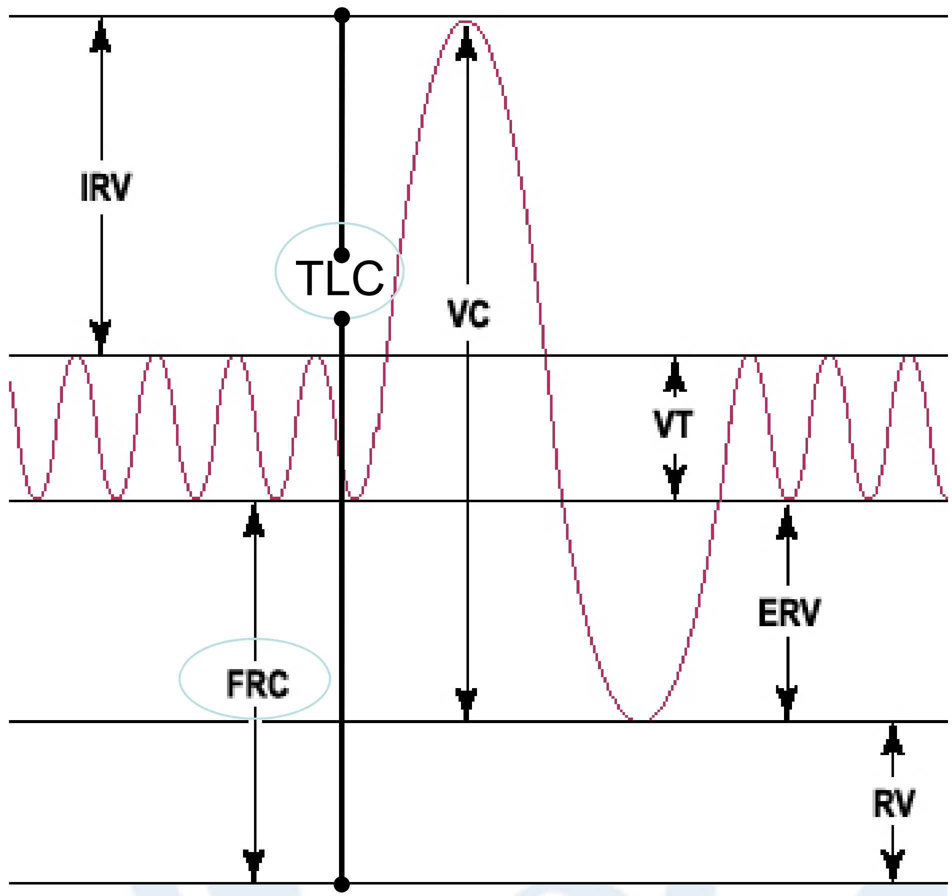


FRC 0 cm H_2O | 5 cm | 15 cm | TLC 25 cm H_2O

Lung Volume Measures

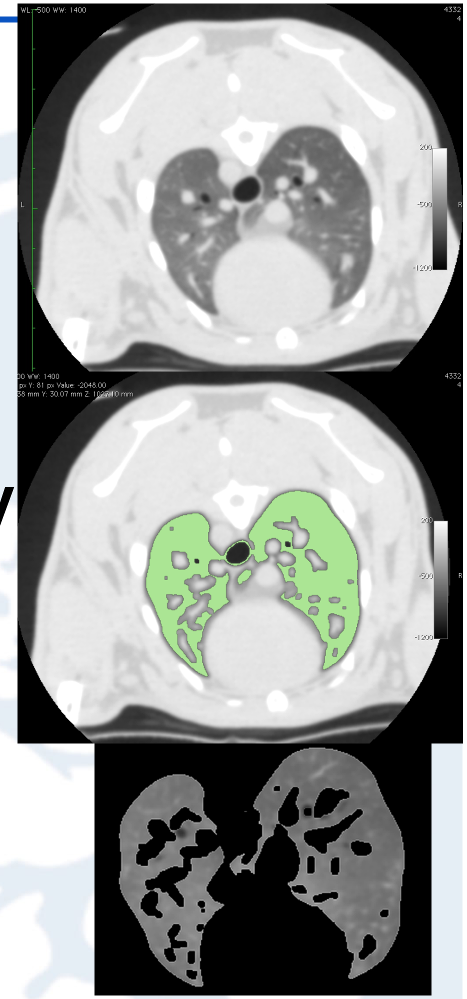
CT based measures

- TLC : Aerated lung volume @ 25 cmH_20 static ETT press.
- FRC : Aerated lung volume @ 0 cmH_2O static ETT press.



Respiratory Volumes

Calculation Lung Mass and Volume

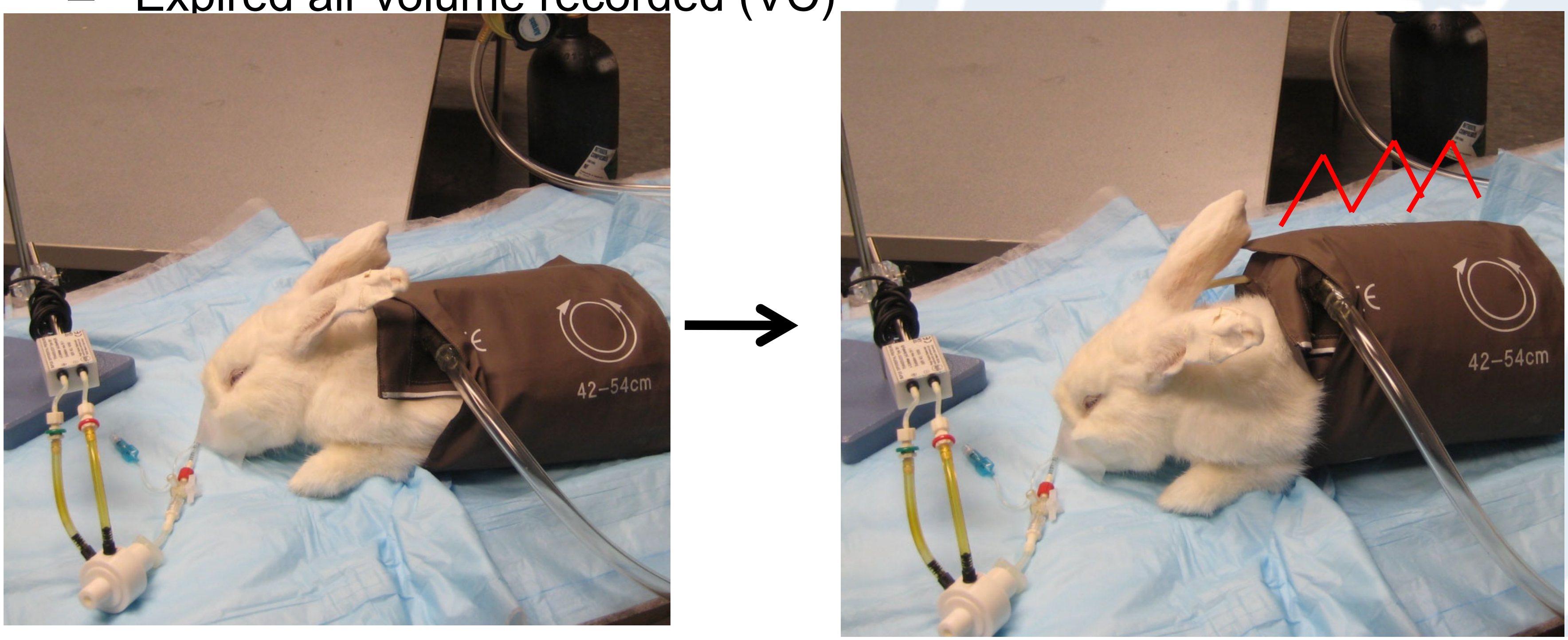


- **Segment Lung:**
  - Based on tissue density threshold
  - Manually remove esophagus and trachea
  - Obtain total lung volume @ sequential "breath hold" pressures 0-25 cmH_2O
  - Separate left and right lungs
- **Hounsfield unit(HU)linearly related to density**
  - HU = 0 equivalent to H_2O
  - HU = -1000 equivalent to air
  - Lung tissue density equivalent water ~1g/mL Air density negligible ~0g/mL
  - $\rho_{voxel} = 1 + (HU/1000)$
- **Calculations:**

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

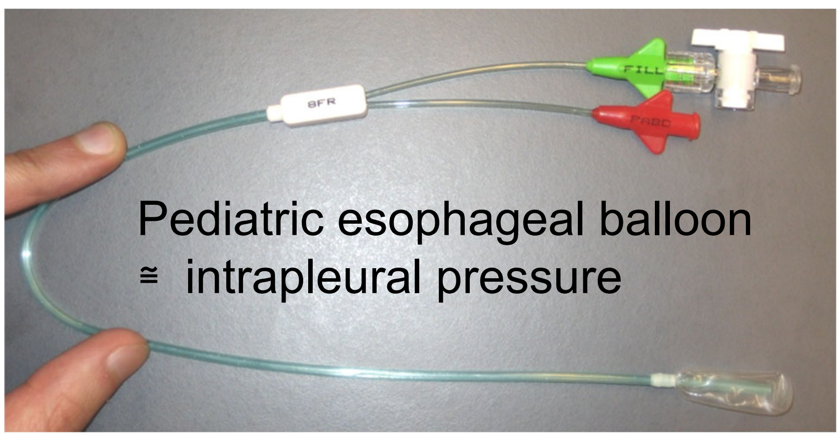
PFT's – Vital Capacity

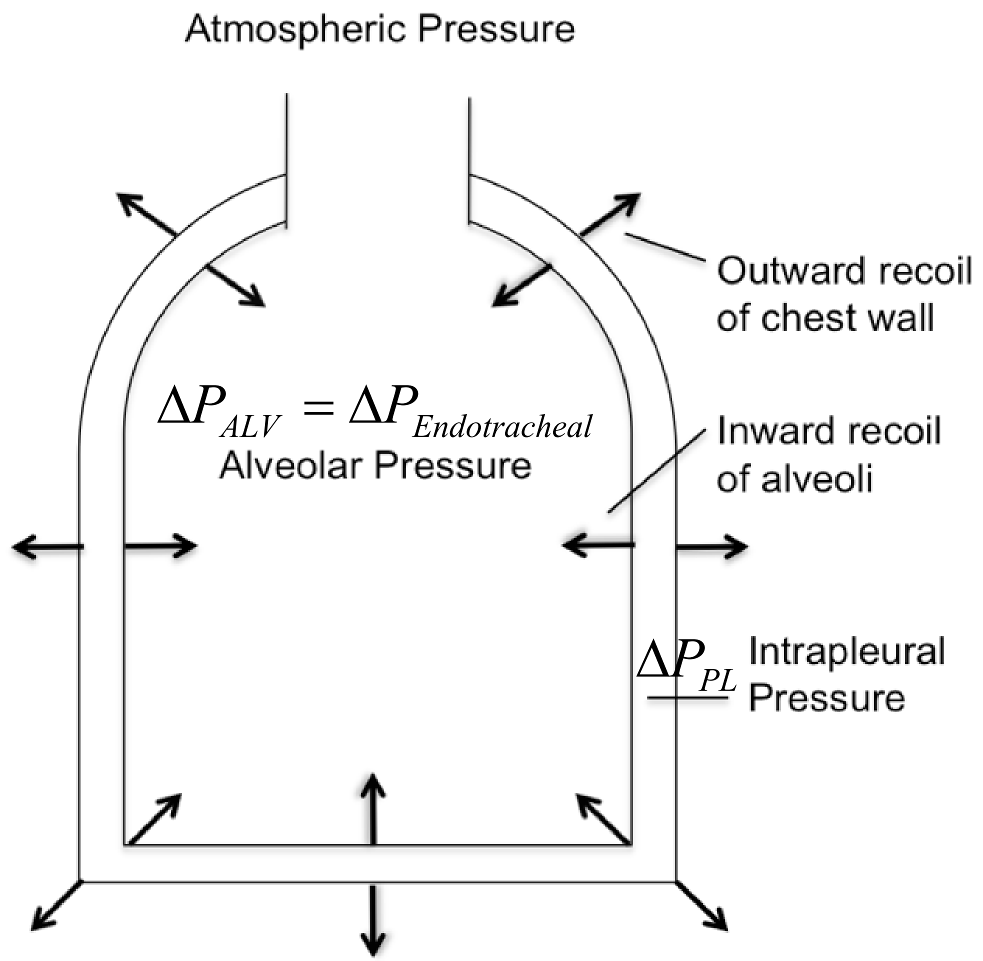
- **Raised Volume Rapid Thoracoabdominal Compression (RVRTC)**
  - Protocol for Infant PFT's
  - Lungs forcefully deflated from TLC to RV
- **<u>Protocol</u>: Anesthetized/Ventilated rabbit**
  - Lungs inflated to 25 cmH_2O (TLC)
  - Thoracoabdominal air bladder rapidly raised to 60 cmH_2O
  - Expired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



Partitioned Compliance/Elastance

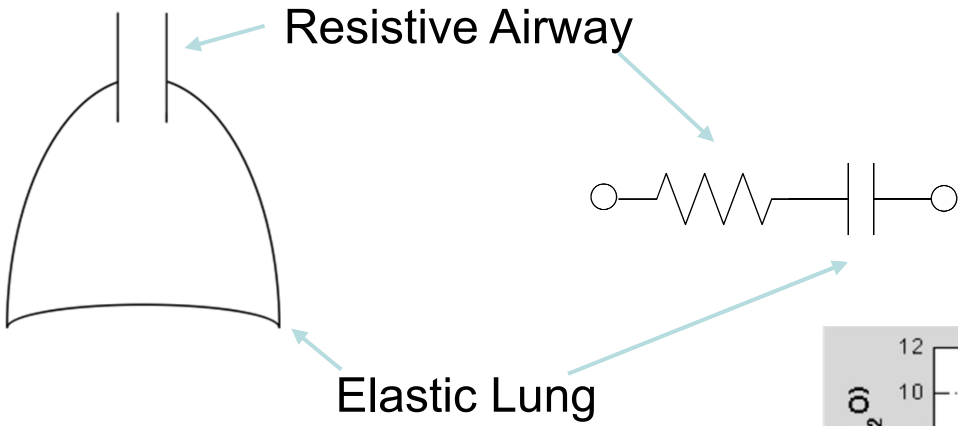
- **Chest wall** $$C_{CW} = \frac{\Delta V_L}{\Delta P_{PL}}$$
- **Lung** $$C_L = \frac{\Delta V_L}{\Delta P_{ALV} - \Delta P_{PL}}$$
- **Total Resp.** $$C_R = \frac{\Delta V_L}{\Delta P_{ALV}}$$





Methods

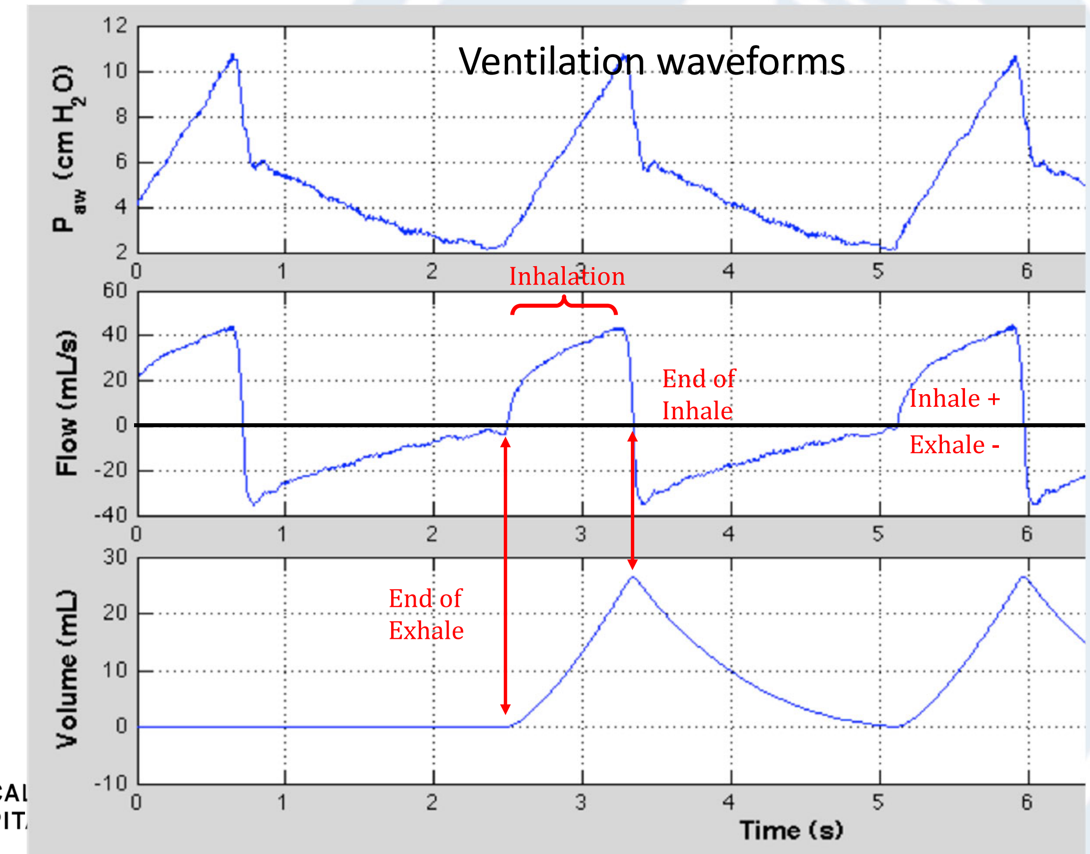
PFT's – Single Compartment Model



Resistance, Elastance, PEEP

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

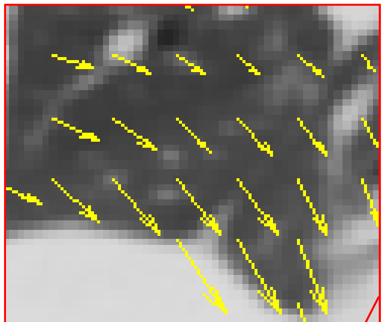
Pressure, Flow, Volume



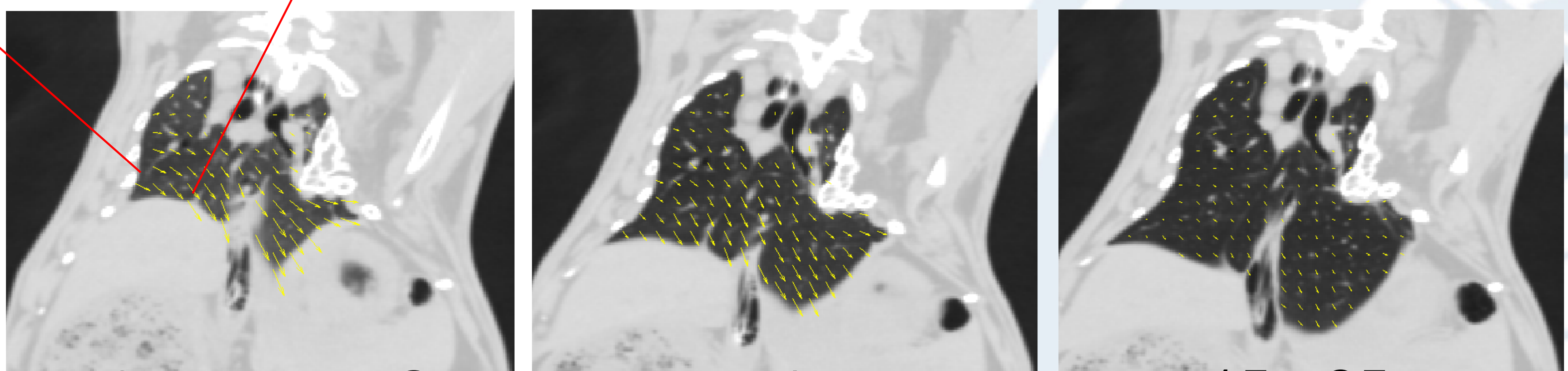
- Least squares fit in time-domain
- Pressure and flow measured at airway opening

Ref: Lauzon AM, JAP 1991

CT Deformable Image Registration (CT-DIR)

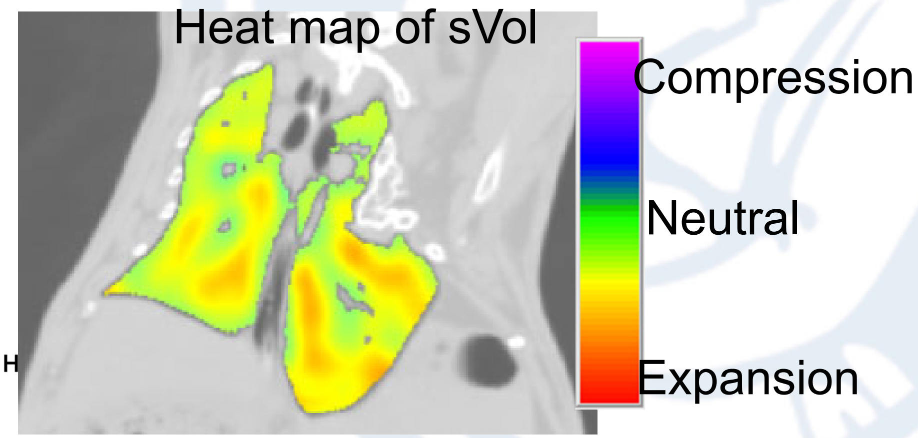


- **Voxel-by-voxel trajectory of lung parenchyma mapped during inflation on each sequential set of CT images[1]**



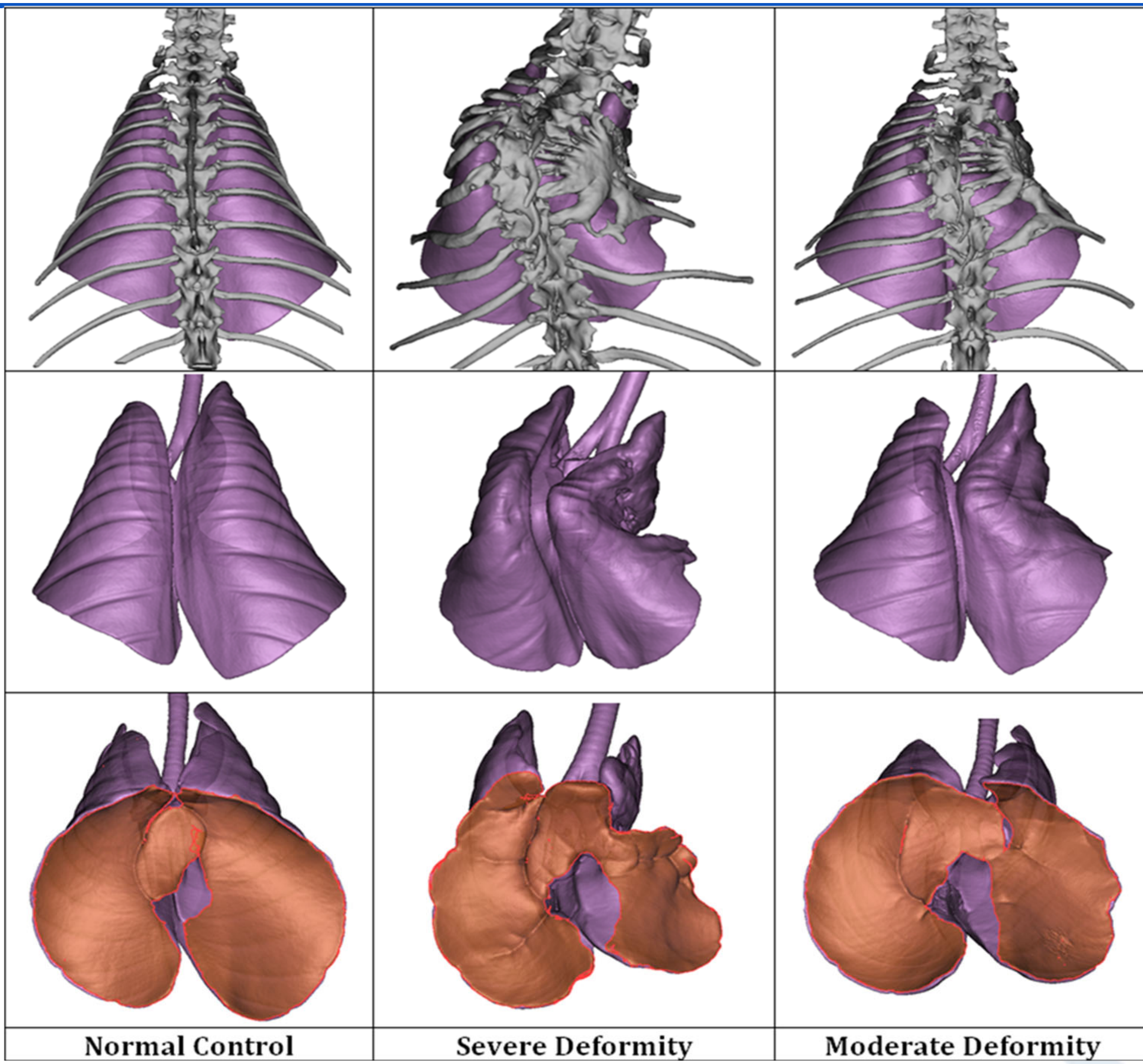
$0\text{->}5cmH_2O$ 5->15 15->25

- 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*

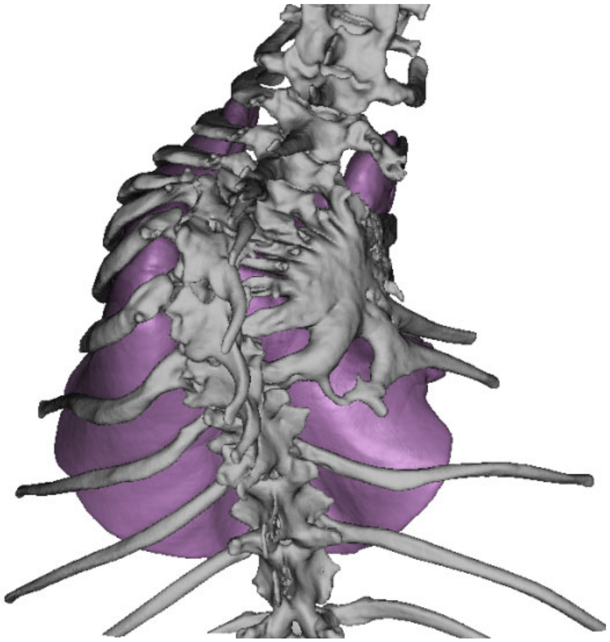


Thoracic Volume

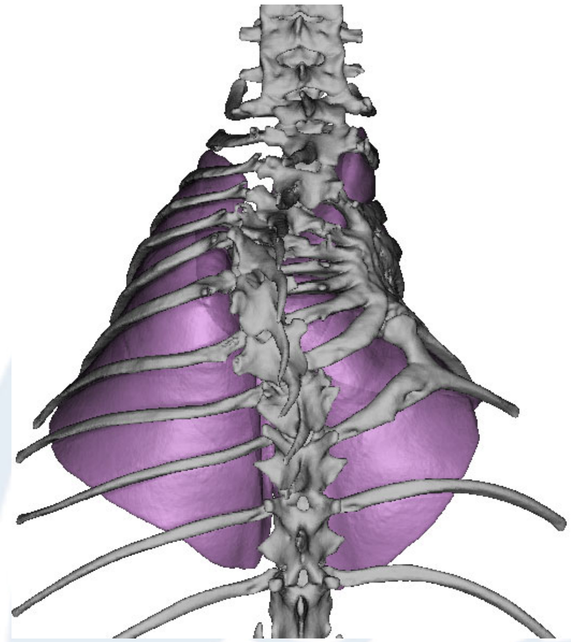
Aerated Lung Volume and Mass

Diaphragmatic Surface Area

Induced Deformity



SEVERE (θ_M >50^o , N=5)

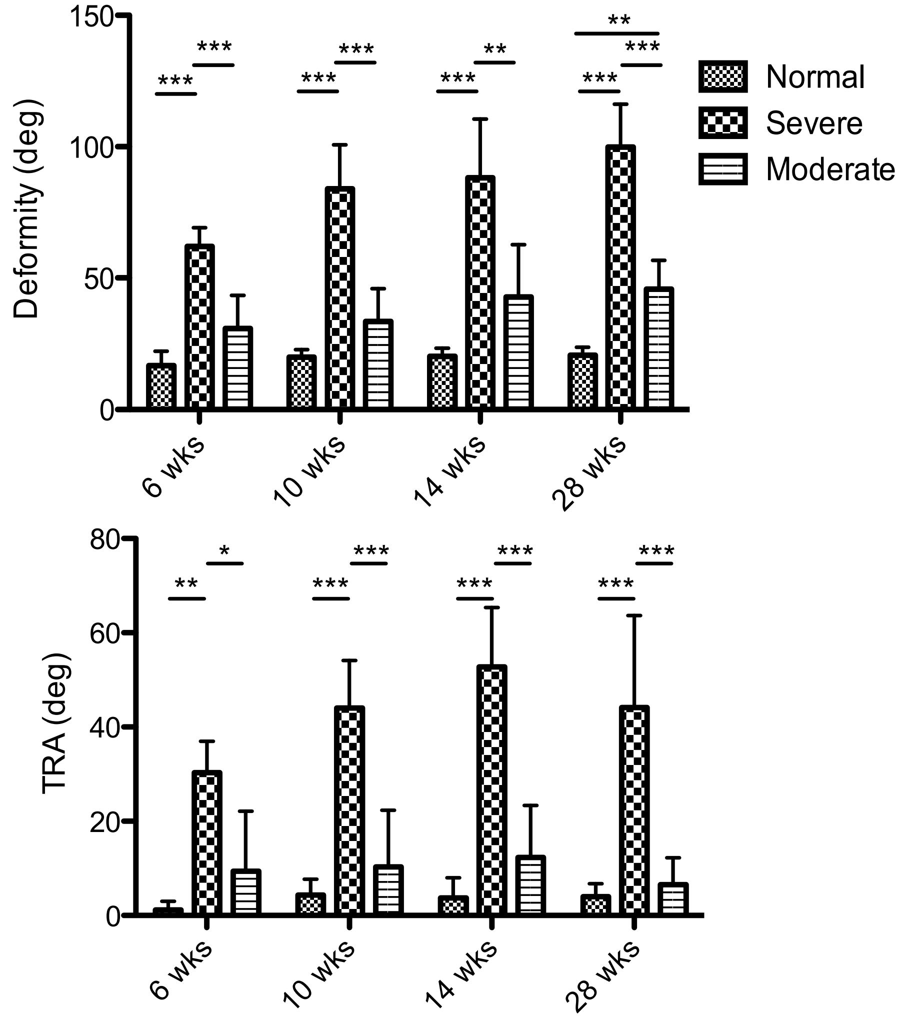


MODERATE (θ_M <50^o , N=5)

- **Progressive spine deformity for all rib-tether rabbits**
- **Variability in disease model**
  - Deformity, θ_M,ranged from 20^o to 71^o by 6 wks
  - Distinction between rabbits with deformity > 50^o

Aim1 – Results

Unilateral Tethering induced Thoracic Deformity



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

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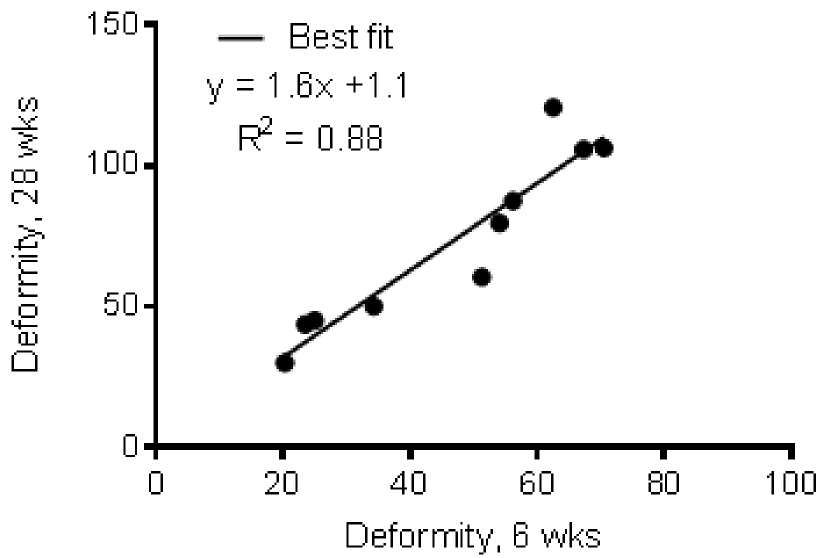
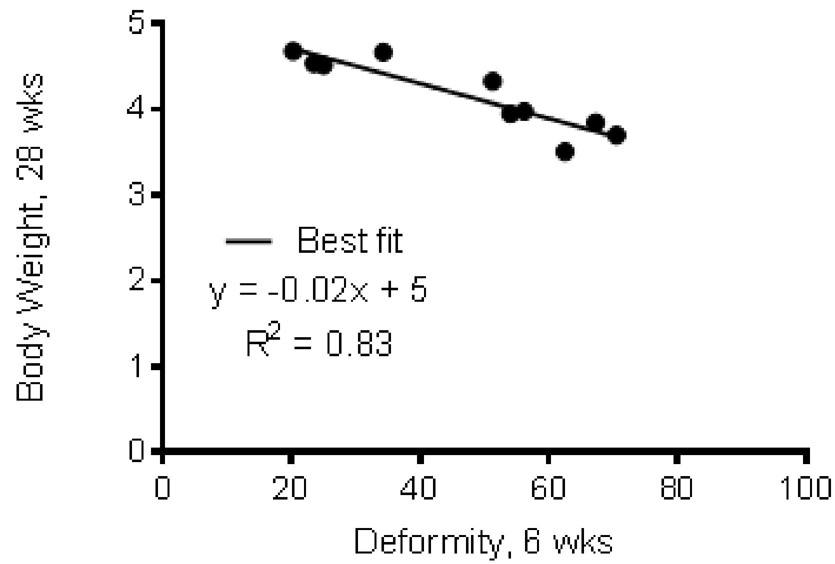
Aim1 – Results

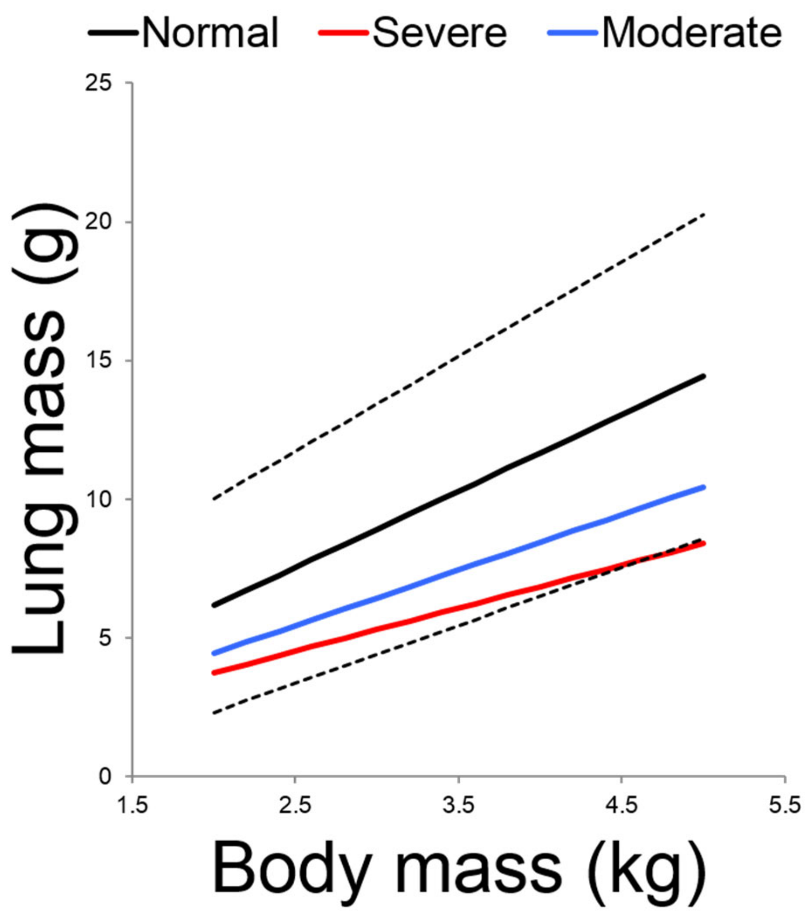
Spinal Deformity @ 6wks Predicts: Deformity and Body Weight @ adulthood

- **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



- **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**

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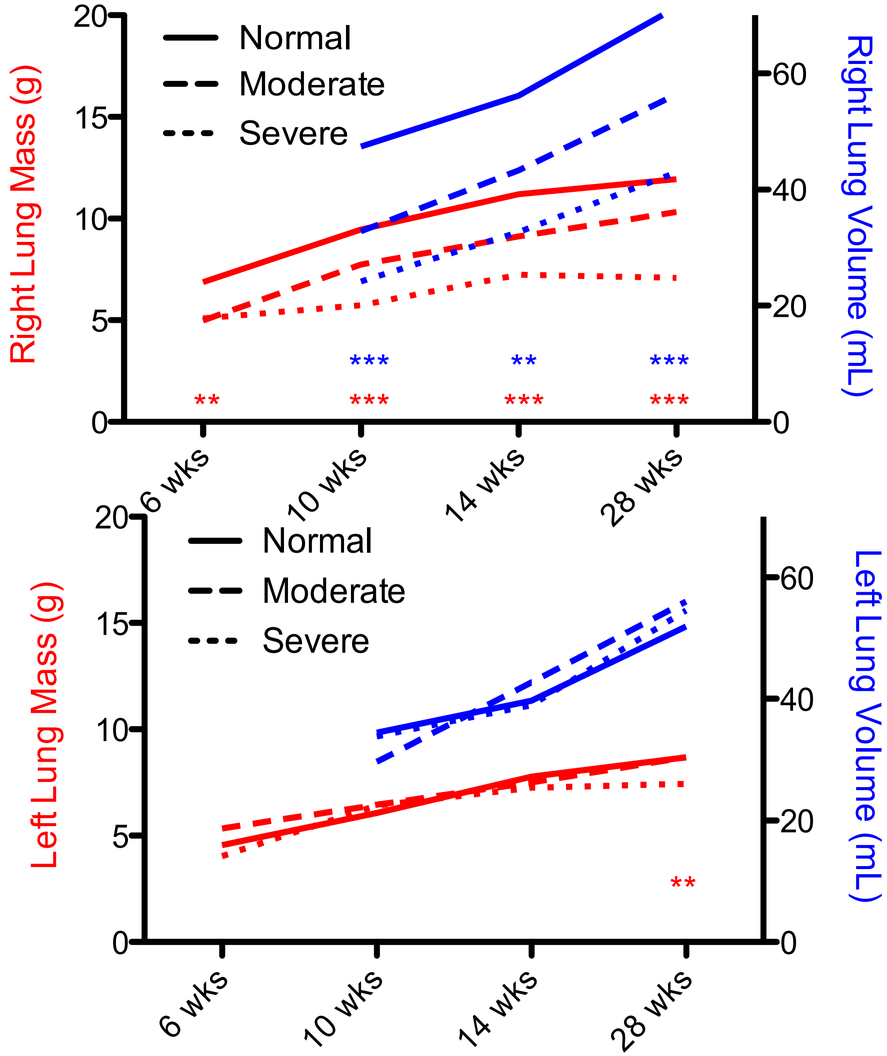
Volume & Mass Right and Left Lung during Growth

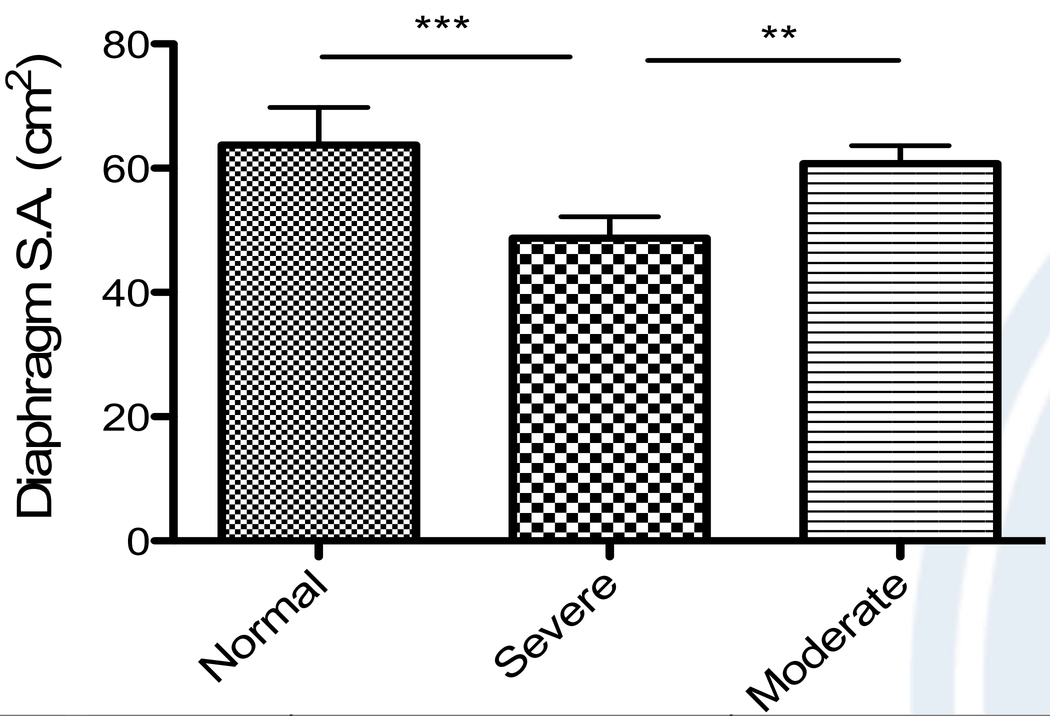


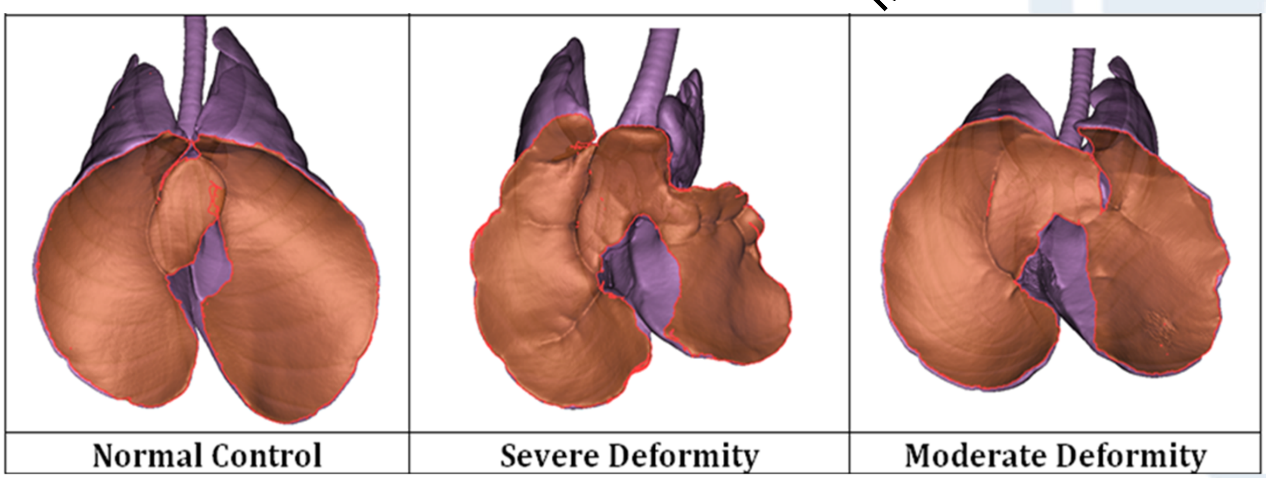
By age 28 weeks

- **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

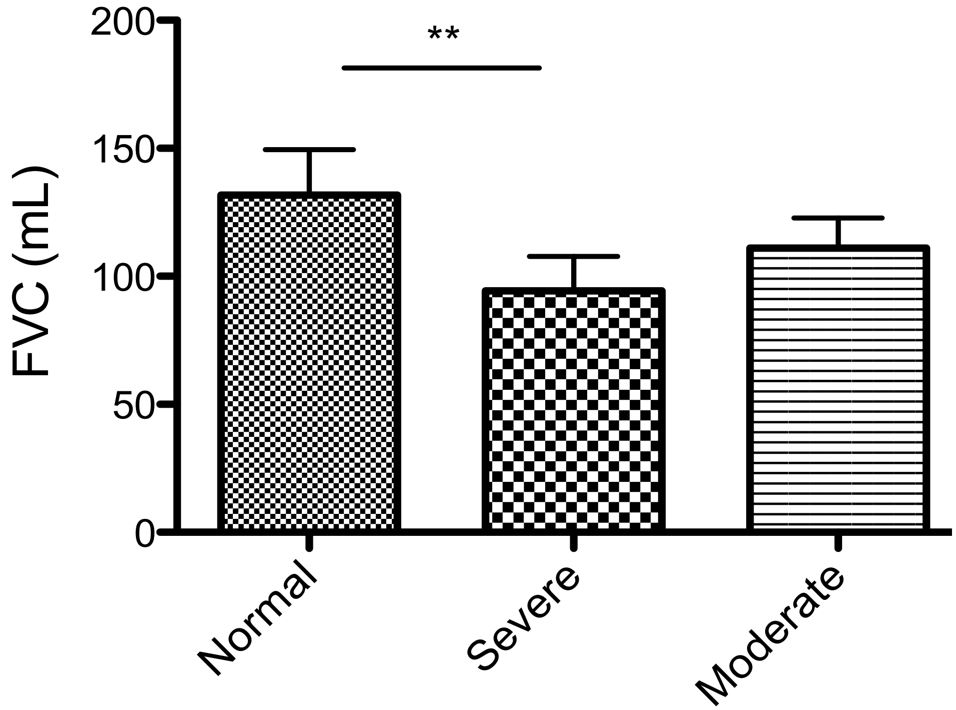
Diaphragm surface area





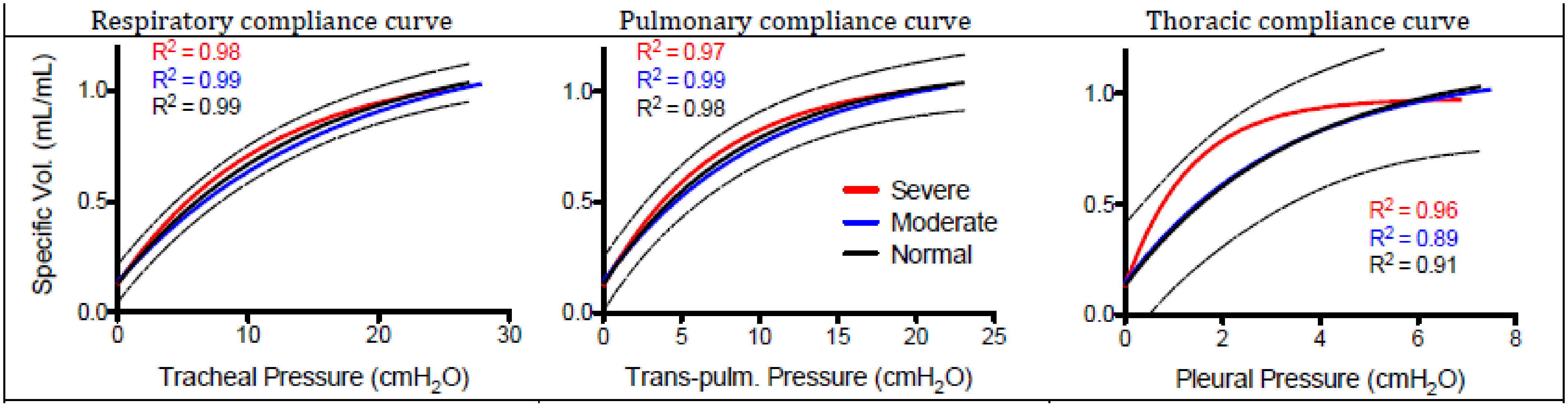
- Surface area of diaphragm in rabbits with severe deformity 76% of normal
- Diaphragm is primary driver (piston) for mass transfer air in/out lung

Forced Vital Capacity



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

Partitioned Compliance



- **V-P curves fit to exponential function:**

$$V = A - Be^{-kP}$$

A = estimate maximal lung capacity, k and B reflect stiffness

- **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”)

Aim1 – Results

Spine Deformity @ 6 wks Predicts Pulmonary Outcomes @ 28 wks

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

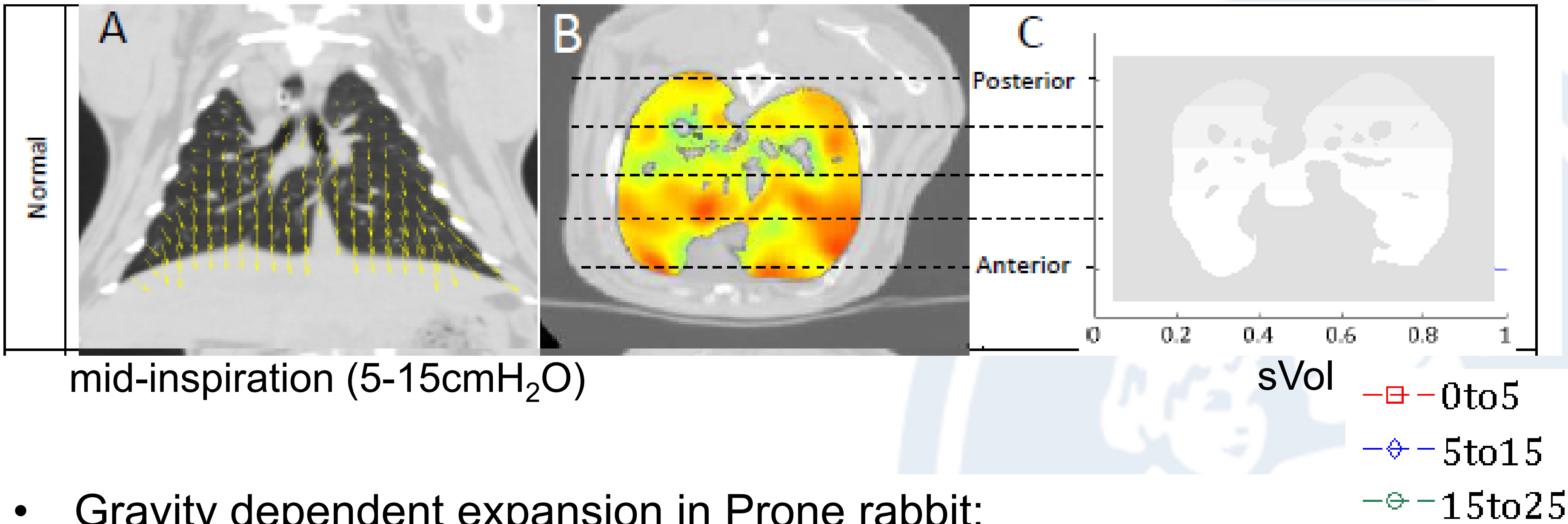
significance

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

Spine Deformity @ 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



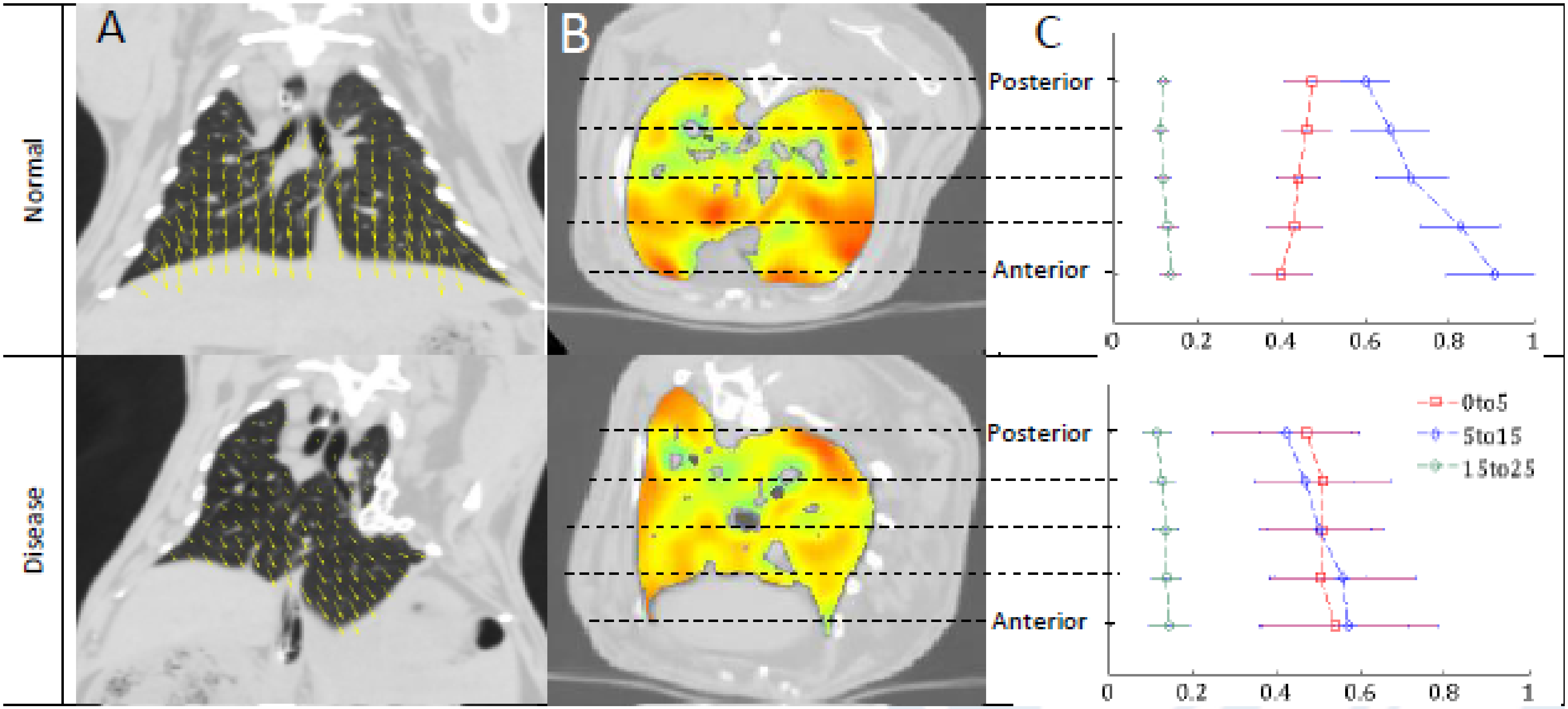
mid-inspiration (5-15cmH_2O)

- Gravity dependent expansion in Prone rabbit:
  - initial-inspiration (0-5cmH_2O) - sVol posterior > anterior
  - mid-inspiration (5-15cmH_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*

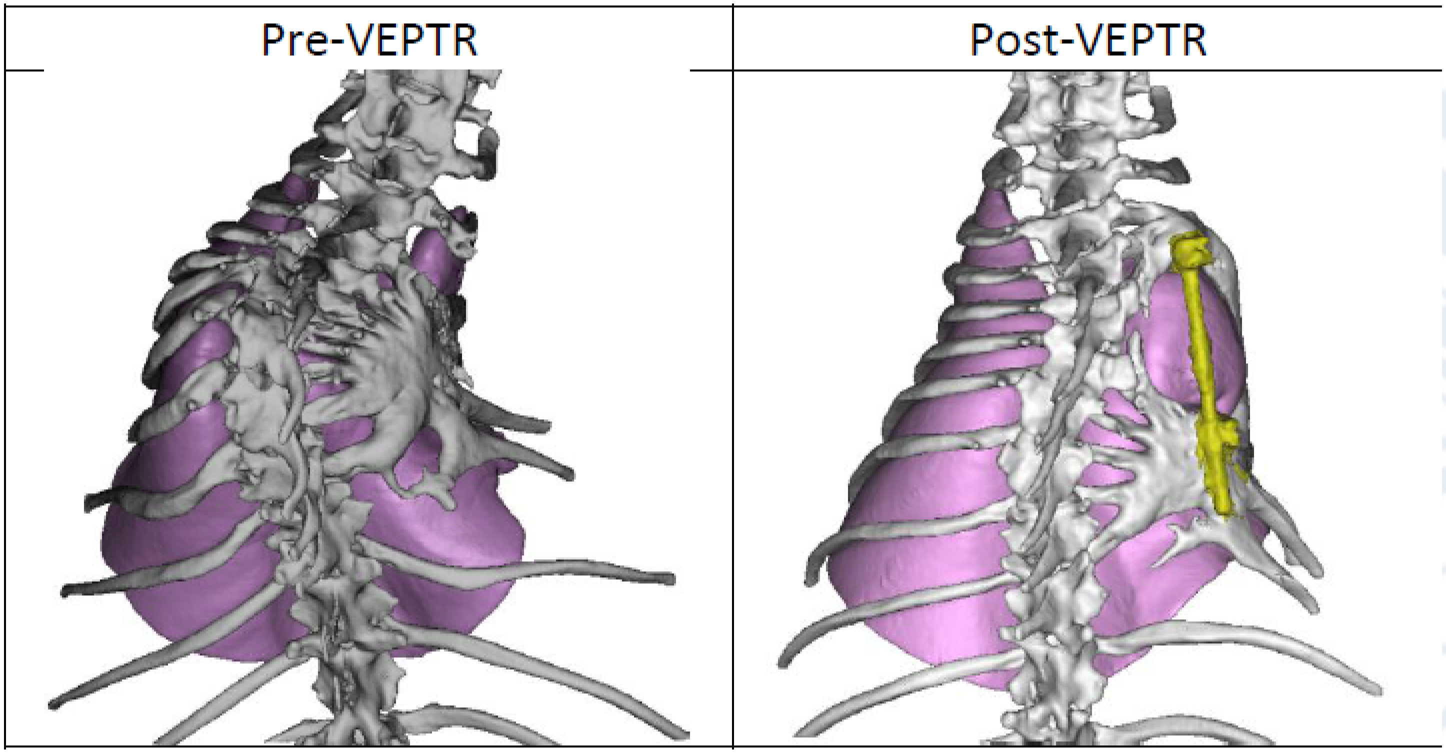
Aim 1 Results

Comparison of sVol Normal vs. TIS



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

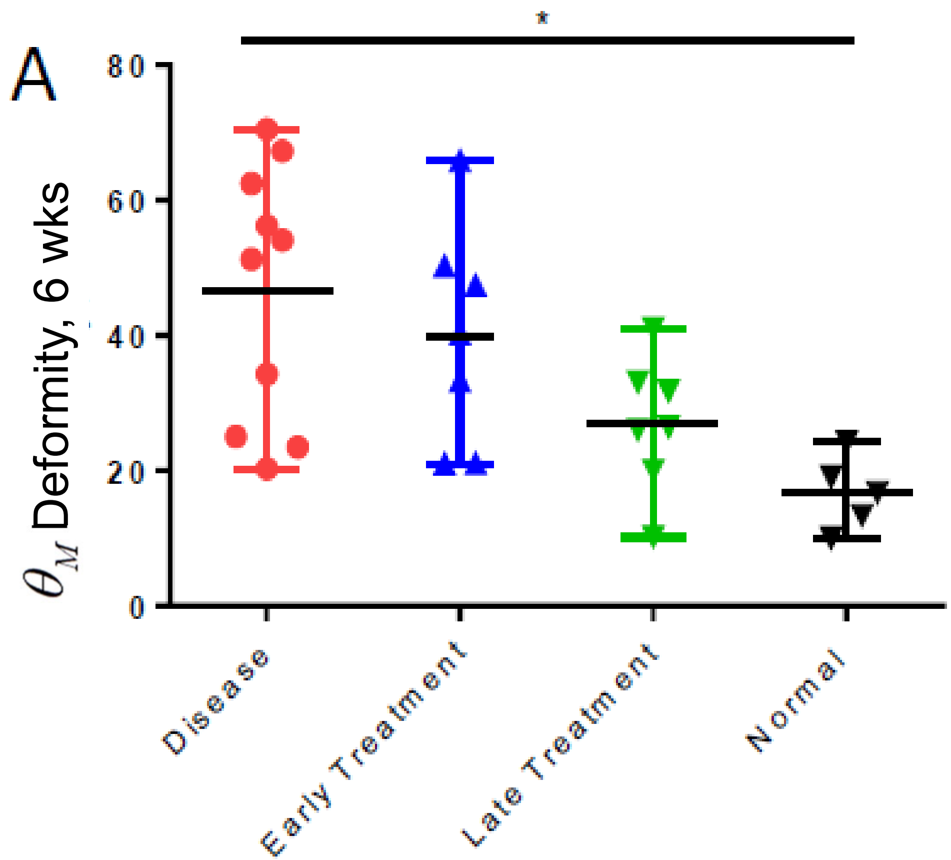
RESULTS: *Aim 2* Expansion Thoracoplasty



Total rib expansion

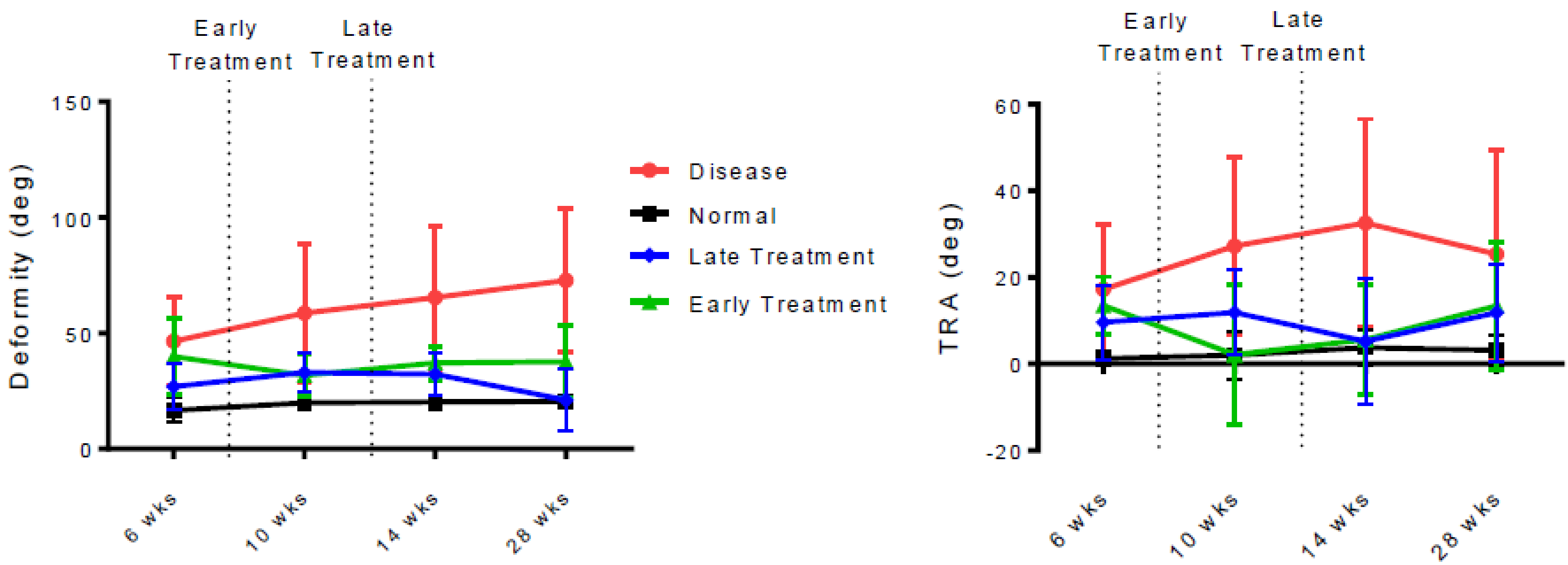
Early treatment [2.7 cm] > Late [2.0 cm] (p<0.001)

Baseline Deformity Among Groups



- **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

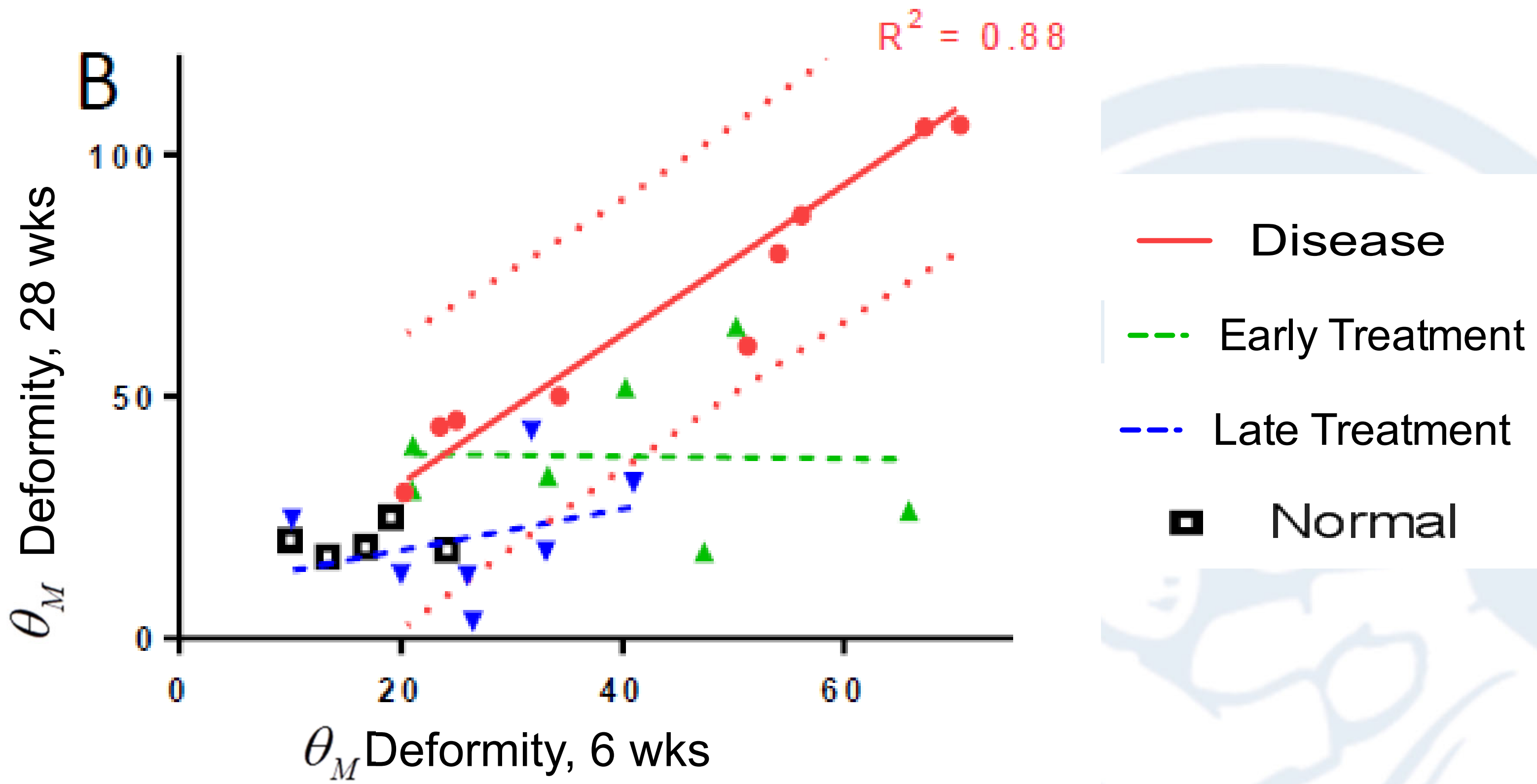
Progression of spine deformity and TRA during growth



- 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 @ age10 & 14 wks

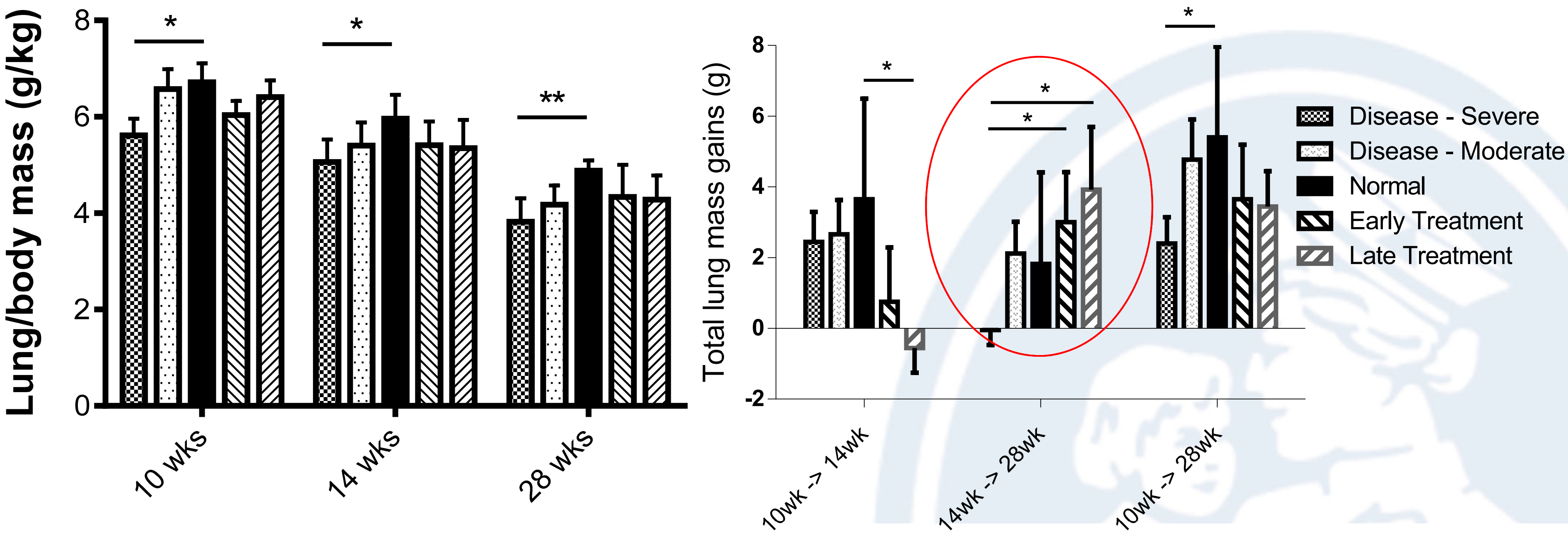
Aim2 – Results

Progression Spine Deformity: Disease vs. Treatment



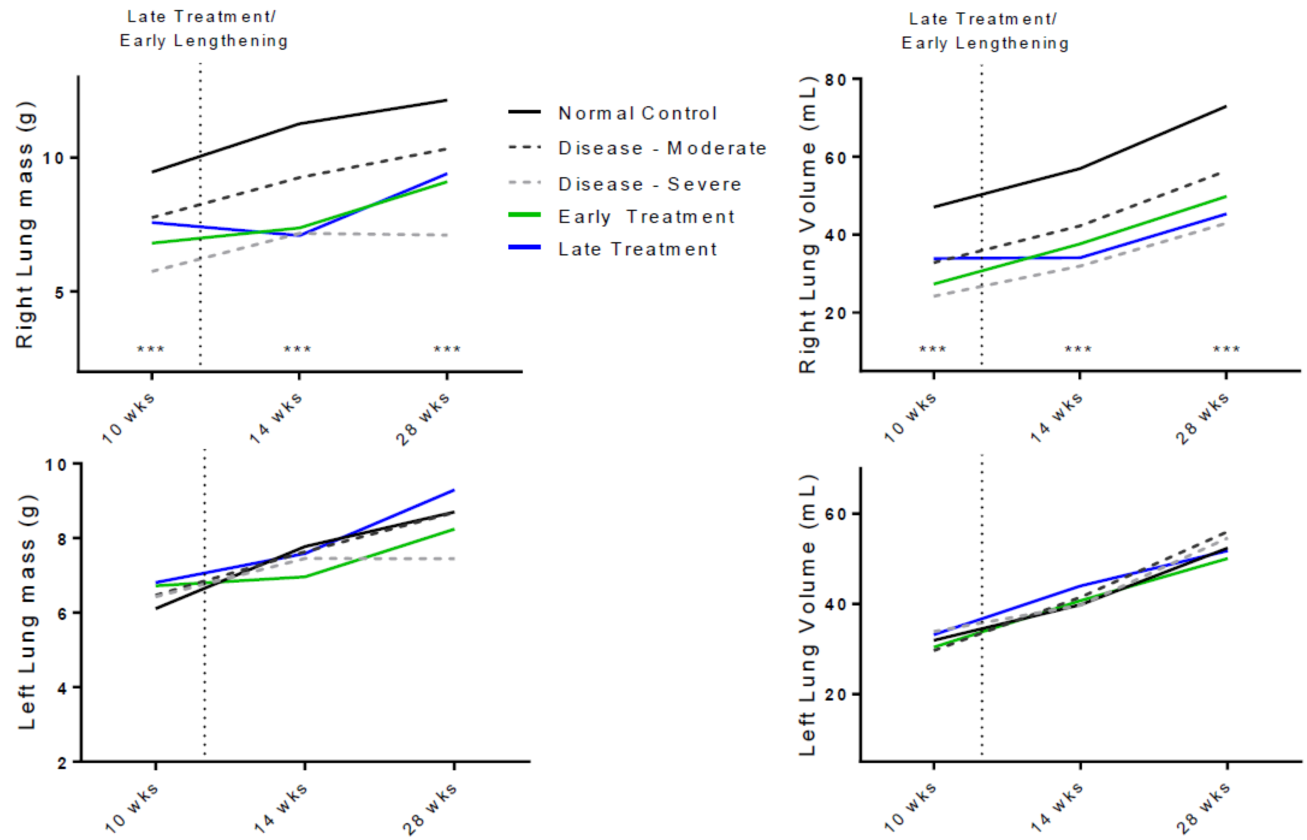
- Expansion thoracoplasty ameliorates predicted spine deformity @ 28 wks (slopes Tx groups different from Disease, p<0.01)

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

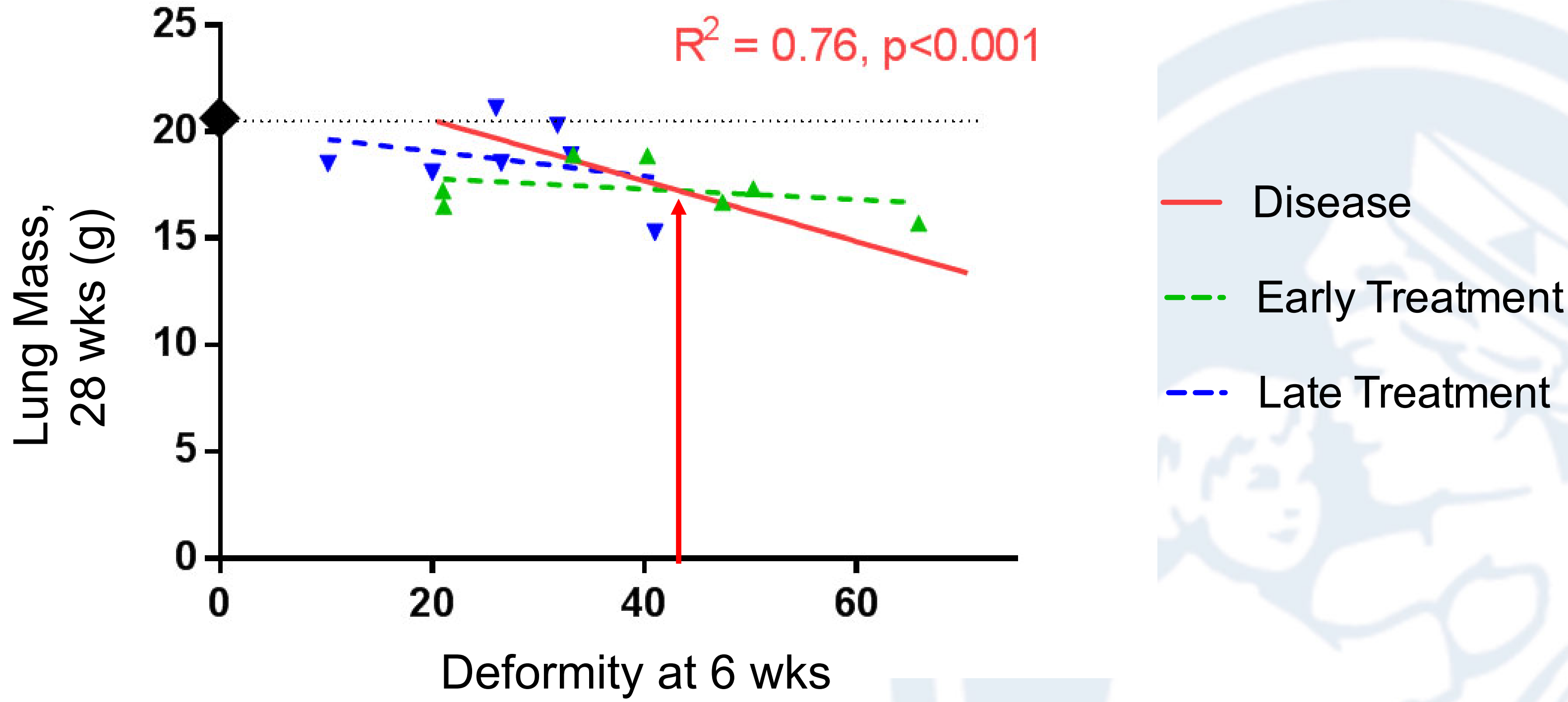
Mass and volume of segmented left and right lung during growth for treatment and disease groups



- @ 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 Early Treatment > Disease (ANCOVA, $p<0.05$)
- <u>Tipping point</u> = Deformity > 45^o: Lung growth early treatment > than expected for disease group

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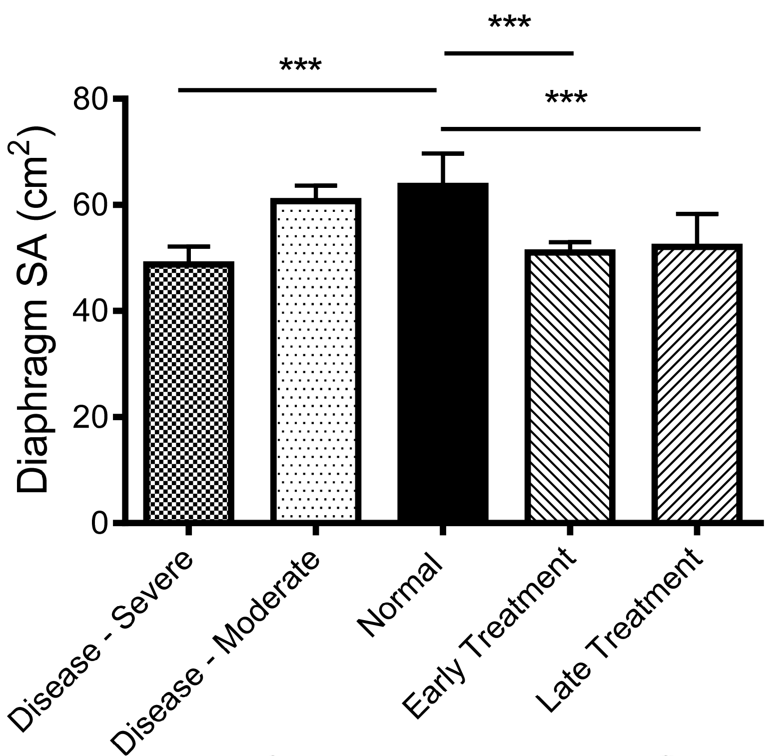
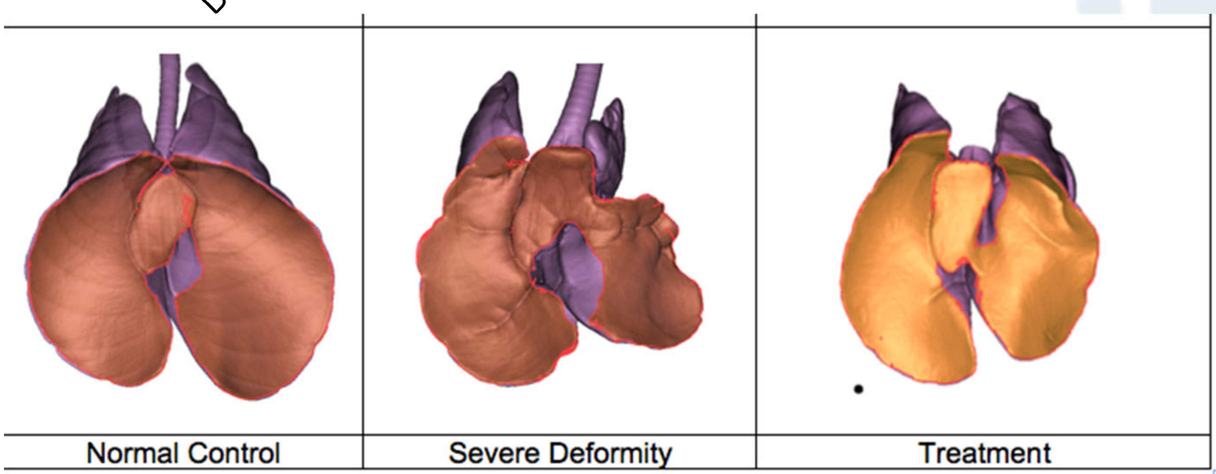
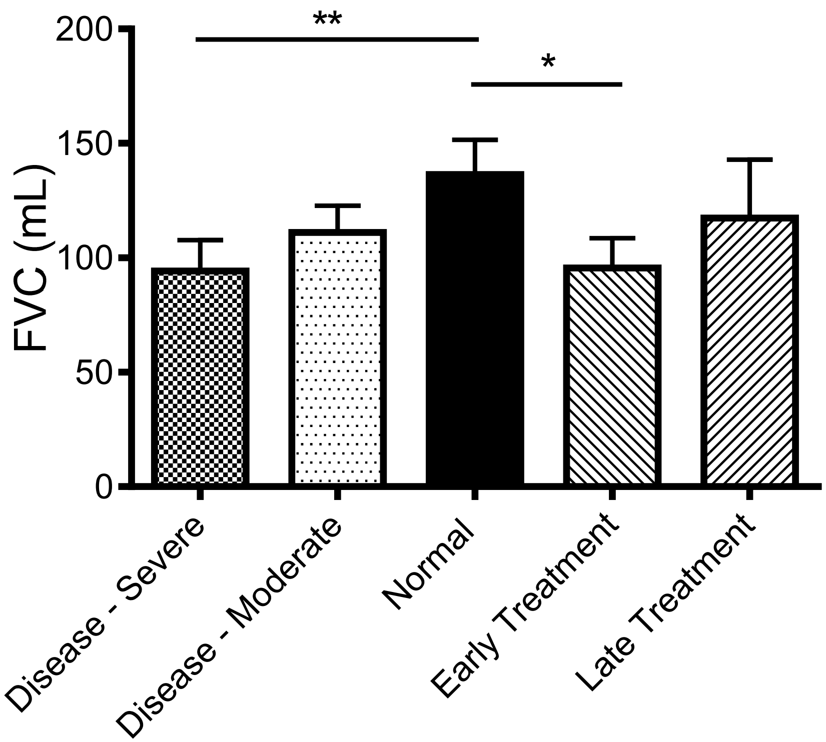
Surface Area of Diaphragm



- **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 ($p<0.001$)



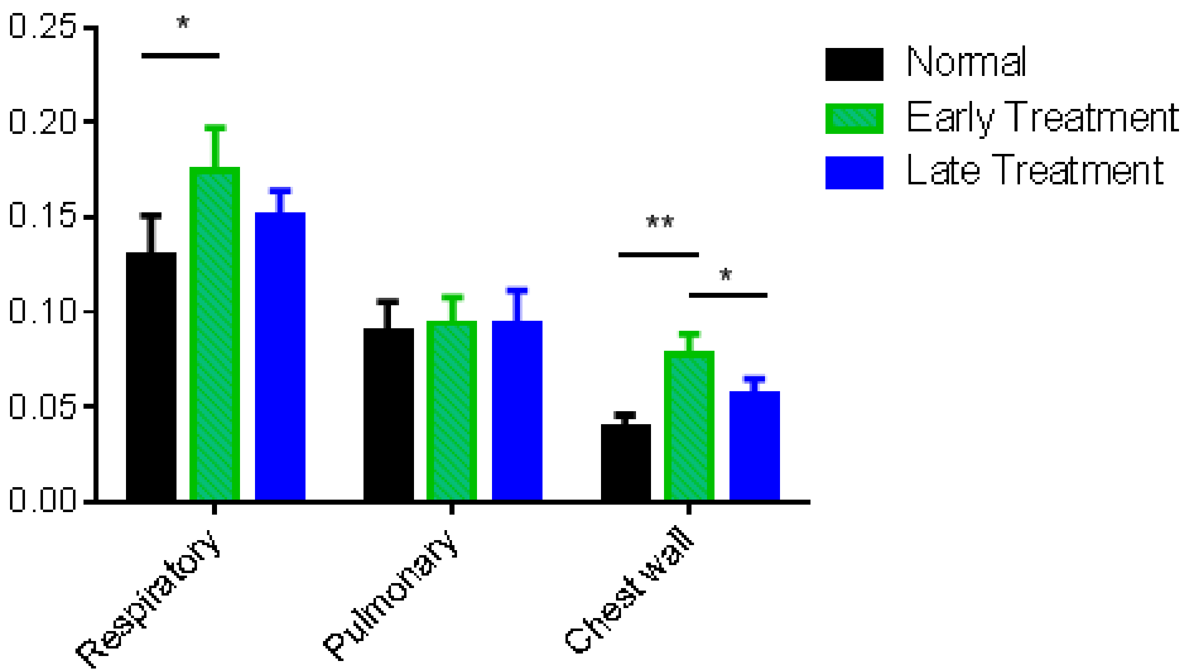
Forced Vital Capacity



- **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 ($p<0.01$)

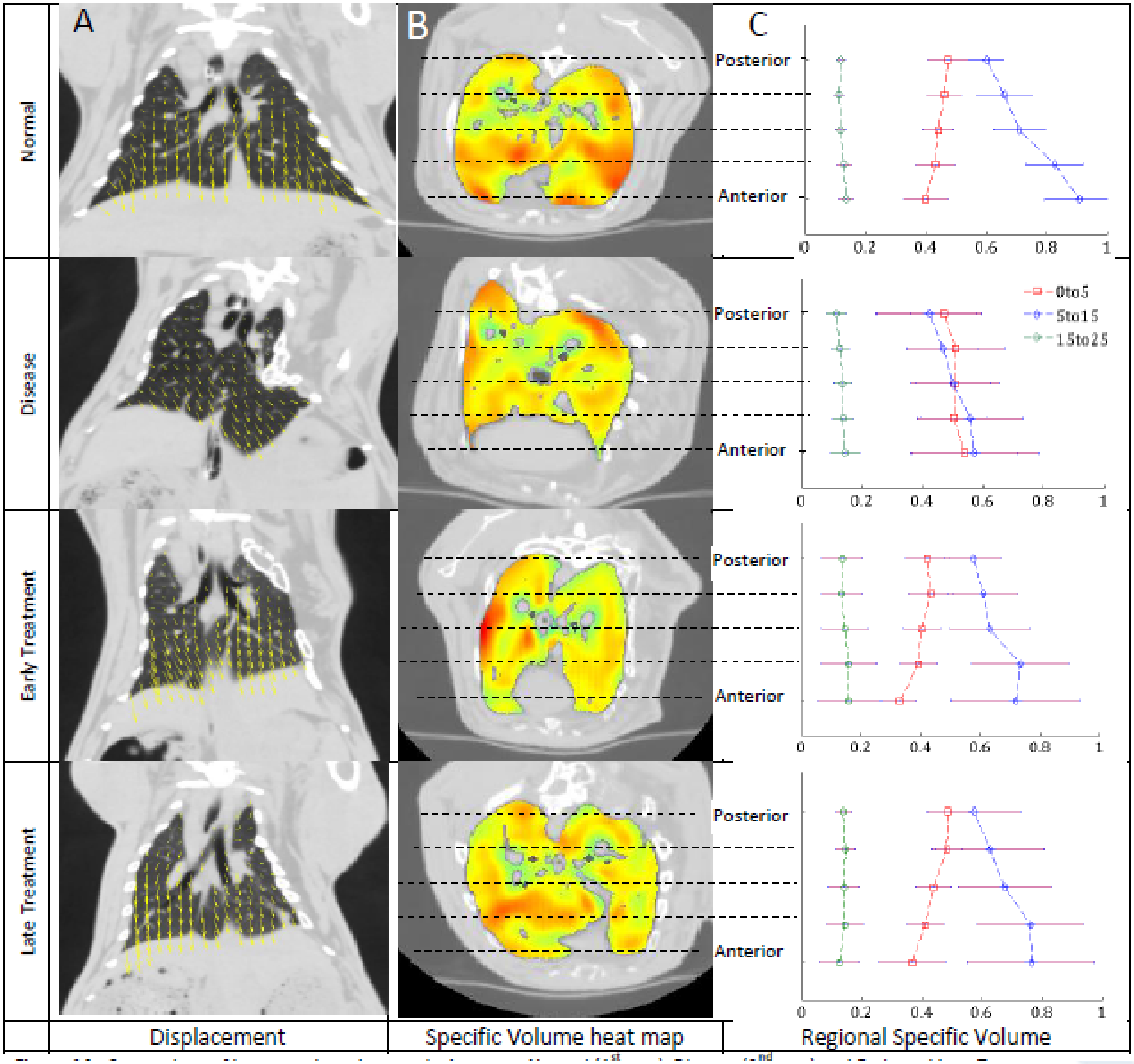
Aim2 – Results

Partitioned Elastance



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

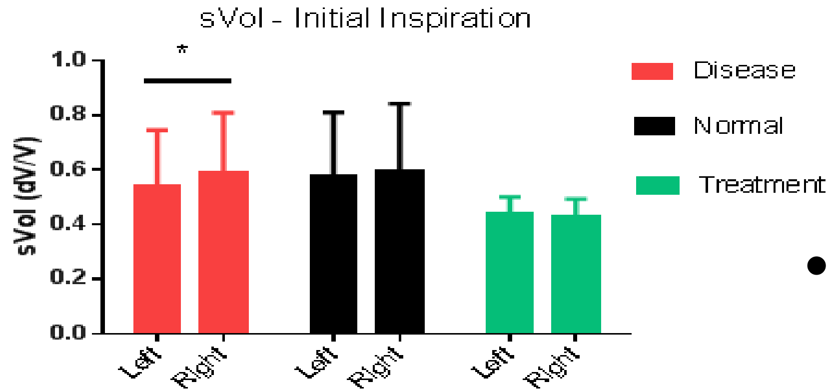
Regional Pulmonary Volumetric strain
(ΔV normalized by initial aerated lung volume, V_0)

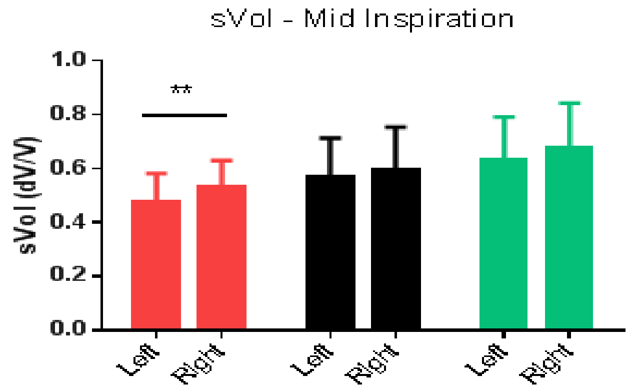


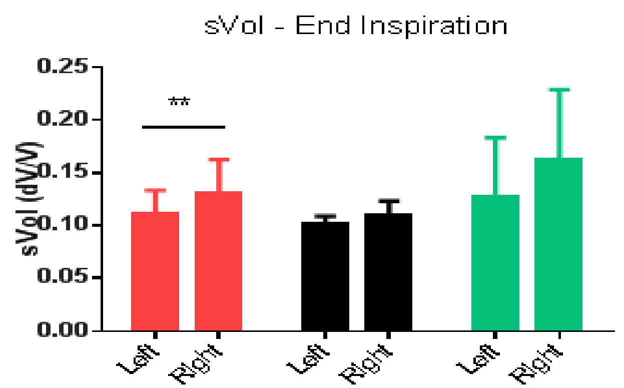
- Treatment normalized regional strain pattern
- Restores reserve capacity that was diminished by the thoracic deformity

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

	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]

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

Brian.Snyder@childrens.harvard.edu

Thank you