Effect of Expansion Thoracoplasty on Pulmonary Microstructure

Evaluation of Pulmonary Growth and Function Using Rabbit Model for Thoracic Insufficiency Syndrome

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How Does Expansion Thoracoplasty Affect Pulmonary Growth and Function?

Pulmonary Cellular Response to Thoracic Insufficiency Syndrome Using Rabbit Model

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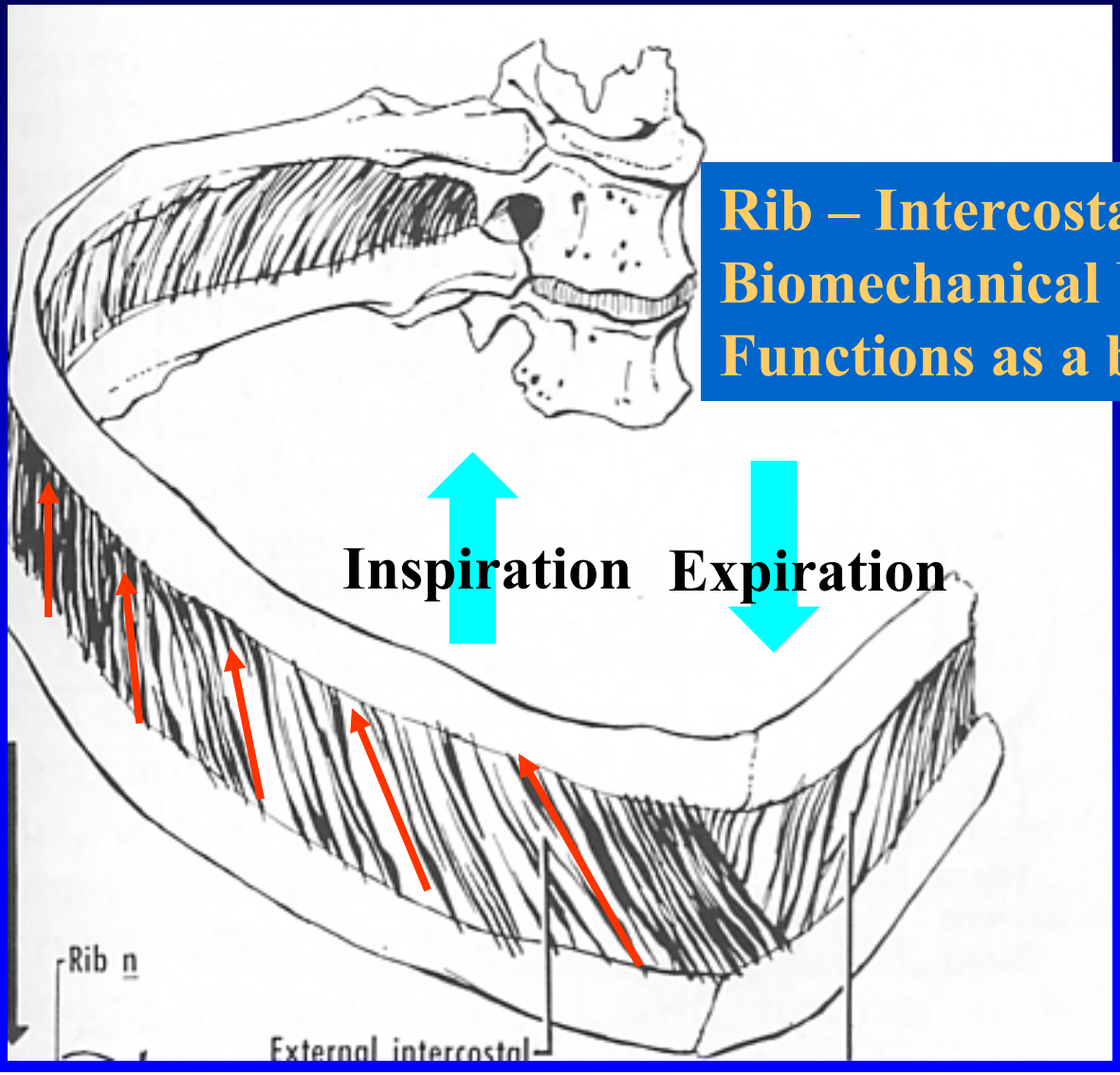
- ✓Scoliosis Research Society
- ✓Chest Wall and Spinal Deformity Study Group
- ✓Synthes Spine, North America

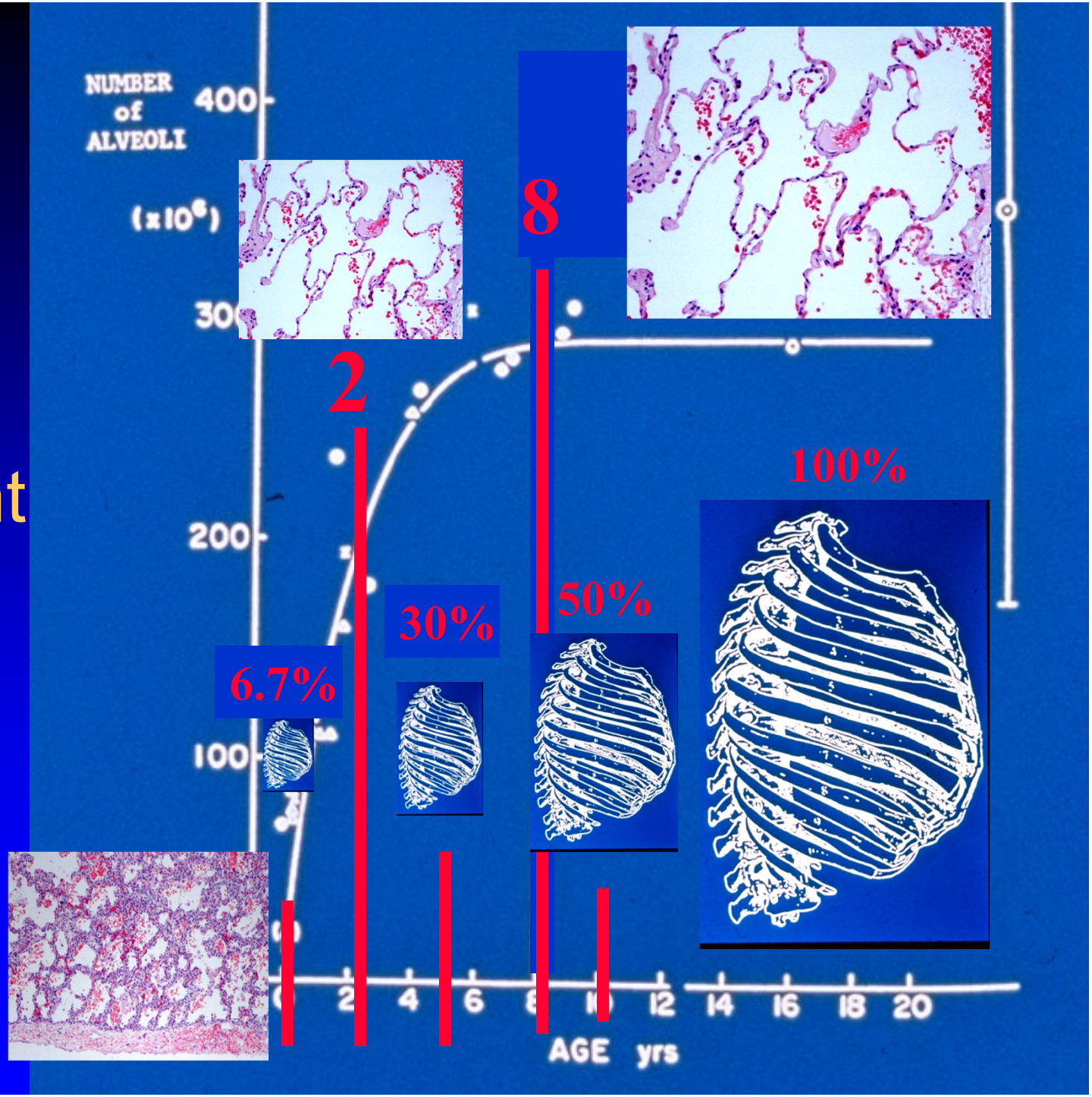
Lungs and thorax directly linked:

- biomechanically in act of respiration
- biologically with respect to lung growth



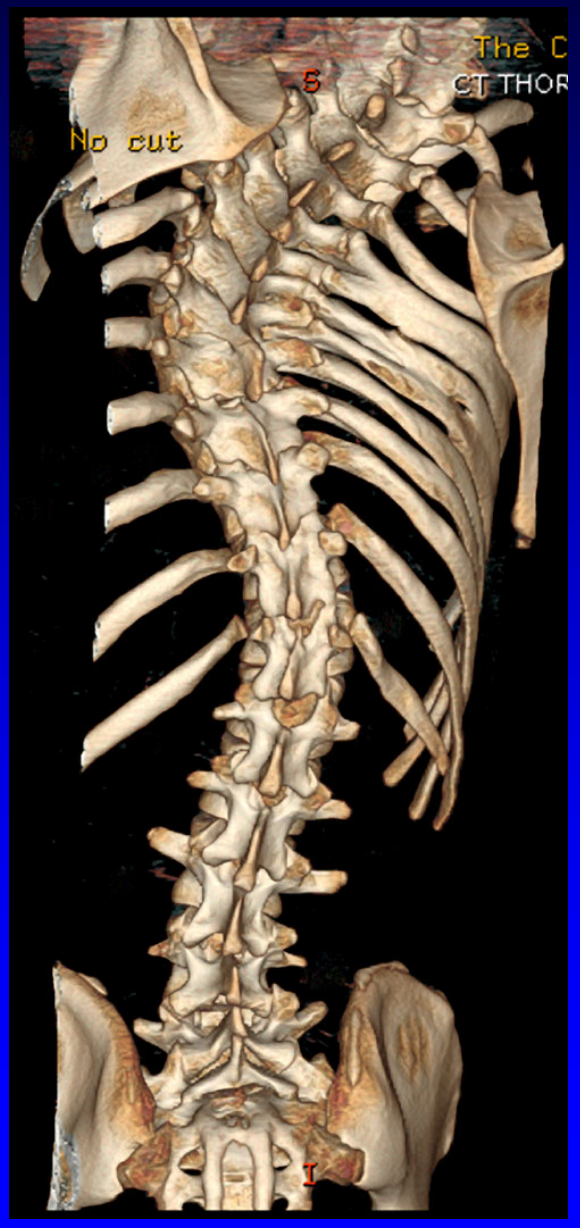
Lung and Thoracic Growth Inter-Dependent

but max number of alveoli attained by age 8



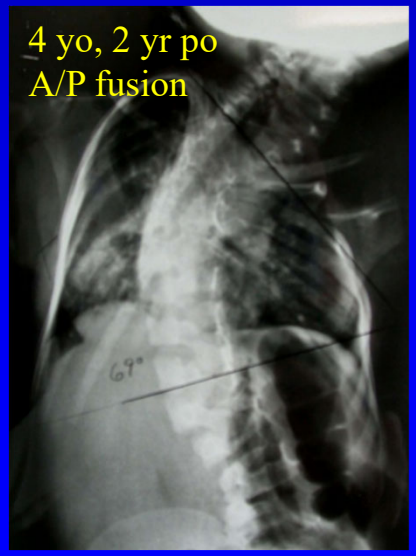
The Growing Thorax

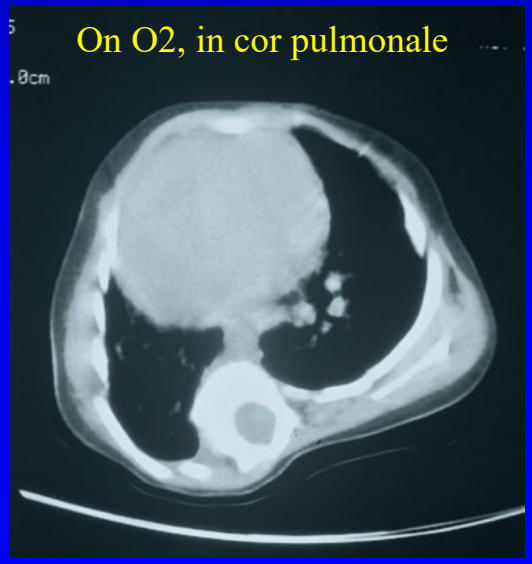
- Growth of thoracic spine and growth of rib cage directly related
- Growth disturbance of one will induce deformity in other

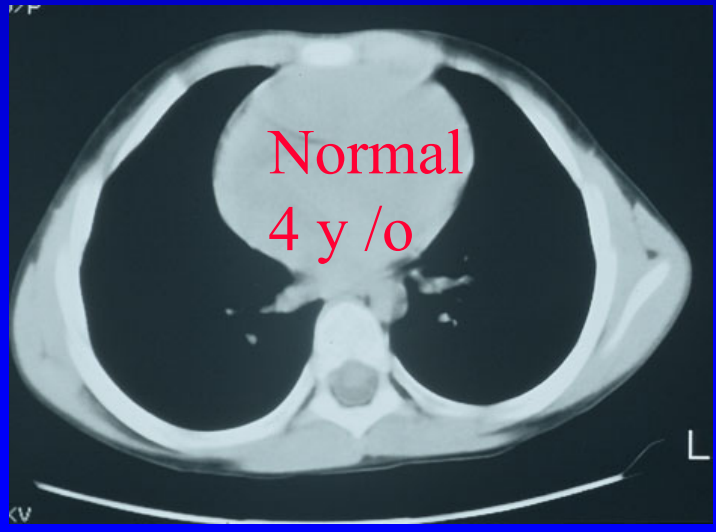


The Growing Thorax

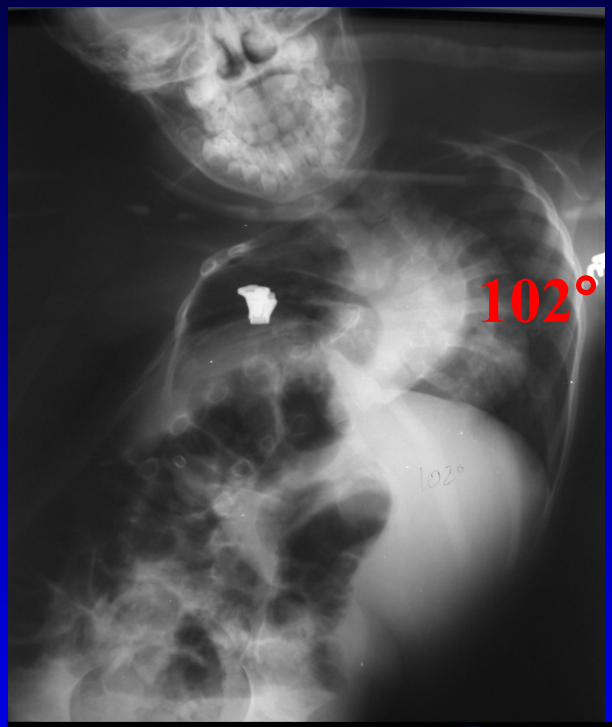
- Must enlarge for lung growth
  - Rib cage provides width and depth
  - Thoracic spine provides height
- Failure of thorax to grow causes extrinsic, restrictive lung disease

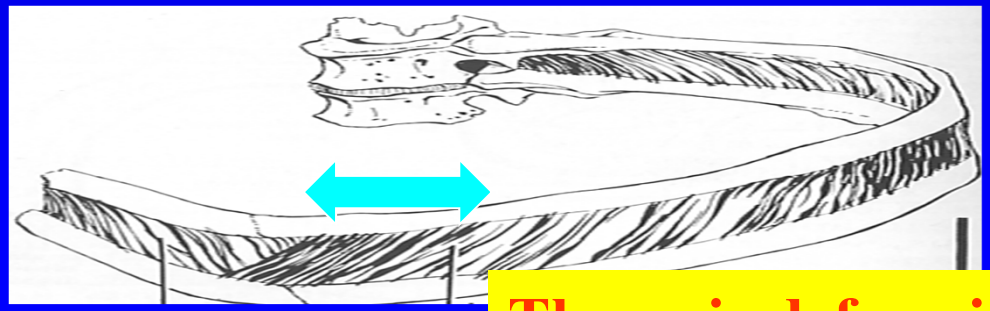






Congenital Scoliosis and Fused Ribs = Failure of Rib Cage to Contribute to Respiratory Function

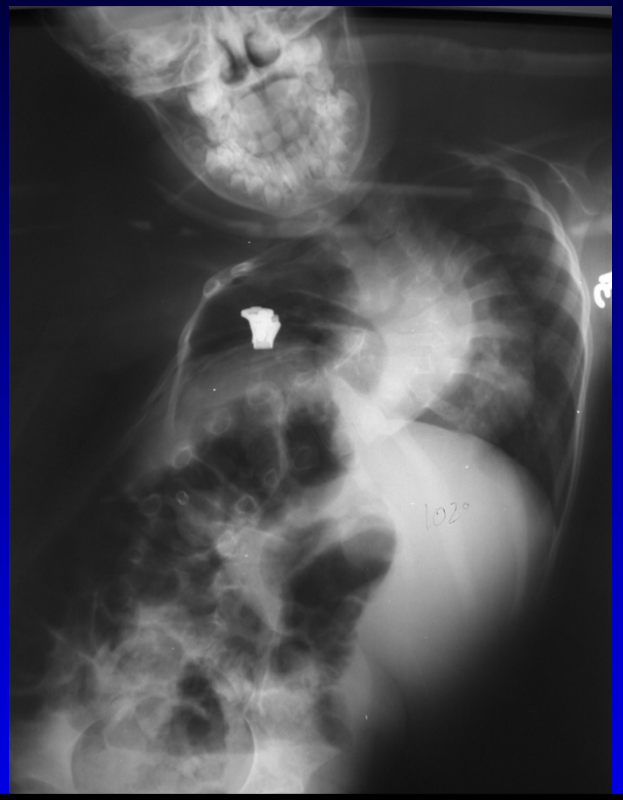




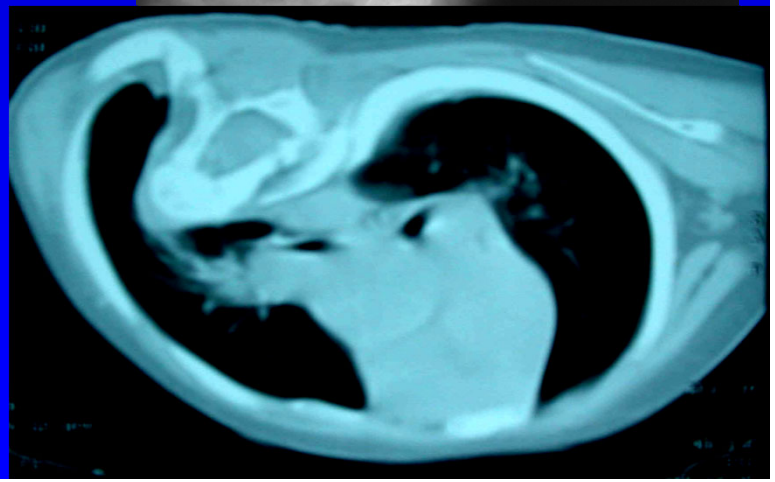
Thoracic deformity interferes with billow action

Thoracic Insufficiency Syndrome

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

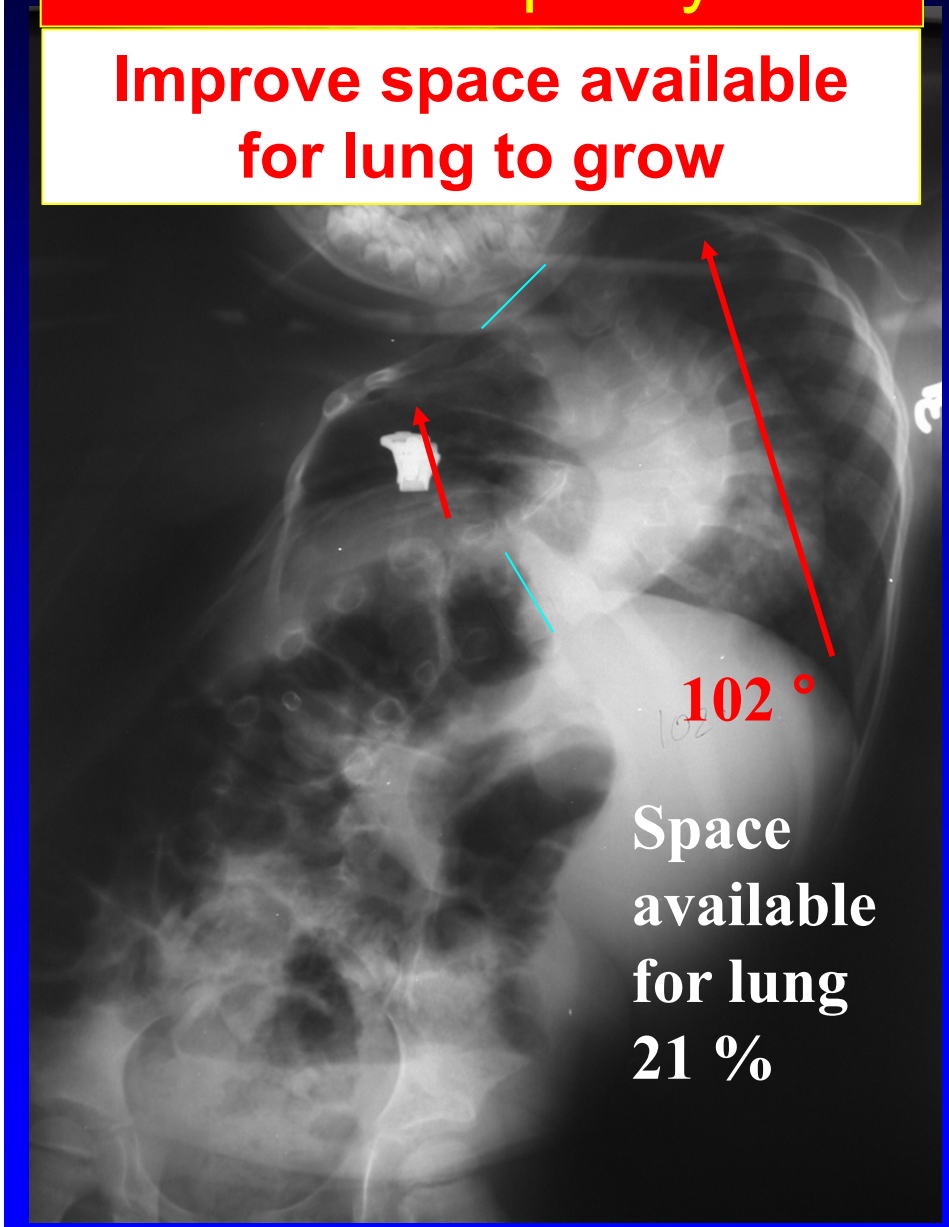


Thoracic Insufficiency is *Extrinsic*, restrictive disease

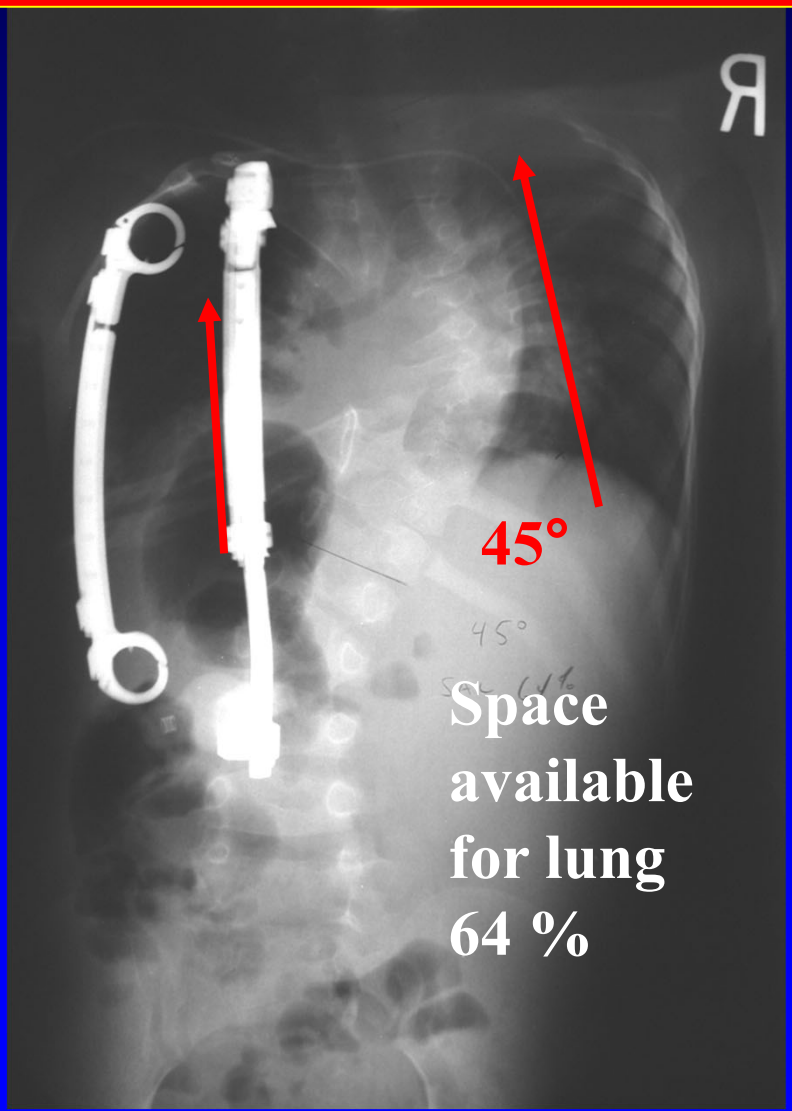


Goal of Expansion Thoracoplasty

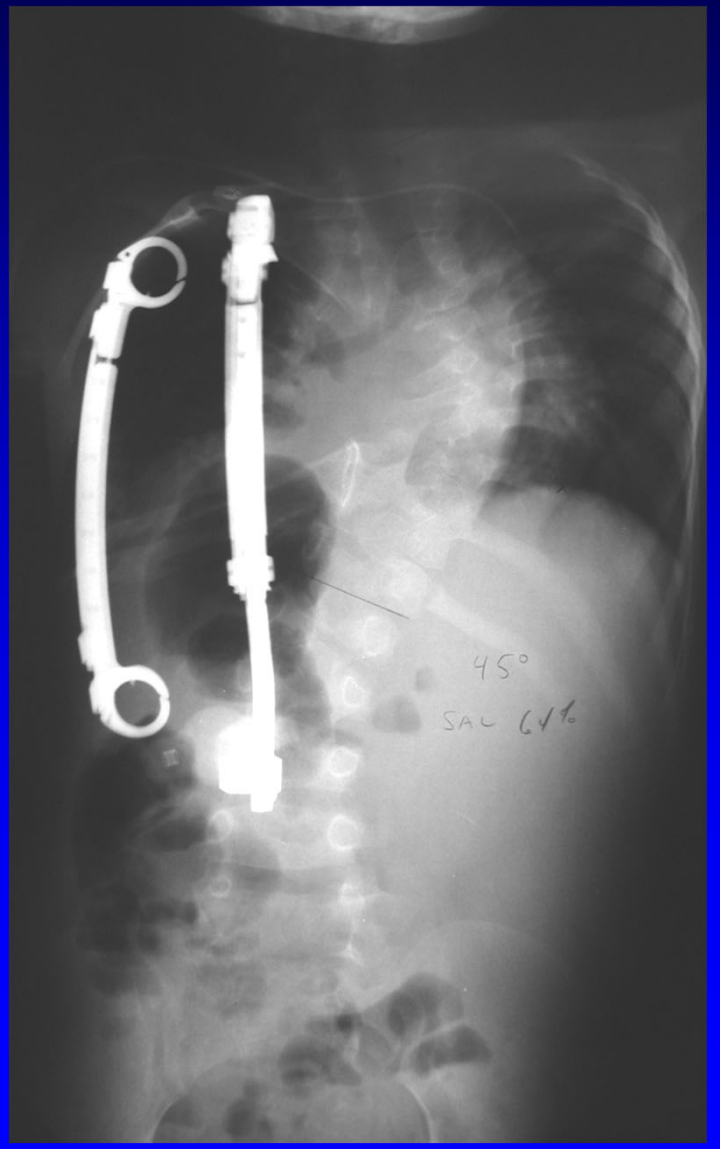
Improve space available for lung to grow



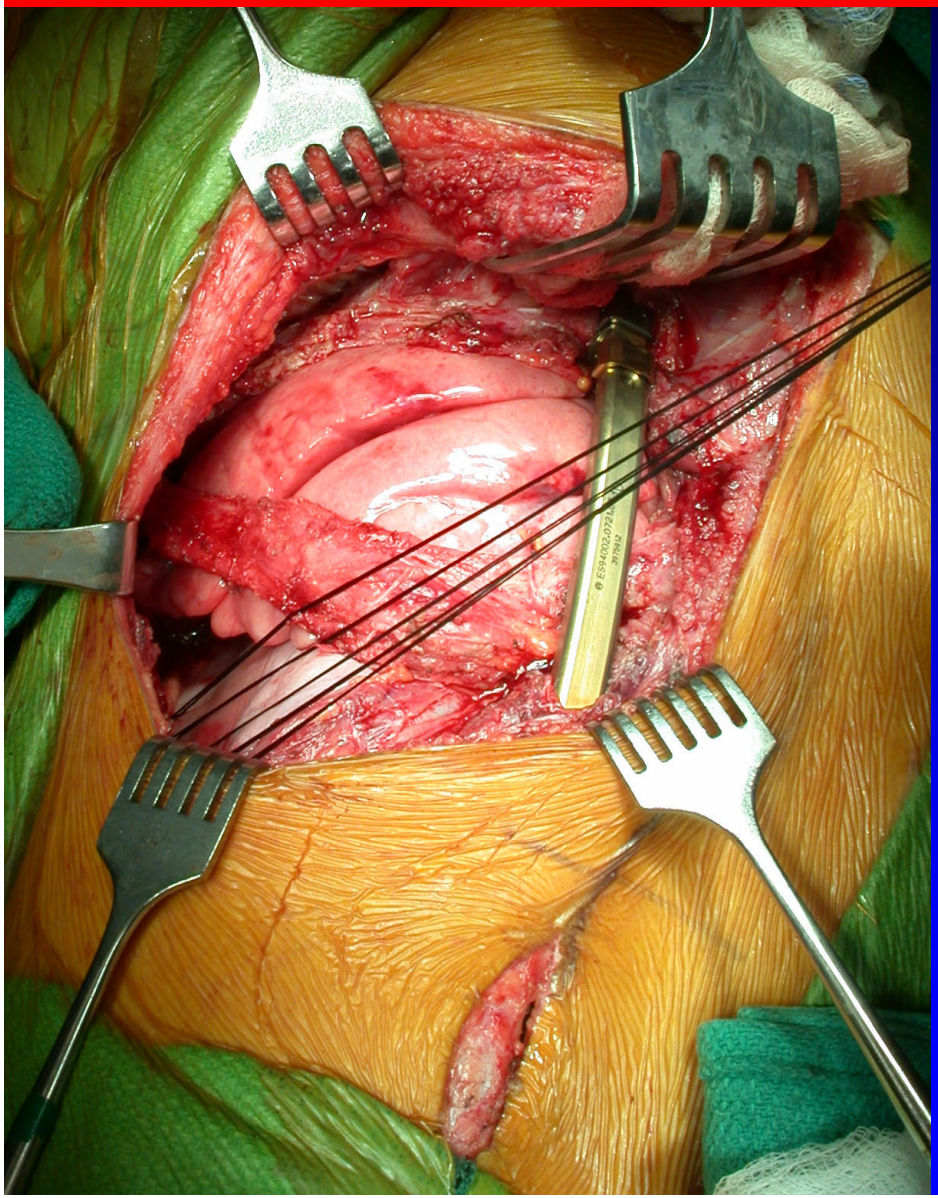
Lengthen concavity constricted hemithorax to ↑ thoracic volume

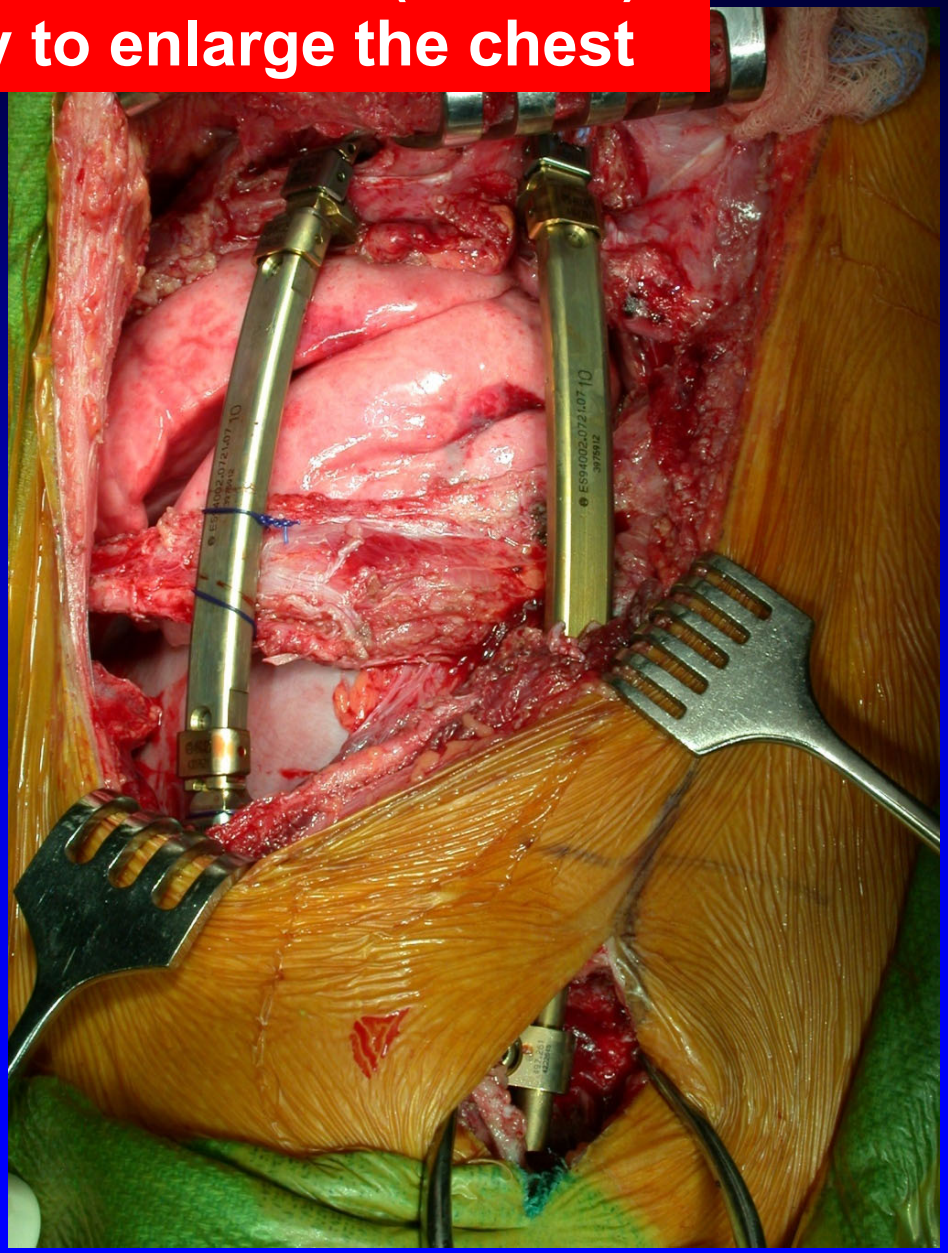


Treatment depends on understanding relationship between growth of thorax and growth/development of the lung



Expansion of hemithorax stabilized by
Vertical expandable prosthetic titanium rib (VEPTR)
Diaphragm transposed distally to enlarge the chest

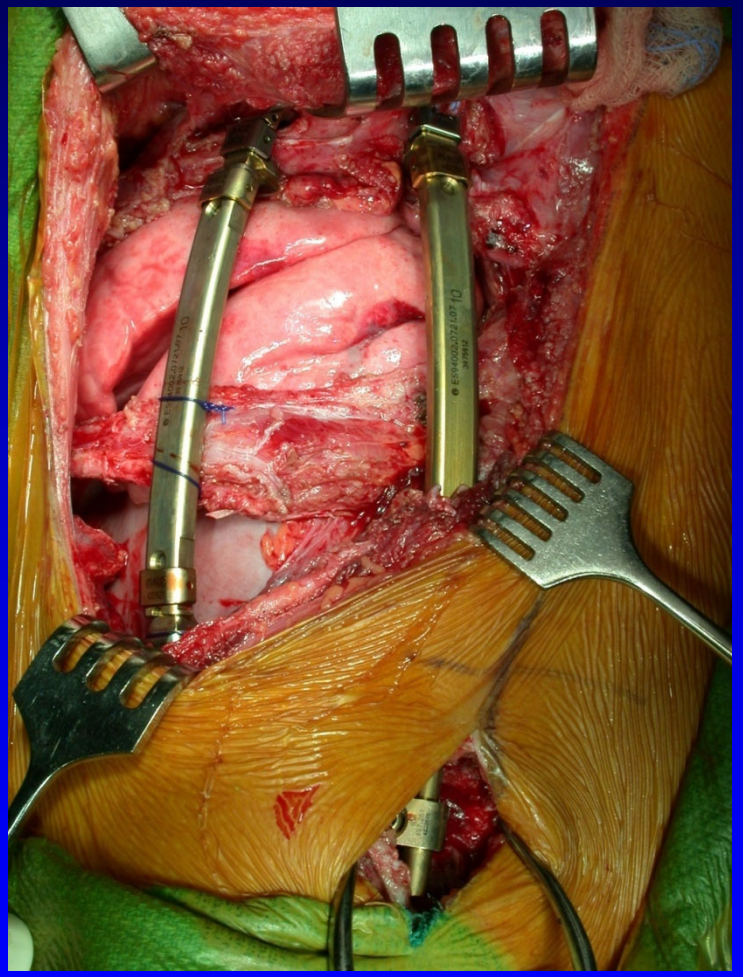




Hypothesis

Expansion of constricted hemithorax improves post-natal pulmonary hypoplasia by:

1. Allowing constricted lung to expand
2. Enhancing respiratory mechanics
3. Stimulating lung growth



Development of Rabbit Model for TIS

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The Reciprocal Relationship Between Thoracic and Spinal Deformity and Its Effect on Pulmonary Function in a Rabbit Model

A Pilot Study

Hemal P. Mehta, MS,*† Brian D. Snyder, MD, PhD,*‡ Natasha N. Callender, BS,†
Carissa L. Bellardine, MS,† and Andrew C. Jackson, PhD†

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Expansion Thoracoplasty Improves Respiratory Function in a Rabbit Model of Postnatal Pulmonary Hypoplasia

A Pilot Study

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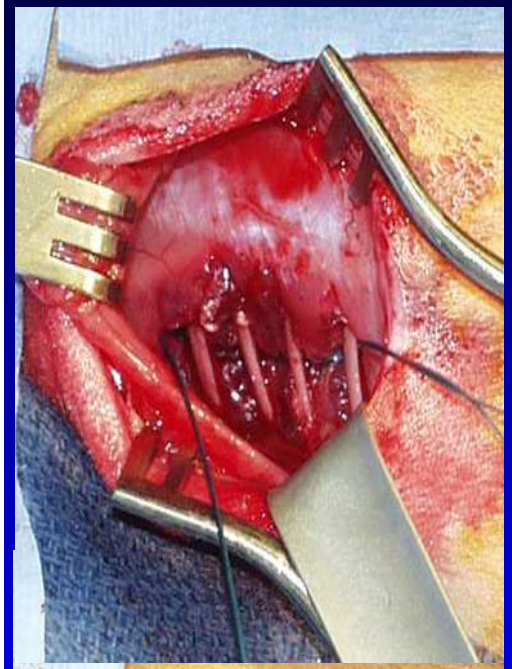
Melissa J. Hayward, MD,§ Michael J. Giuffrida, MD,§ Vahid Entezari, MD,*
and Andrew C. Jackson, PhD†

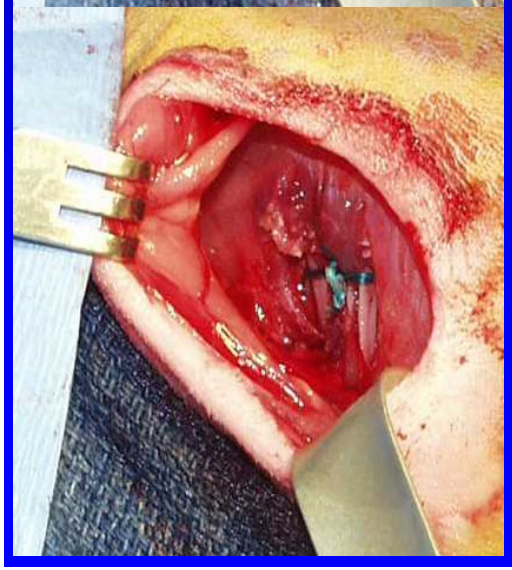
Specific Aims

- Use rabbit model of TIS to quantify how expansion thoracoplasty affects:
  - ✓Thoracic volume
  - ✓Aerated lung volume
  - ✓Alveolar cell growth
    - Number and Volume
    - Cellular markers of lung growth and development

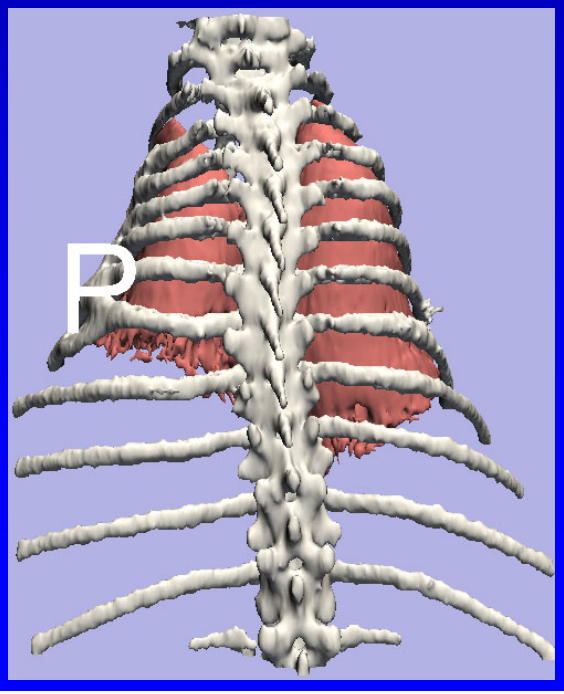
Induce TIS: Create Unilateral Rib Tether

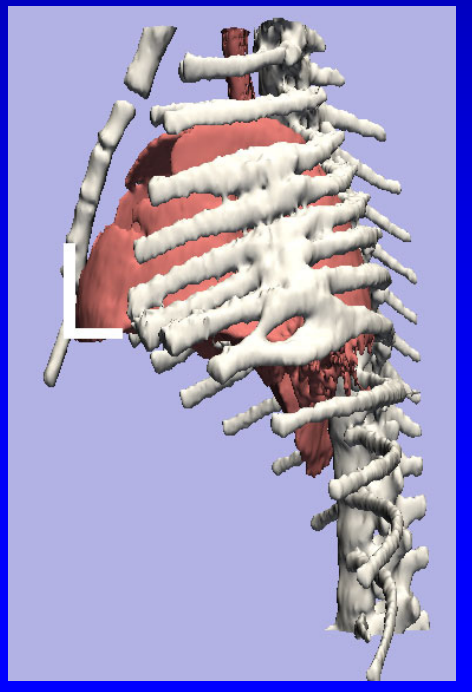
5 week old rabbits (n=7)



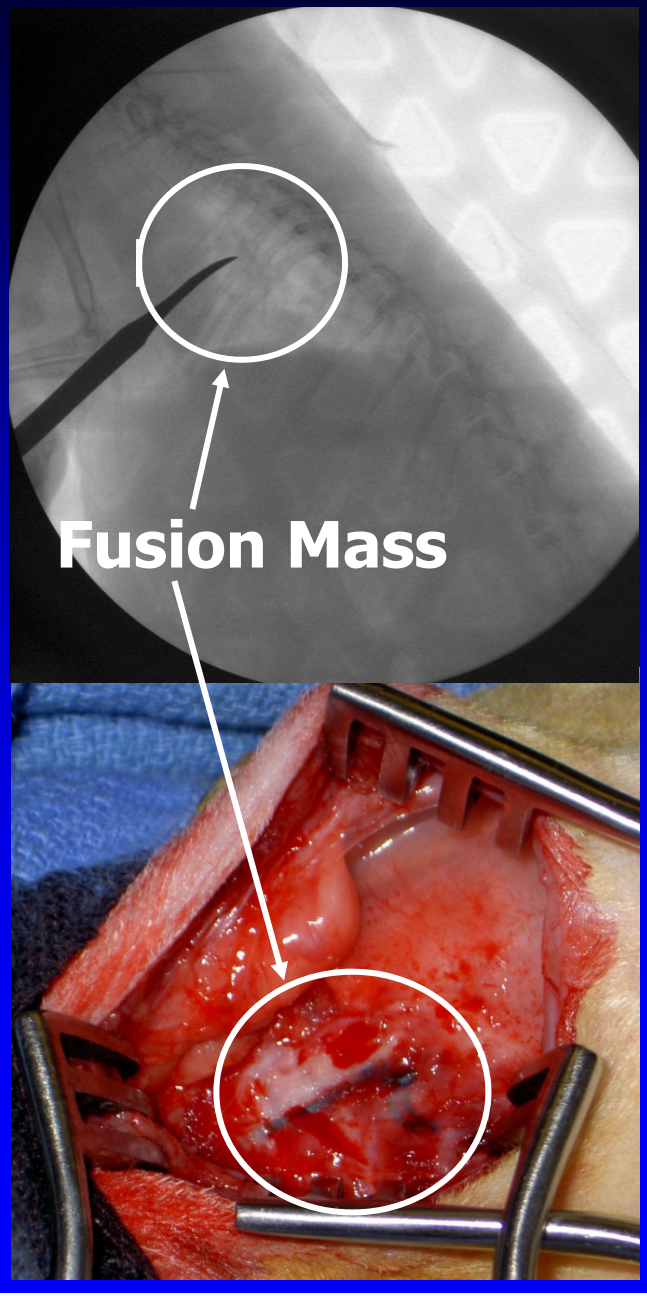


- Sub-periosteal *Figure-of-8* ligature around posterior angle ribs 4-8
- Creates asymmetric rib cage deformity left hemithorax
- **Solid fusion developed by 8 wks**

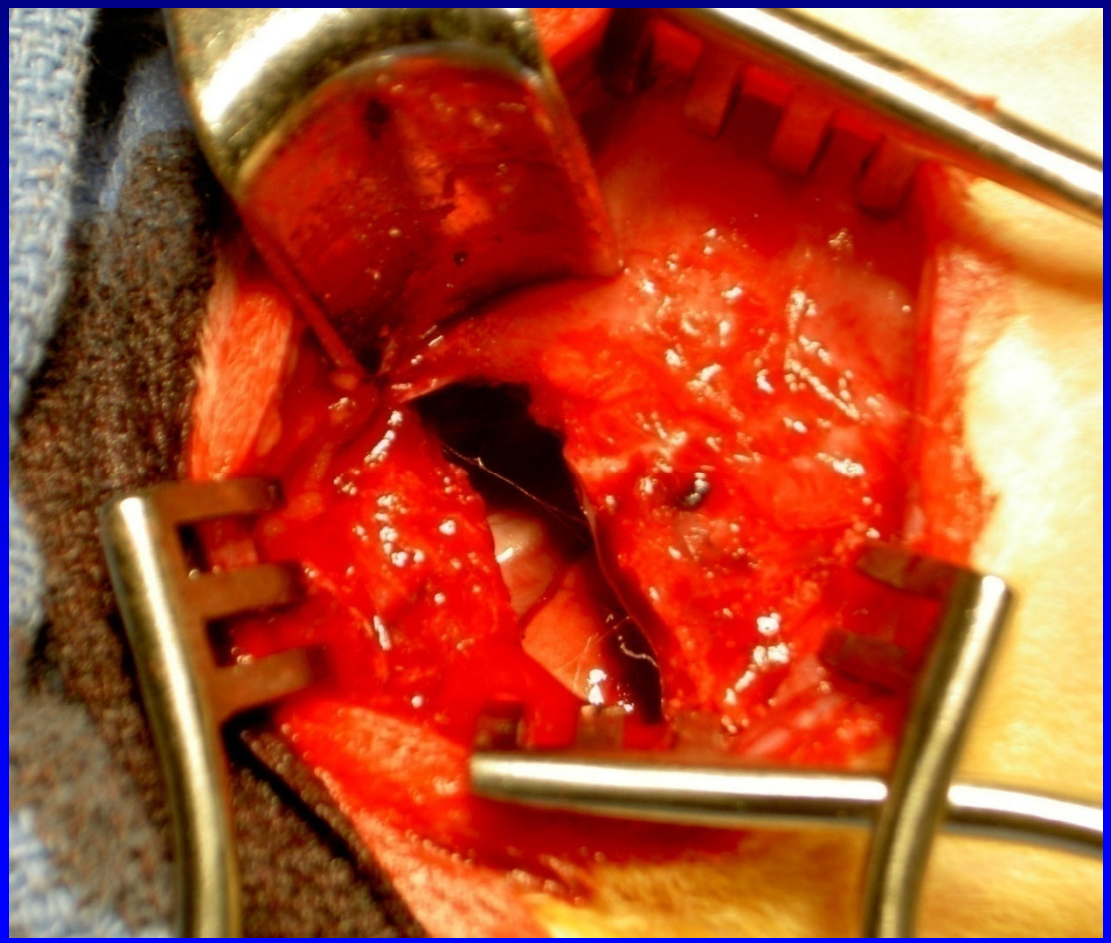




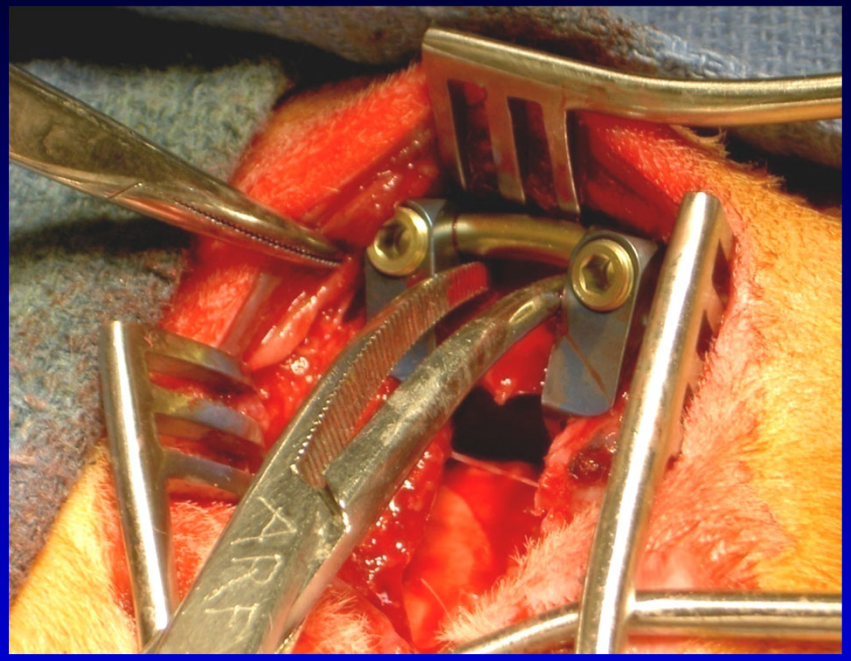
Thoracostomy of Constricted Hemithorax

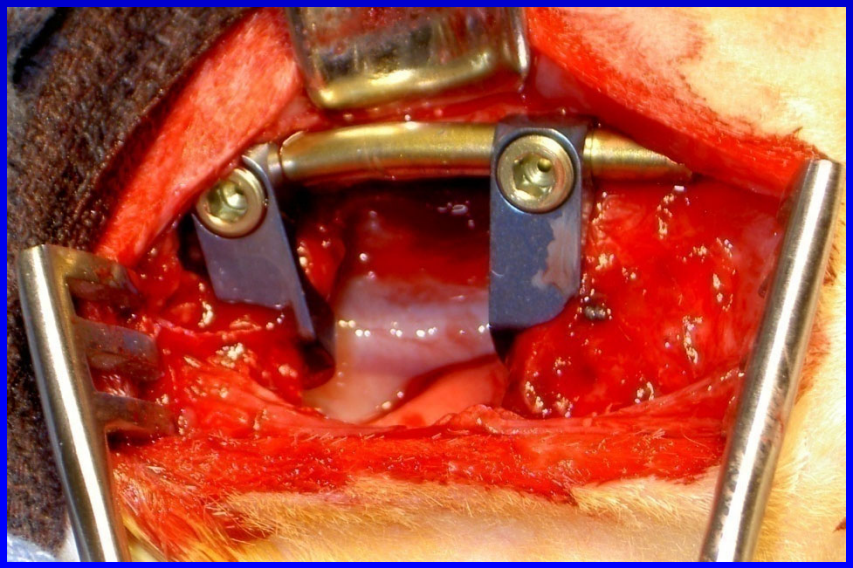


- Performed @ 10 wks (n =4)
- Apex of deformity
- Using dental burr



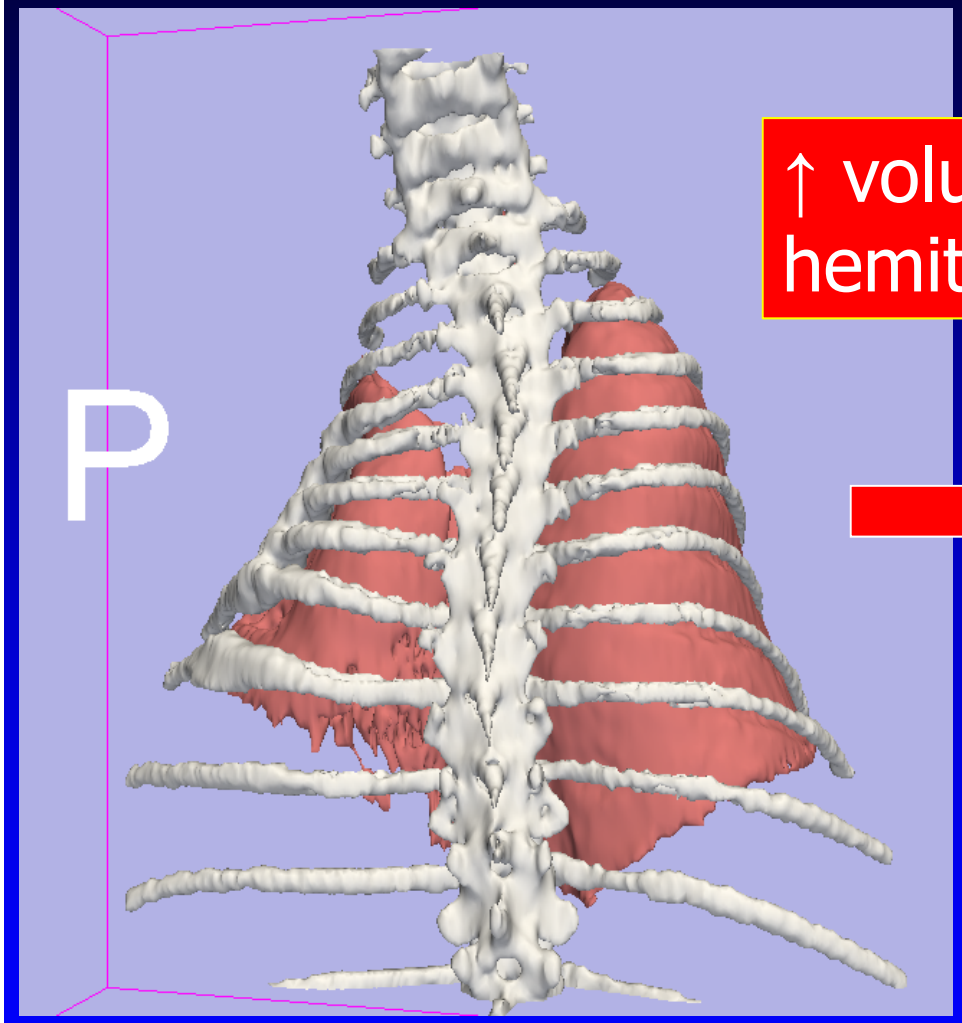
Expansion Thoracoplasty



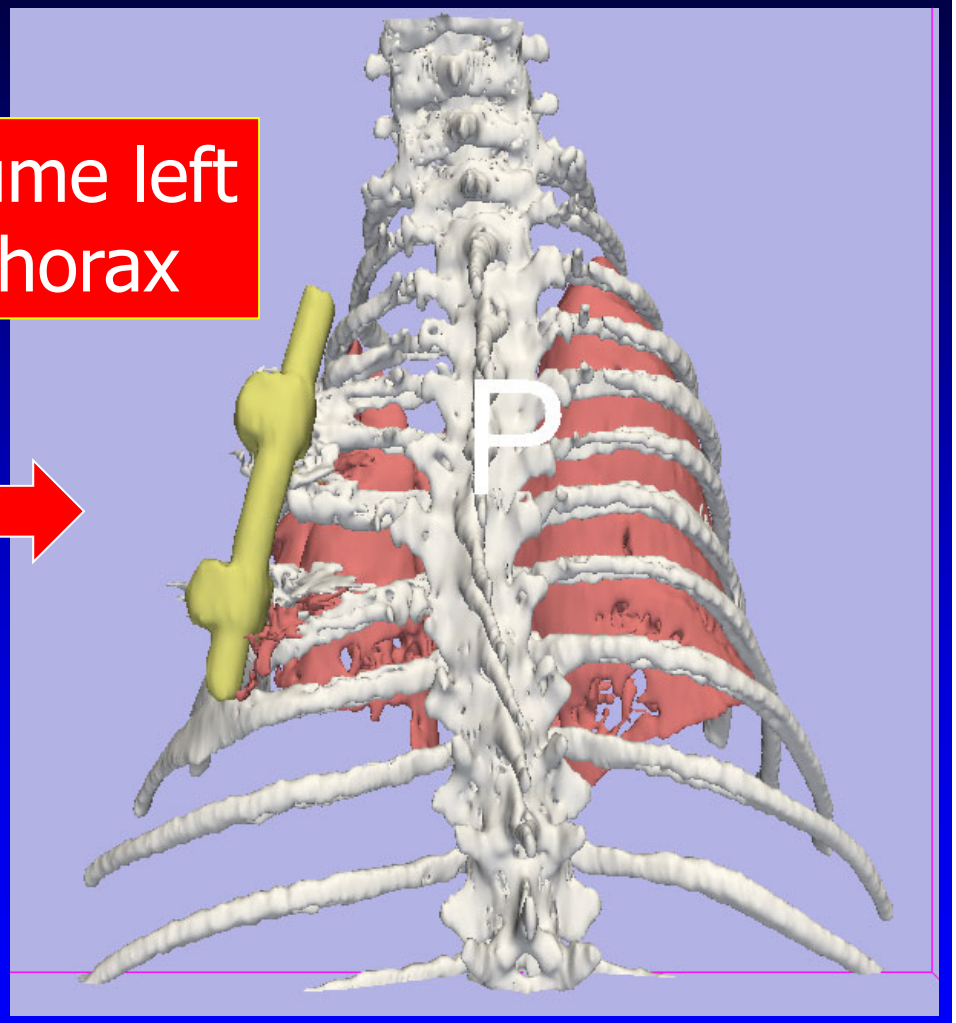


- Thoracostomy distracted open
- ↑ volume of hemithorax
- Synthes Cervifix system used as mini-VEPTR
- Implanted @ 10 wks
- n = 4

Pre- & Post Expansion Thoracoplasty



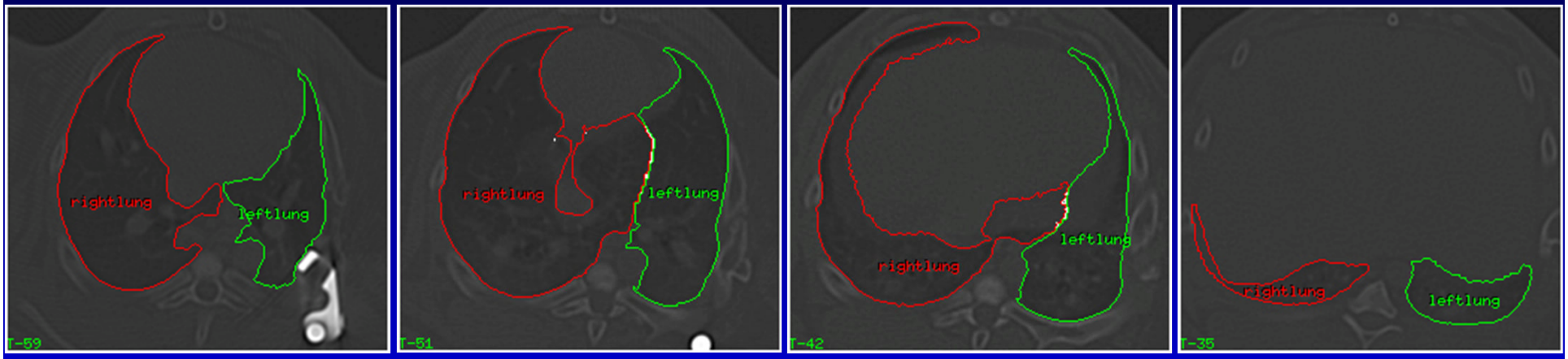
↑ volume left hemithorax



Rabbit 5: 8 wks of age

Rabbit 5: 12 wks of age

Lung Volumes Calculated from Segmented Images Transaxial CT



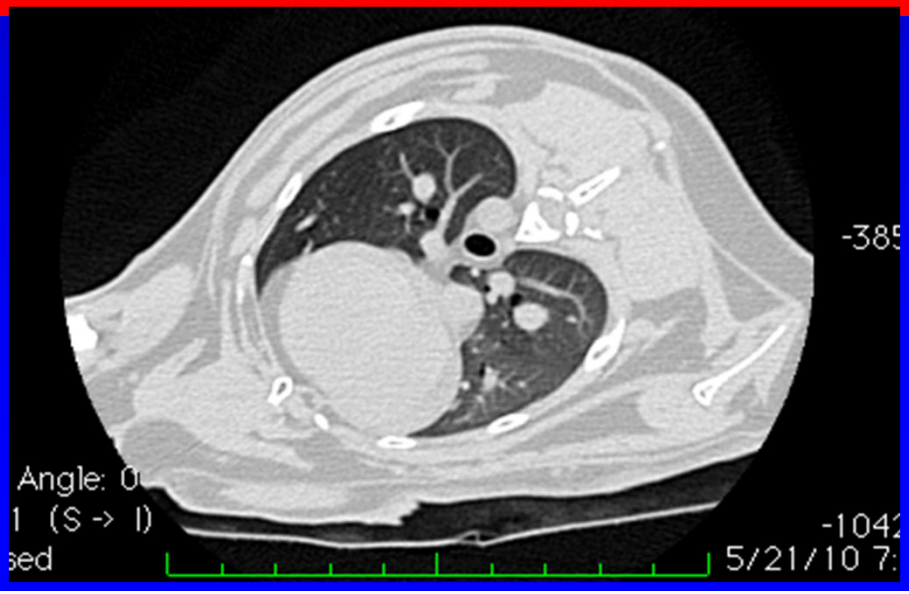
- Branching of bronchial tree used to determine right and left lung volumes
- Thresholding algorithm used to segment *aerated* lung tissue for each transaxial cross-section T1-T13
- Lung volumes calculated by summing aerated lung tissue over ***all*** sequential cross-sections T1-T13

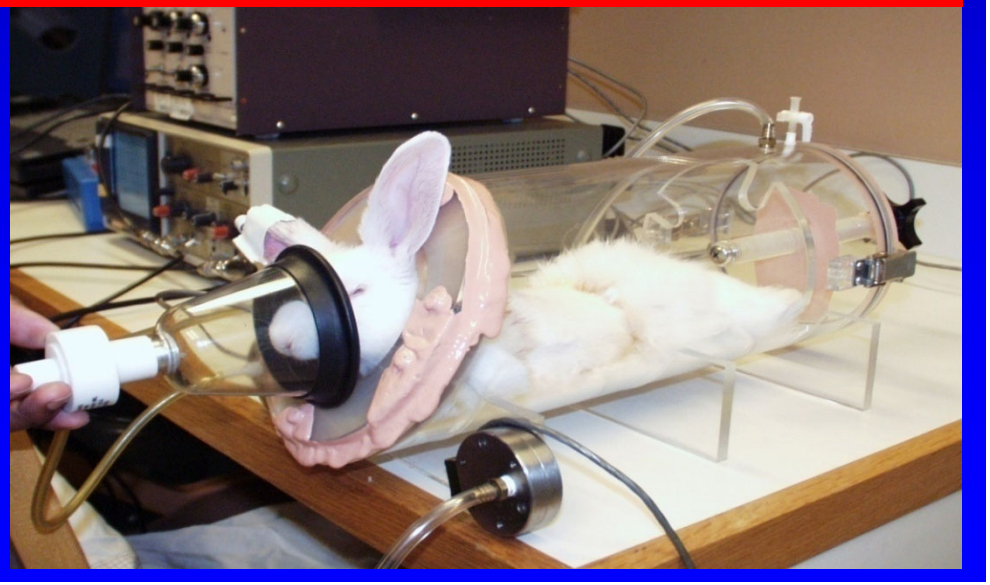
Pulmonary Mechanics

Functional Residual Capacity:

- Aerated volume of lung from Breath Hold-CT at 0 cm H_2O
  - X-ray attenuation lung proportional to ratio air space : lung tissue
- Box Plethysmography (28 wks)
  - ΔV thorax from box plethysmograph
  - Airway opening pressure during occlusion

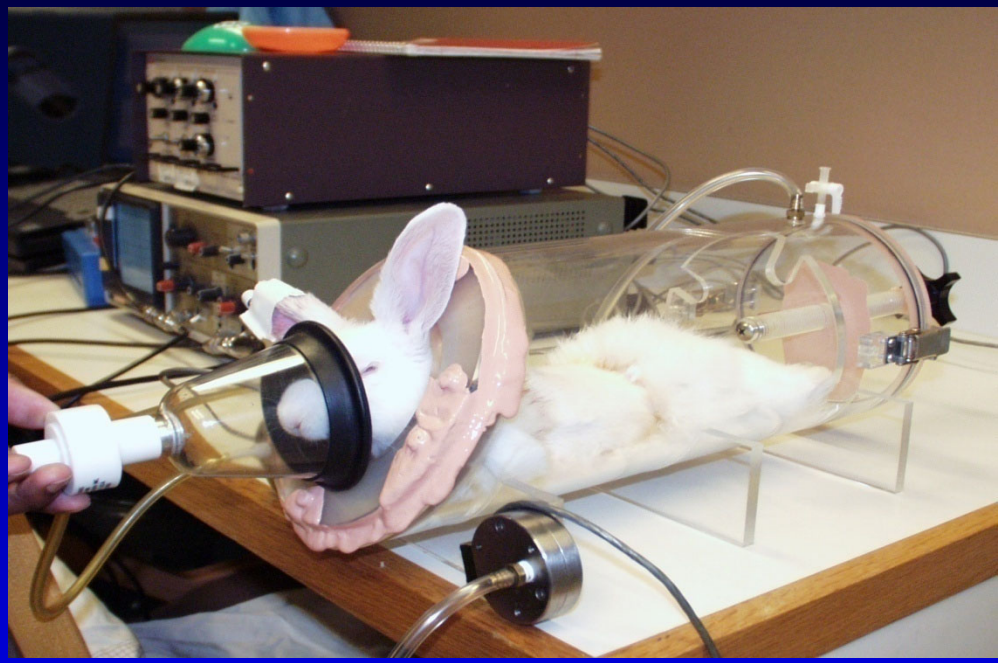
$$FRC = \frac{\Delta V * P_{Ai}}{(P_{Ae} - P_{Ai})}$$

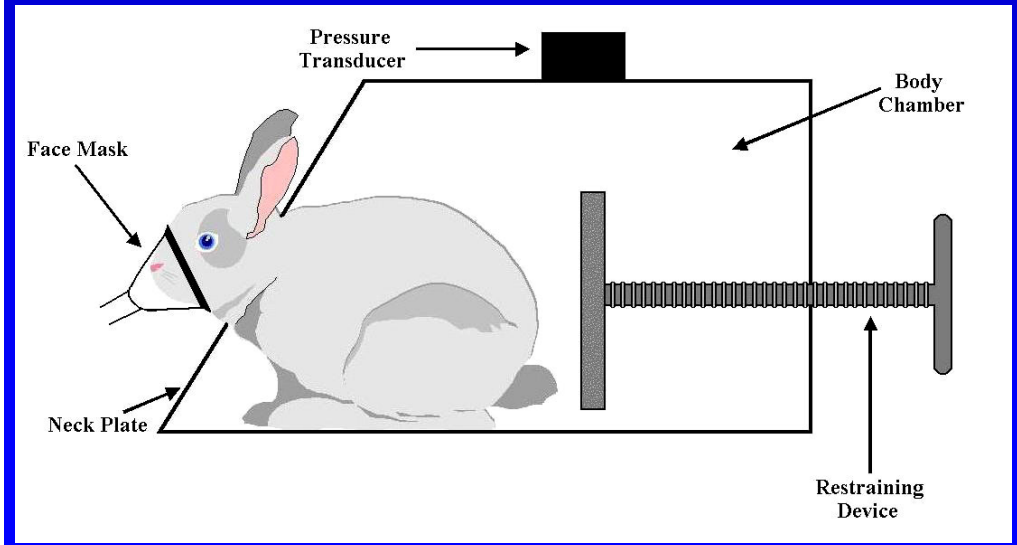




Whole Body Plethysmography

- 18 wks of age
- Ketamine/Xylazine anesthetic

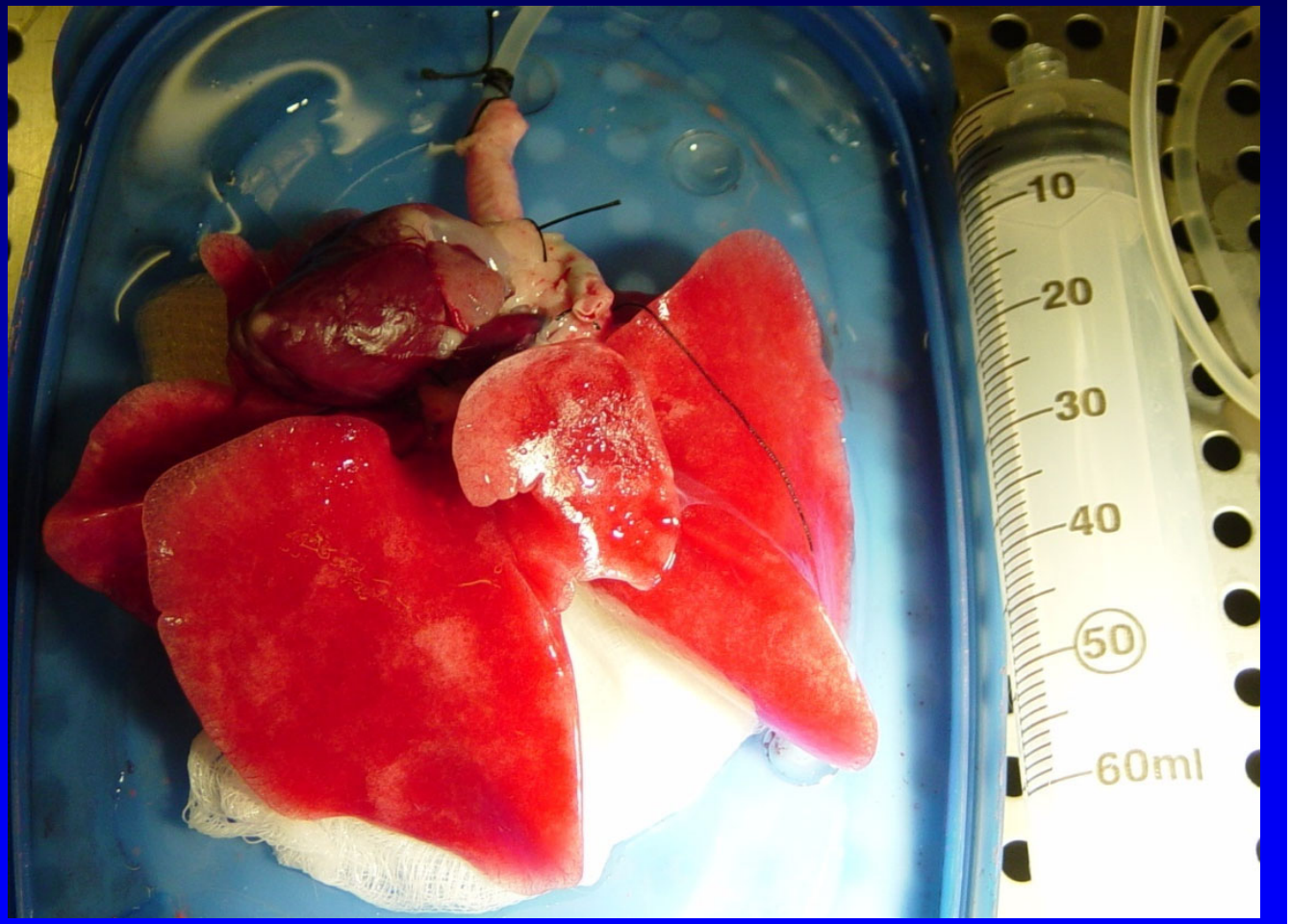




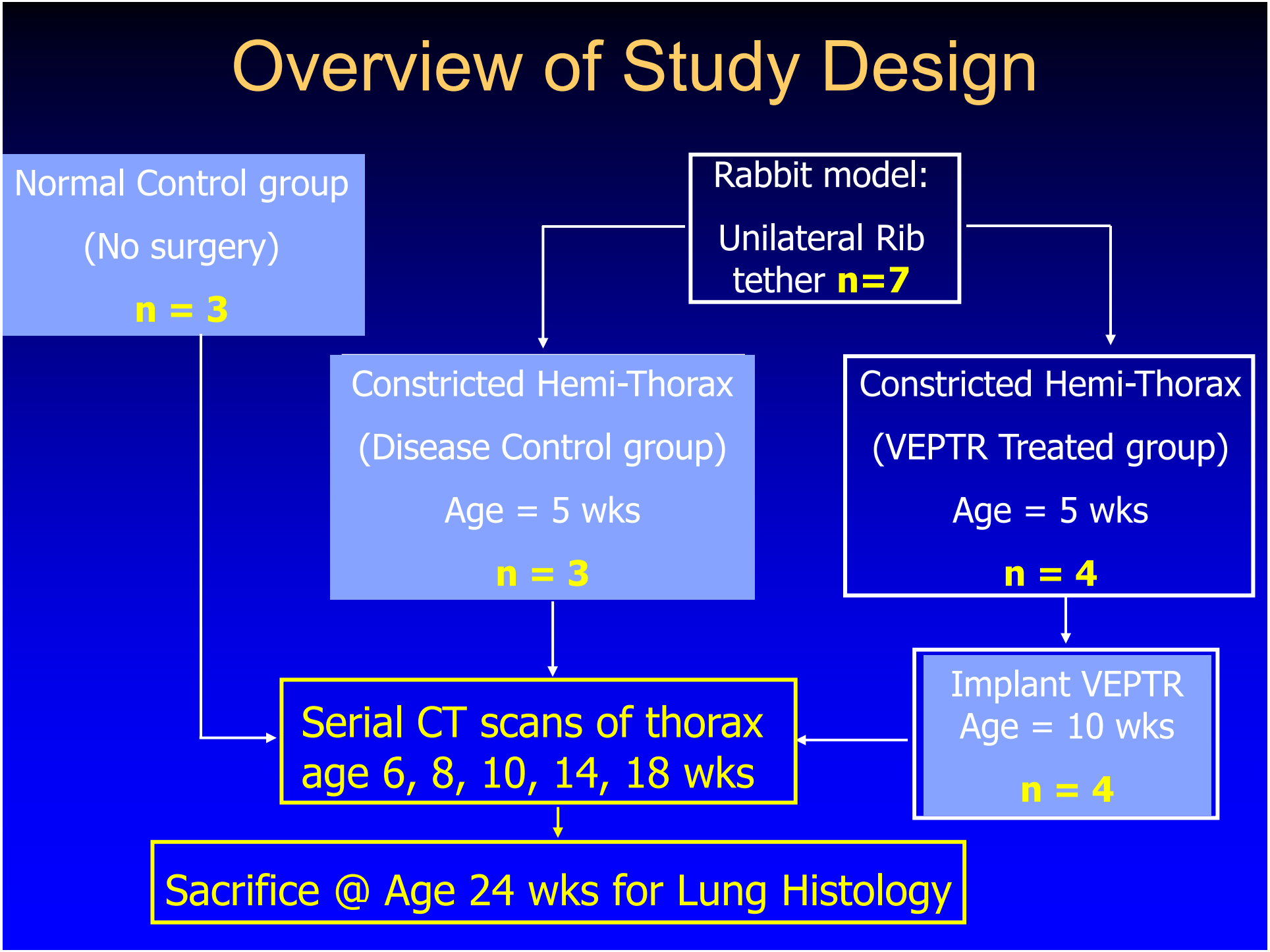
- FRC calculated from measures of:
  - Box Pressure (P_{box})
  - Airway Opening Flow (V_{ao})
  - Airway Opening Pressure (P_{ao})

Lungs Excised for Histology at 24 wks

- Excised lung infiltrated with formalin to 25 mm Hg for 48 hours
- Fixed lung tissue processed for histological analysis



Overview of Study Design

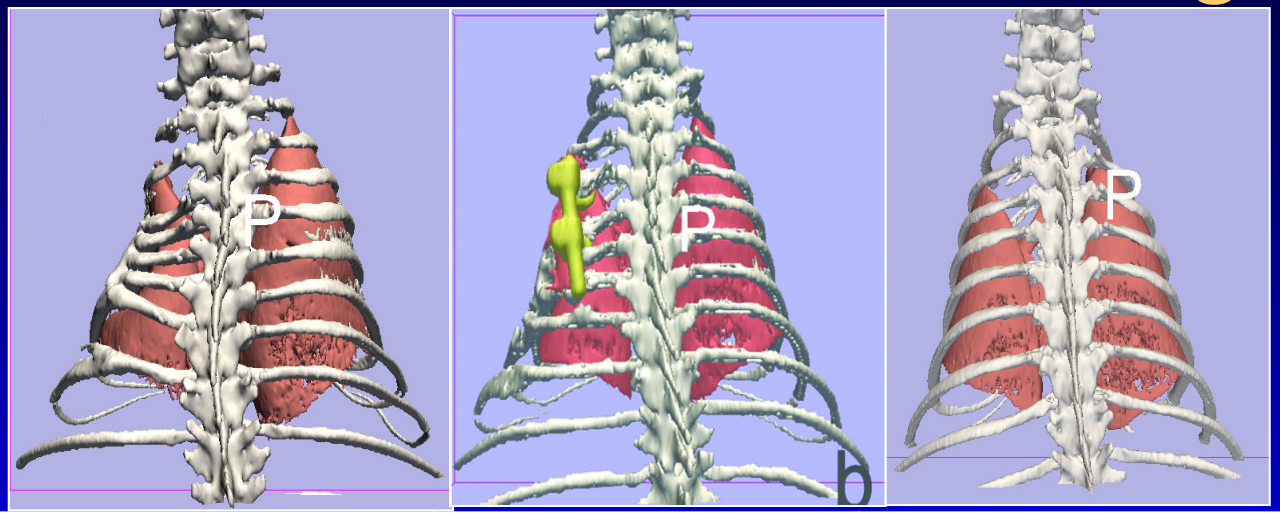


Result: Lung Volumes at 18 weeks

	Disease Control (n = 3)	VEPTR Treated (n = 4)	Normal Control (n = 3)
Weight	3.207 kg	3.020 kg	3.257 kg
Norm. Total Lung Vol.	7.457 mL/kg	7.971 mL/kg	7.094 mL/kg
Left Lung/ Total Lung Vol. Ratio	34.7% *	35.7% *	41.3% * *
Left/ Right Lung Vol. Ratio	53.4% *	55.6% *	70.3% * *

- All rabbits thrived
- **Constricted left lung of Disease and VEPTR groups *smaller* than Normal**
- **Total lung volumes *not* different among groups**

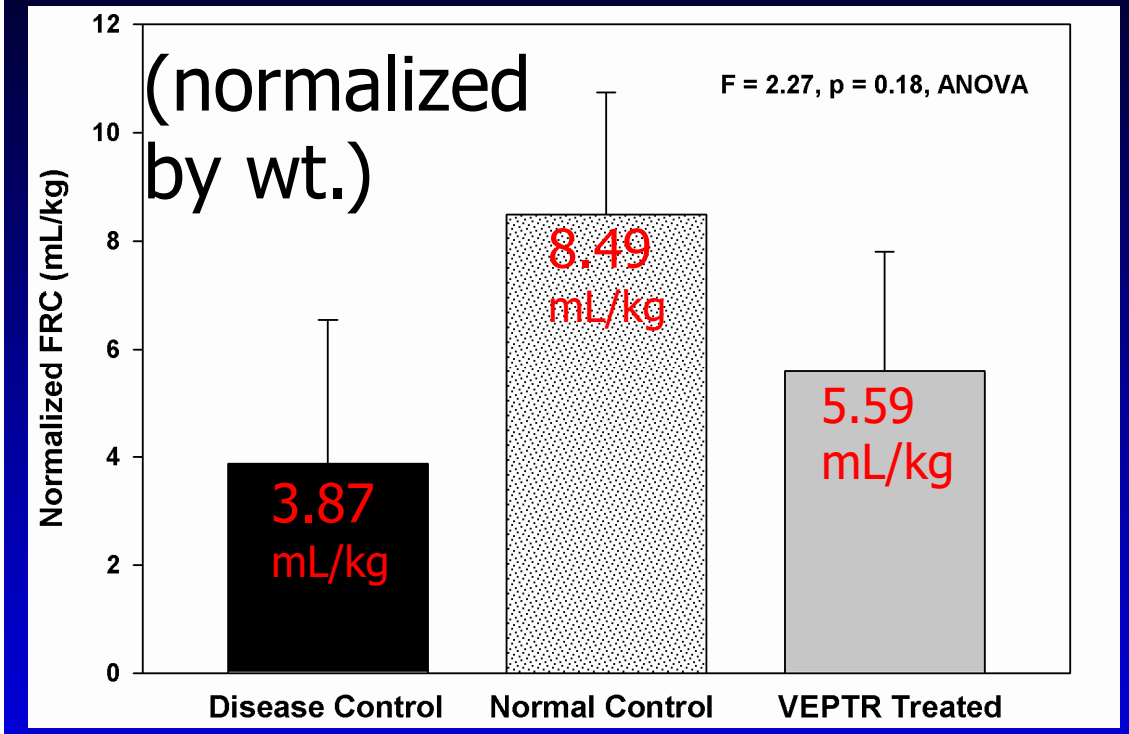
Right Lung Hypertrophied to Compensate for Constricted Left Lung



	Disease Control (n = 3)	VEPTR Treated (n = 4)	Normal Control (n = 3)
Left Lung Compared to Normal Control	-12%	-3%	---
Right Lung Compared to Normal Control	+17%	+23%	---

-Expansion Thoracoplasty did little to increase total lung volumes

Result: Functional Residual Capacity

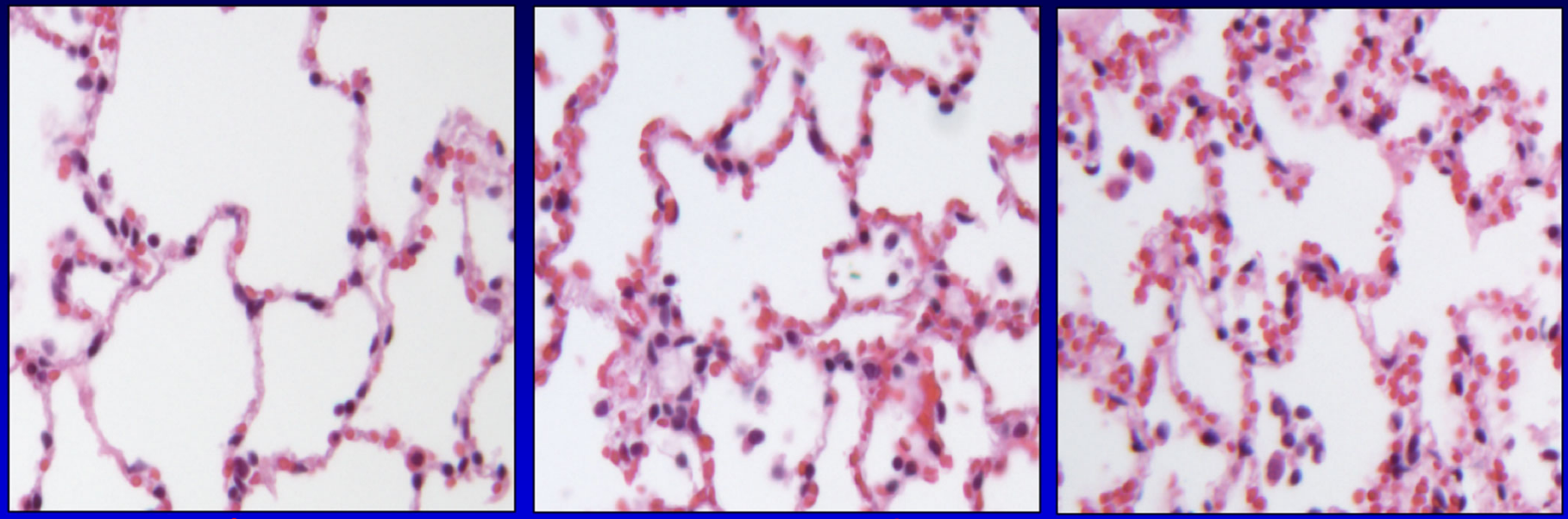


- Decreased FRC indicates restrictive lung disease

- No difference between groups (small sample size)
- *Trend:* Expansion Thoracoplasty partly compensates for ↓ FRC of TIS disease group
  - ✓ $FRC_{Disease}$ 46% of Normal
  - ✓ FRC_{VEPTR} 66% of Normal

Result: Lung Histology

Morphology VEPTR Treated lungs approached Normal

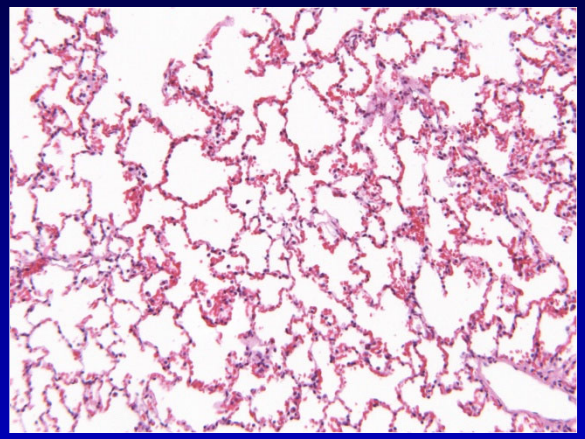


Disease Normal VEPTR

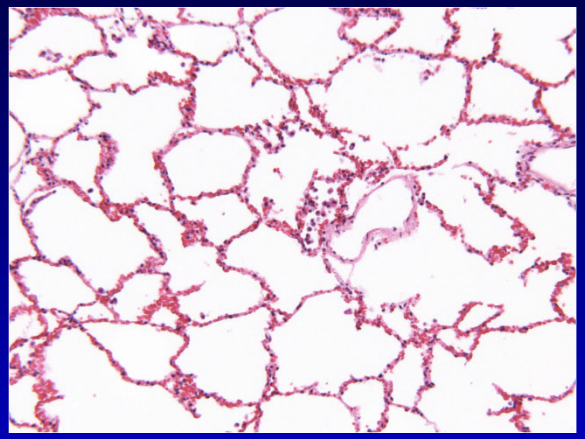
Disease group: thinned alveolar walls, greater airspace fraction (emphysema), poor perfusion

VEPTR : Alveolar air space fraction approaches normal, Prominent capillaries adjacent alveoli

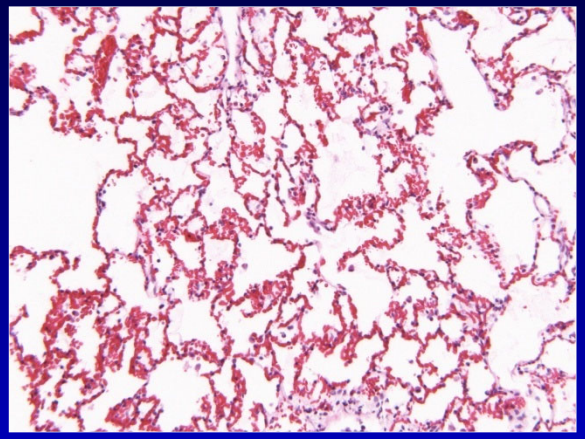
Result: Pulmonary Microstructure



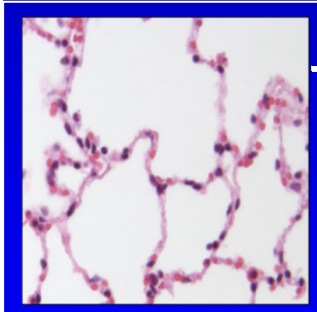
Normal



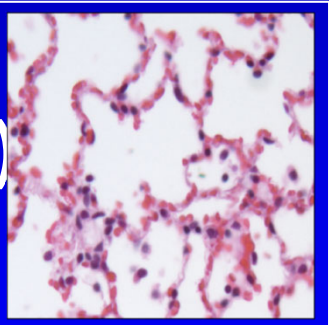
Unilateral Fused Rib

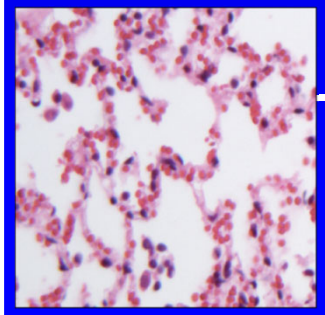


VEPTR



- **Fused Rib (Compared to Normal):**
  - **↑ airspace fraction (emphysema)**
  - **↓ perfusion**





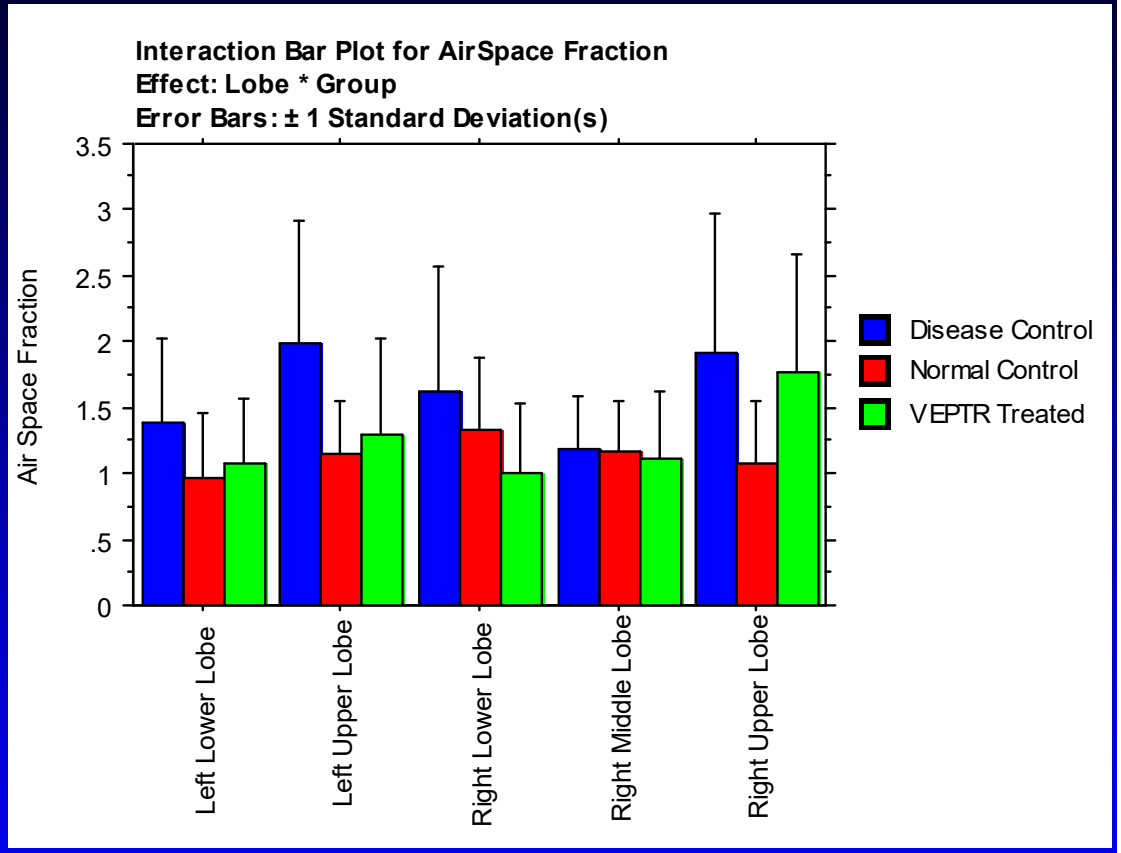
- **VEPTR treated (Compared to Disease)**
  - **↓ airspace fraction (no emphysema)**

Quantitative Histology: Air Space fraction

- **Disease Group**:

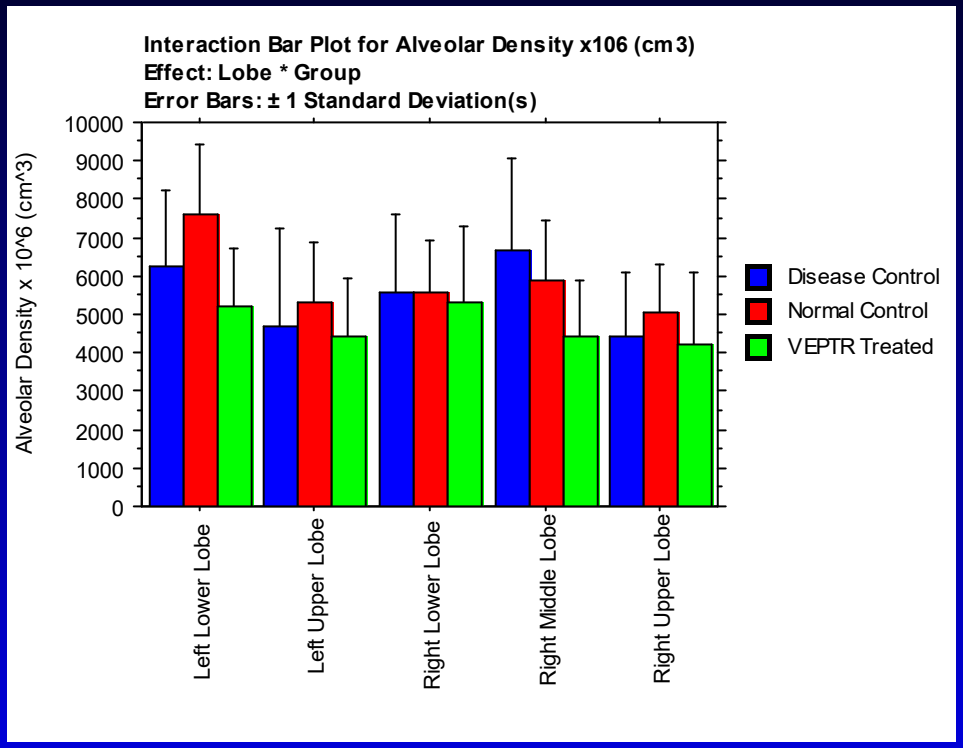
  Air space fraction significantly greater all lobes except Right Middle

- **Indicates emphysematous change**
  - ✓ Similar to congenital diaphragmatic hernia (pre-natal pulmonary hypoplasia)



- **VEPTR rabbits approach Normal air space fraction**

Quantitative Histology: Normalized Alveolar



Left lower lobe (constricted)

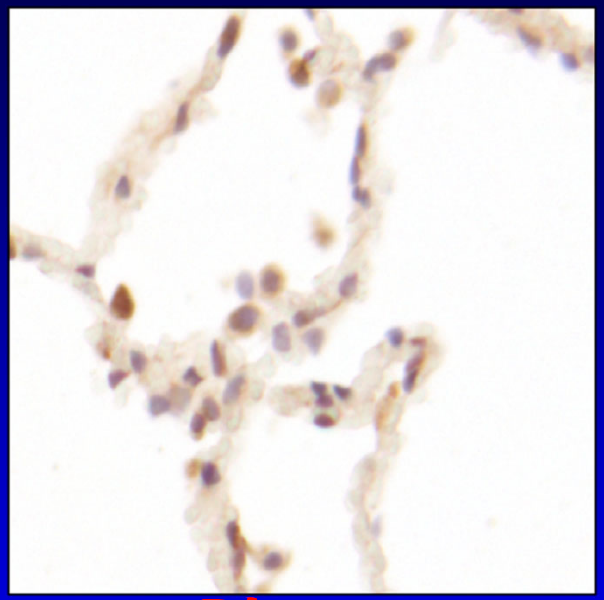
- **Normal > Disease & VEPTR**
- **Disease > VEPTR**

Right Middle Lobe (hypertrophied)

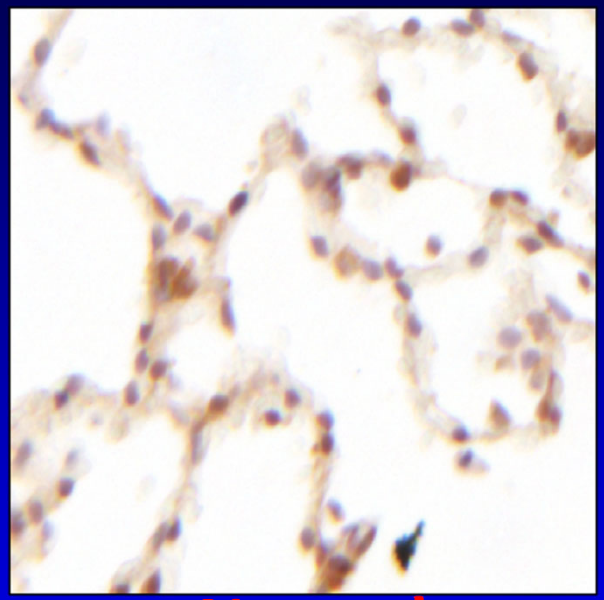
- **Disease & Normal > VEPTR**

Except for Left Lower and Right Middle Lobes, # Alveoli ***not significantly different among lung segments for VEPTR, Normal and Disease Groups***

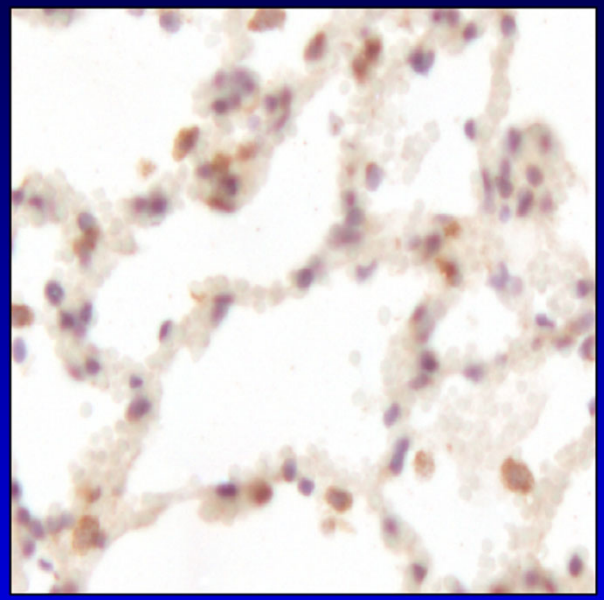
Result Immunohistochemistry: VEGFR-2 (KDR)



Disease



Normal

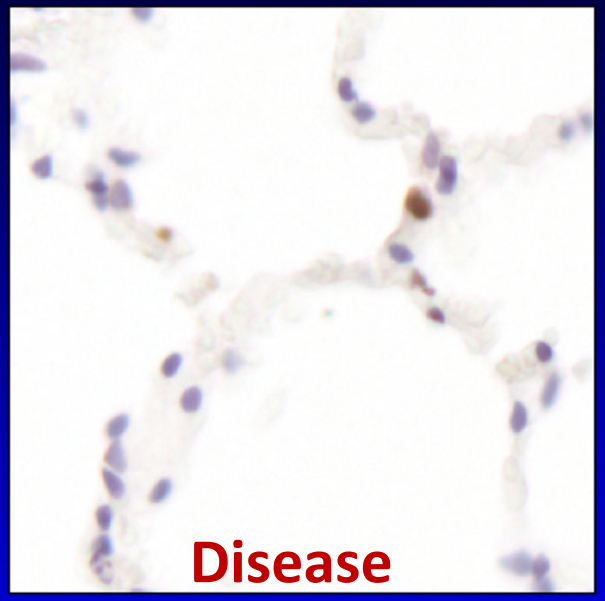


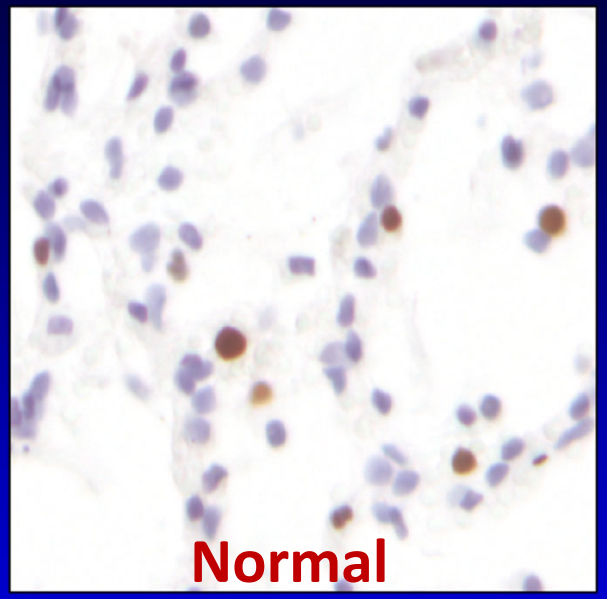
VEPTR

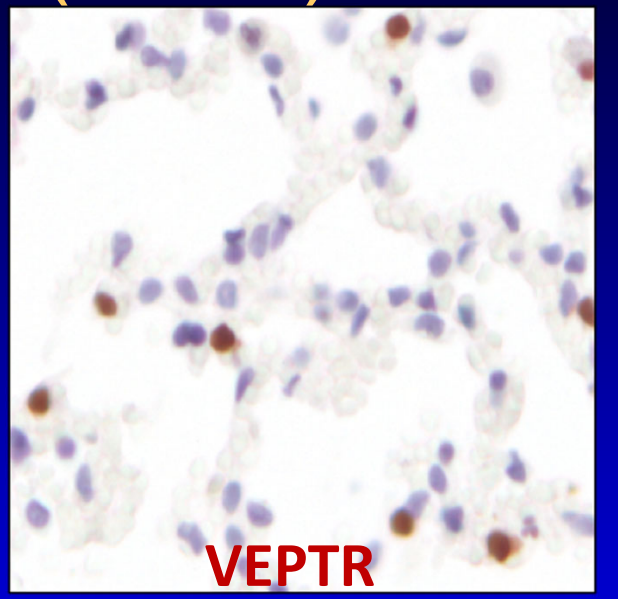
VEGF Receptor-2 up-regulated during angiogenesis

Bronchial and alveolar epithelium stain more strongly in Normal and VEPTR groups

Result Immunohistochemistry: Cell Proliferation Marker (KI-67)



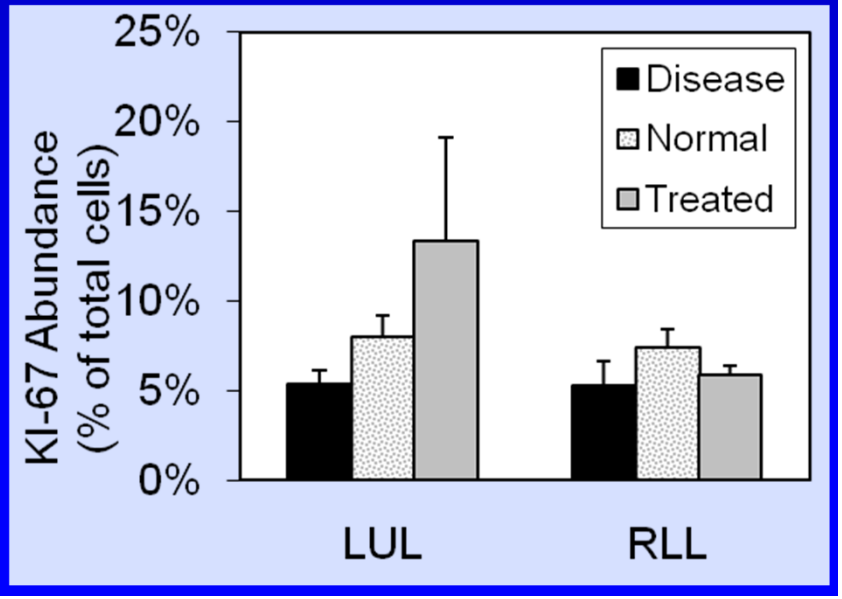




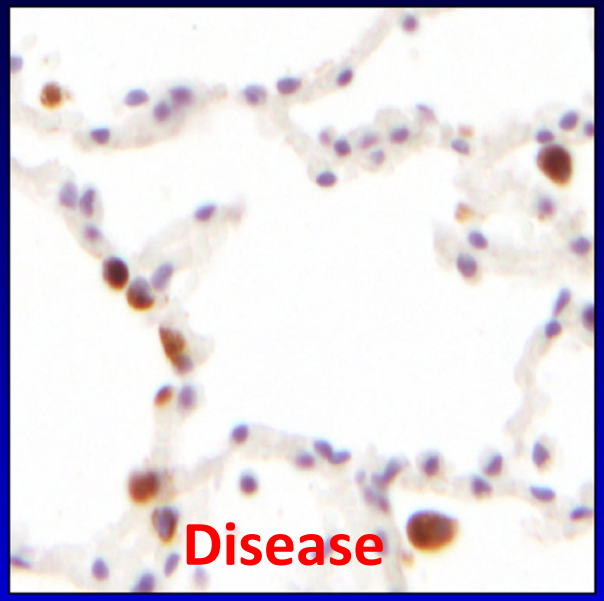
KI-67 nuclear antigen appears exclusively during active cell phase

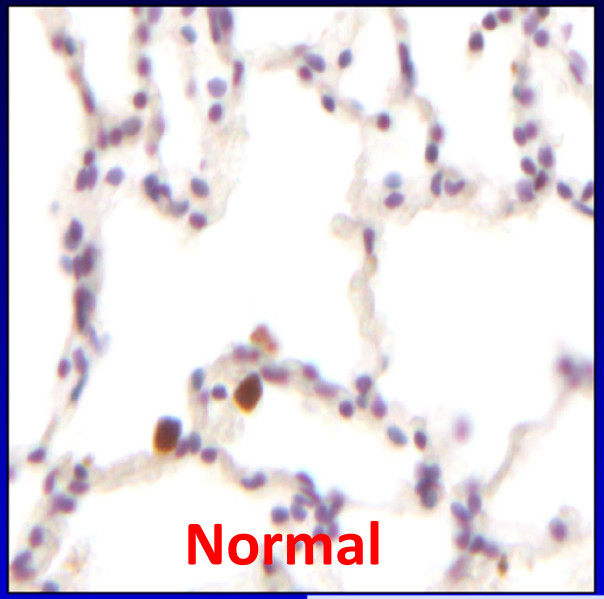
"+" stained cells (brown) normalized to total number cell nuclei (blue)

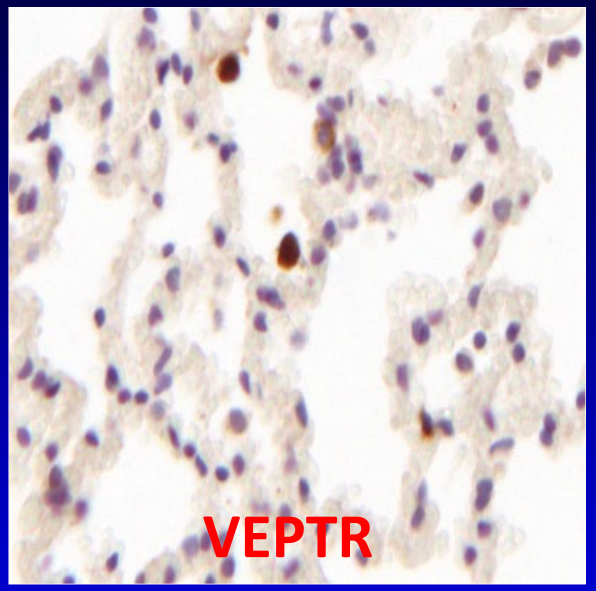
Significantly larger KI-67 cell populations in lung tissue from Normal and VEPTR compared to Disease



Result Immunohistochemistry: Macrophage (RAM-11)

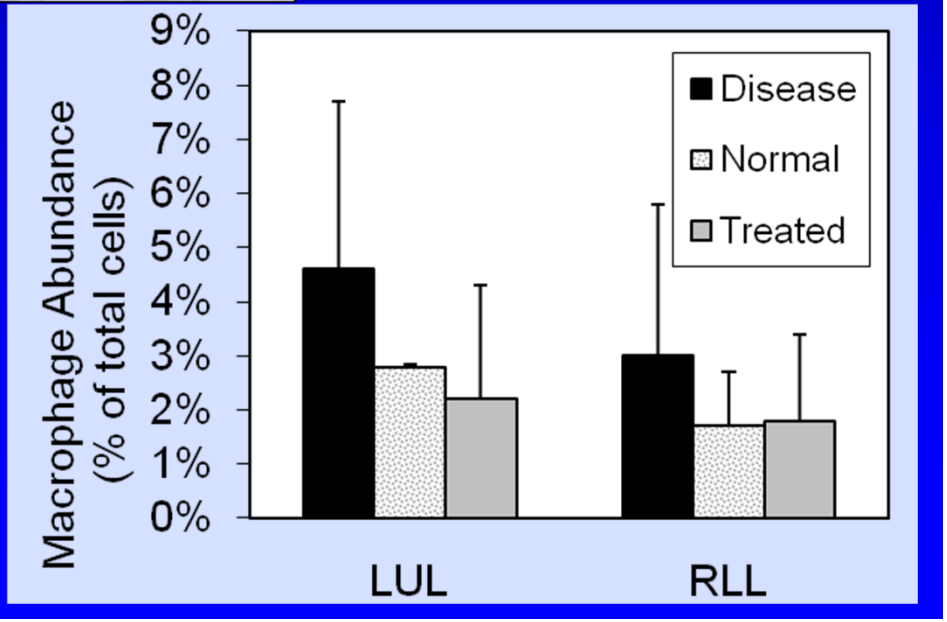






Macrophage - positively stained cells (brown) normalized to total number of cell nuclei (blue)

While not statistically significant, lung tissue from disease group appears to have more Macrophages

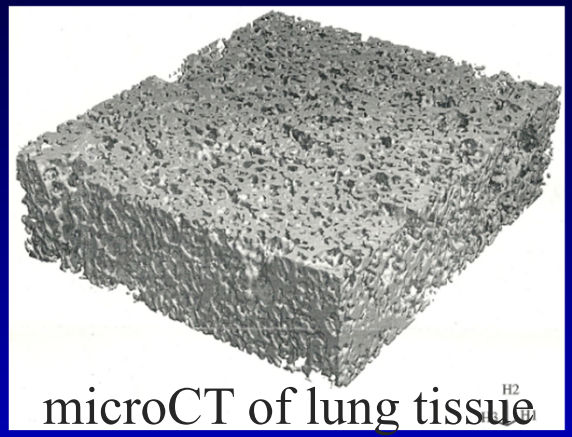


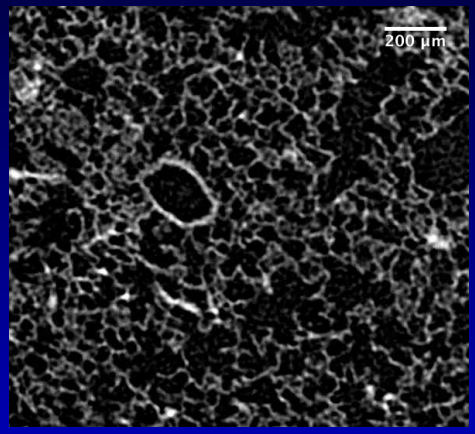
Discussion: Lung Growth

- **Constricted hemithorax - reduced ipsilateral lung volume**
- **Expansion Thoracoplasty - increased volume of constricted hemithorax *but did NOT restore ipsilateral lung volume to normal***
- **Disease & VEPTR groups - Contralateral lung hypertrophied to compensate** so **total lung volume remained equivalent** among groups

- Shortcoming: Rabbit model produced only mild deformities compared to children with TIS
  - consequence of quadruped model

Discussion: Alveolar Morphology

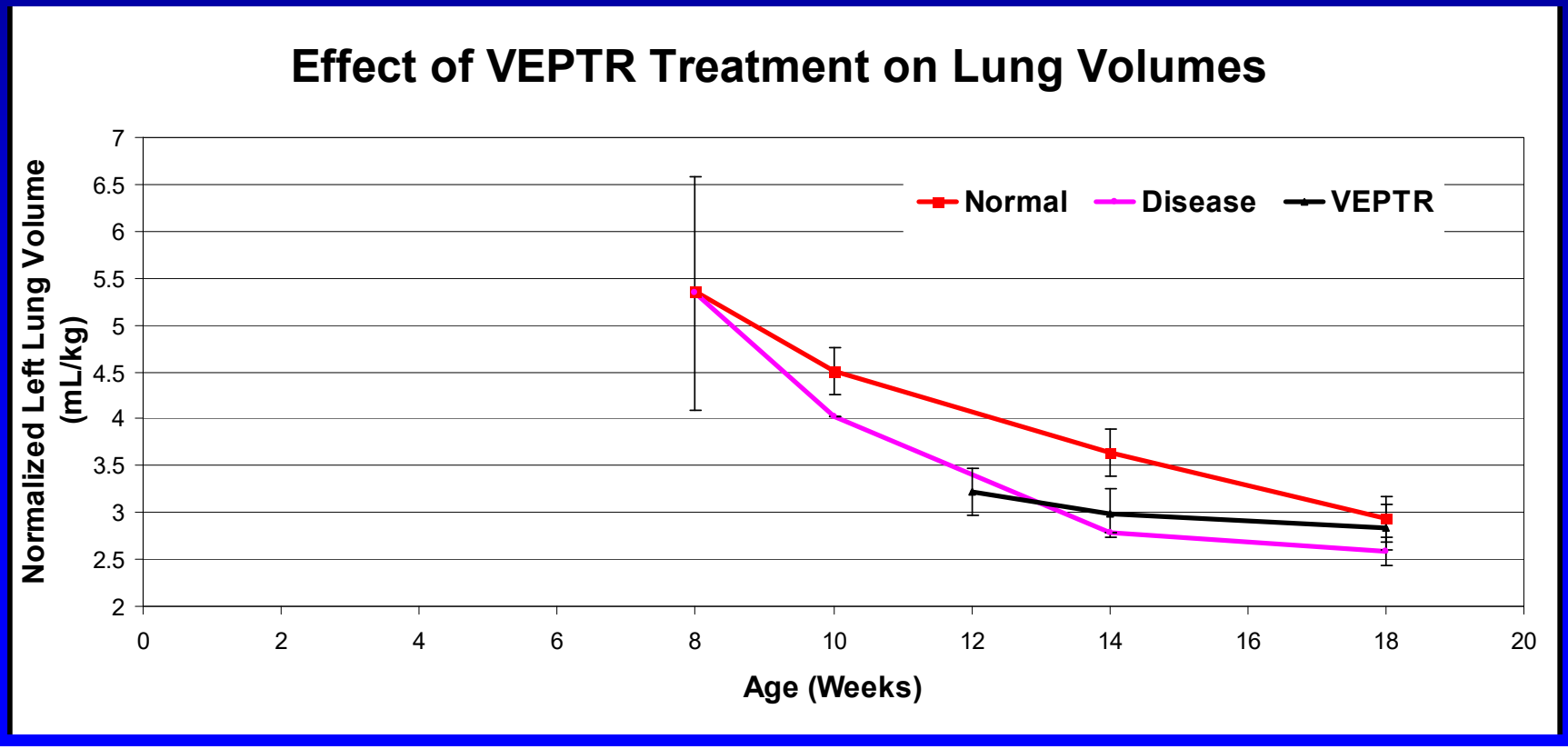




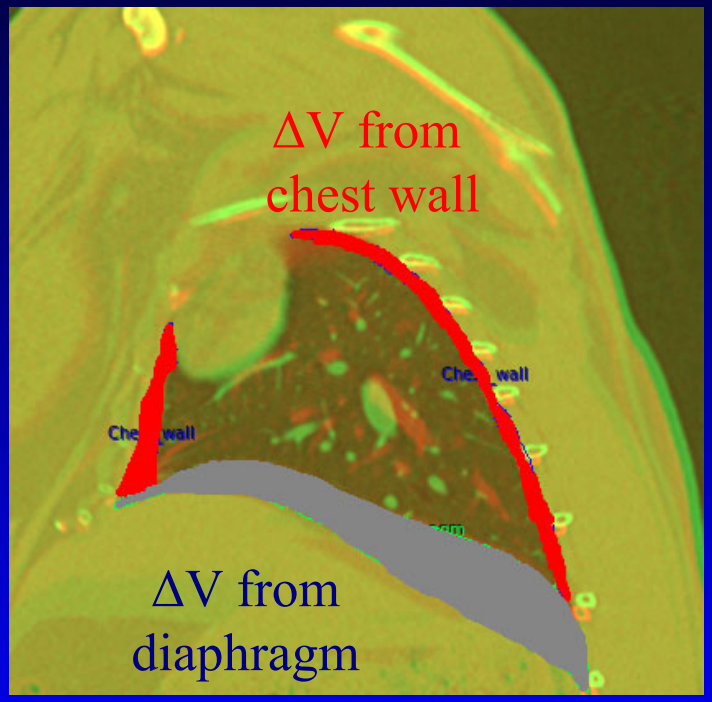
- **Hypoplastic lungs**: expanded alveolar air space (**emphysema**), thinner alveolar walls, ↑macrophages, decreased capillary network (**underdeveloped endothelium**)
- **VEPTR Treated lungs: normalization of alveolar morphology, ↑cell proliferation, ↑angiogenesis**
  - ***BUT No increase alveolar # density or volume***

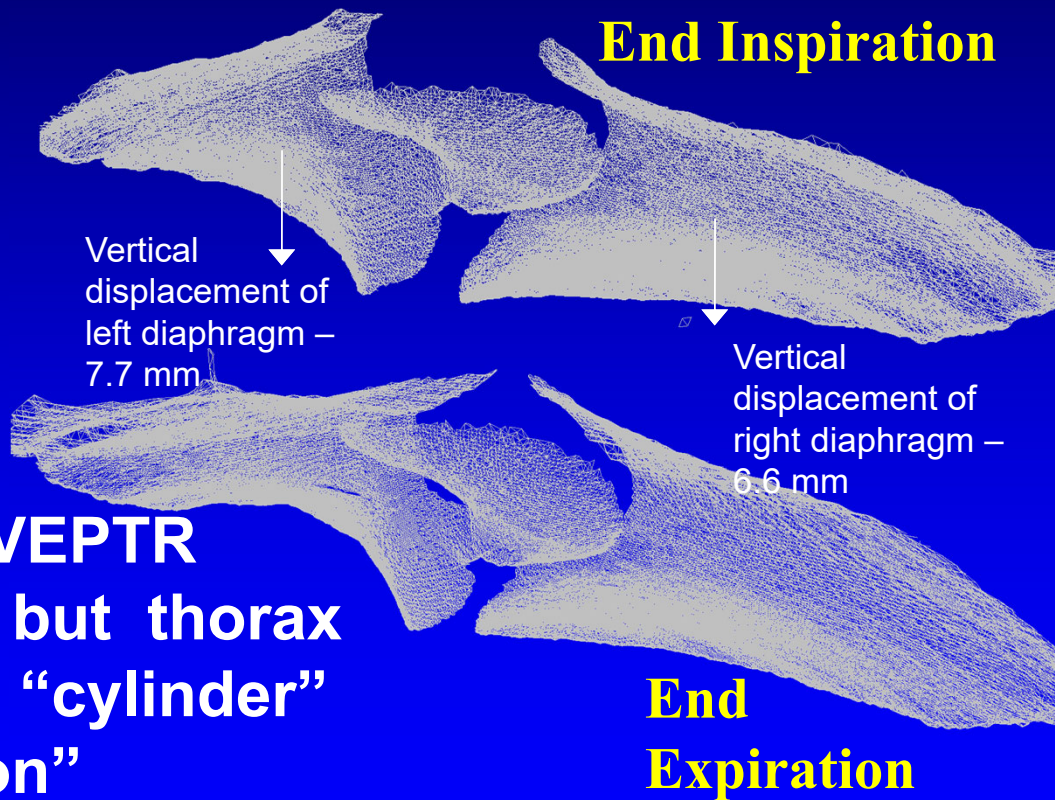
Clinical Implications

- **Expansion Thoracoplasty reverses inhibited lung growth *in proportion to lung growth remaining***
- Expansion Thoracoplasty @ 10 wks may be too late to effect lung growth in rabbit (mature @ 28 wks)



Clinical Implications: Excursion of Rib Cage & Diaphragm





- **Rib cage remains rigid – VEPTR increases thorax volume, but thorax essentially functions as a "cylinder" with "diaphragmatic piston"**
- **Δ V depends on contour + excursion diaphragm**

New Hypothesis?

- ***Improved respiratory function attained by preventing emphysematous changes and by increasing capillary network adjacent alveoli, thereby enhancing O_2 and CO_2 gas exchange***

Micro-CT Fixed Lung Tissue

•3-D view identifying vasculature

Thank You