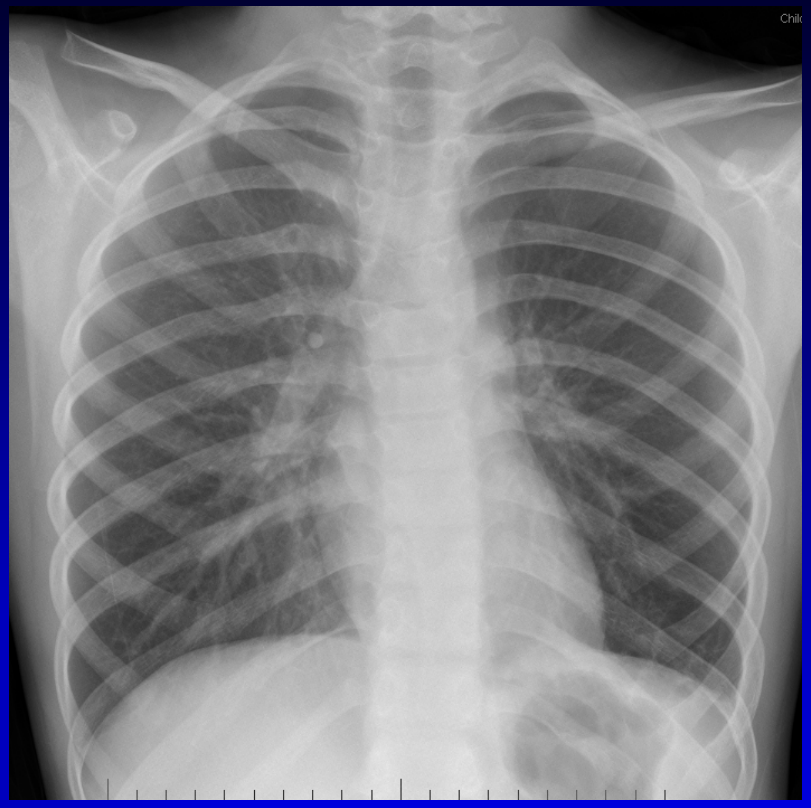
Pulmonary Hypoplasia and Postnatal Lung Growth



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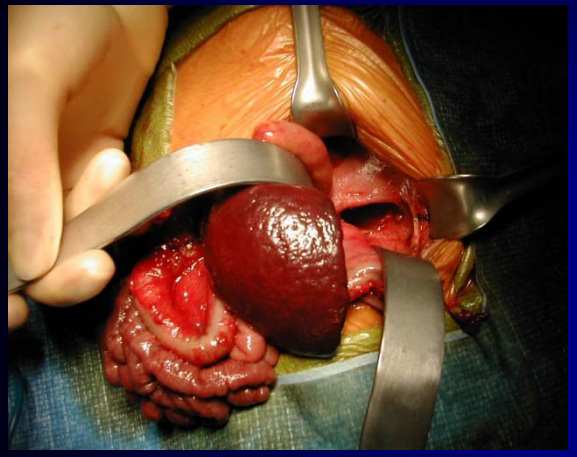
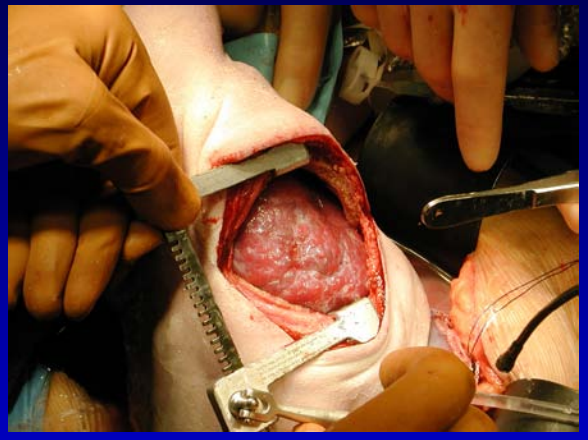
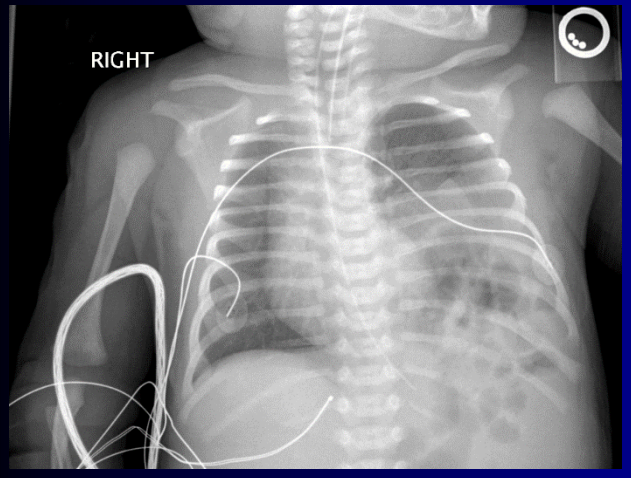
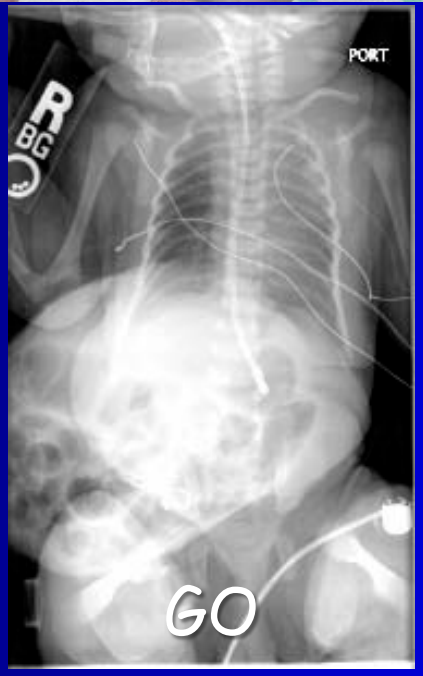
Pulmonary Hypoplasia







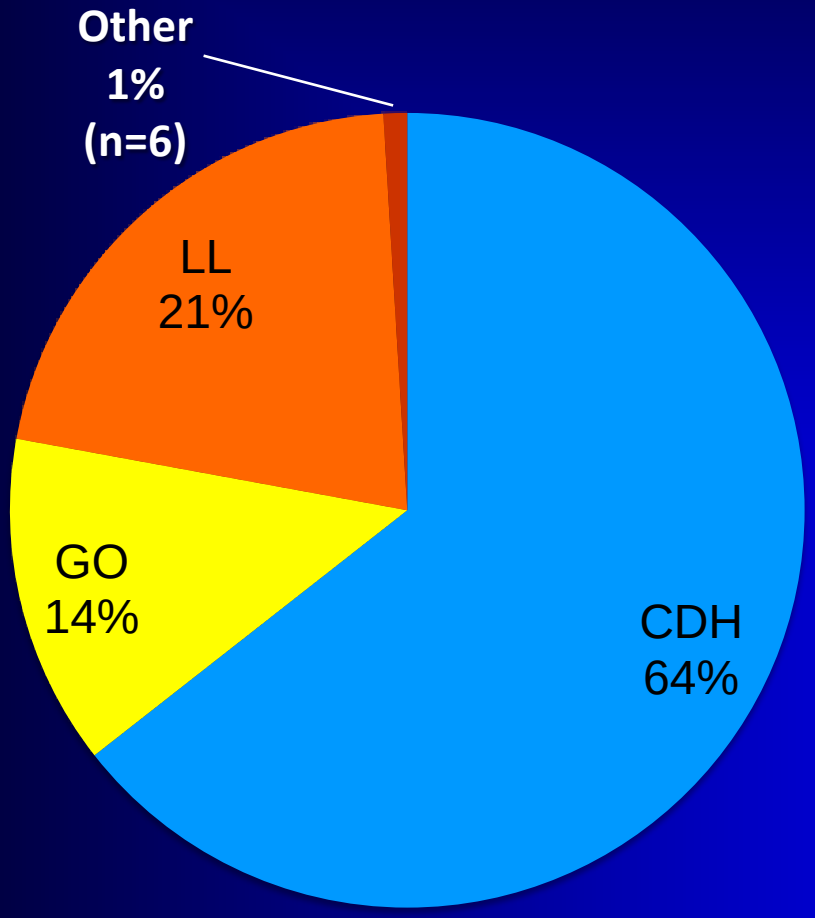
CDH



GO

Lung Lesion
(CPAM)

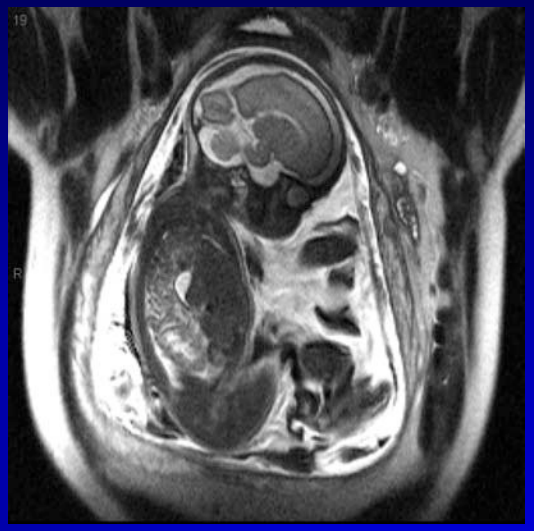
PHP Enrollment by Diagnosis

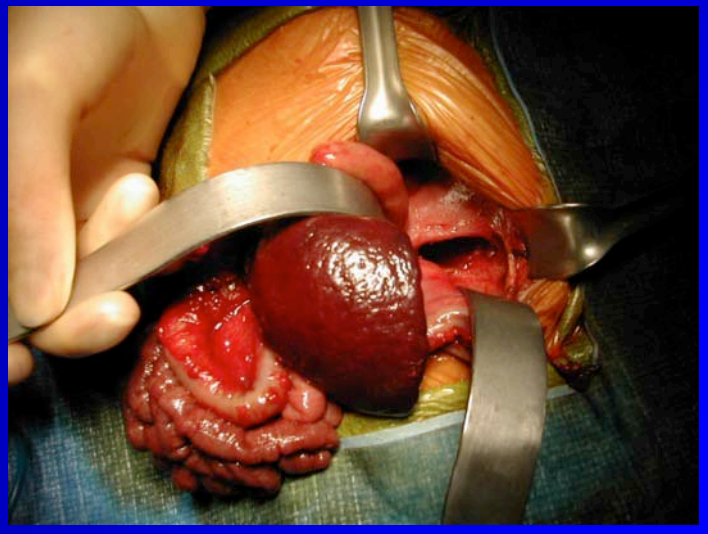


DX	Number Enrolled
CDH	433
CDH/GO	7
CDH/LL	23
GO	90
LL/GO	2
Lung Lesion	125
Other	6
Grand Total	687

Congenital Diaphragmatic Hernia

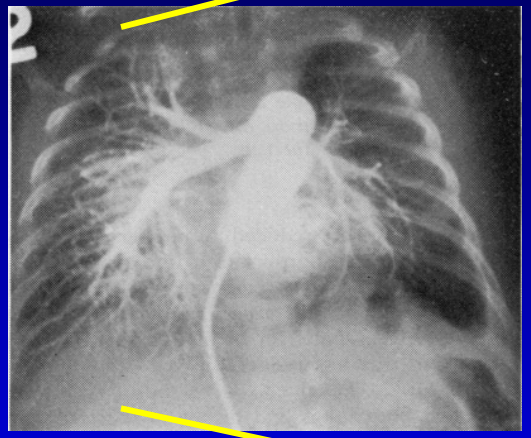
- 1:2500 – 4000 live births
- 3.3 – 3.8/10,000 total births
- 4 types
  - Posterolateral
    - ~90% of all
    - 70-90% left-sided
  - Anterolateral
  - Pars sternalis
  - Morgagni





Pulmonary Abnormalities in CDH

- Lungs physically smaller
- Fewer airway branches
- Fewer terminal units
- Decreased surfactant



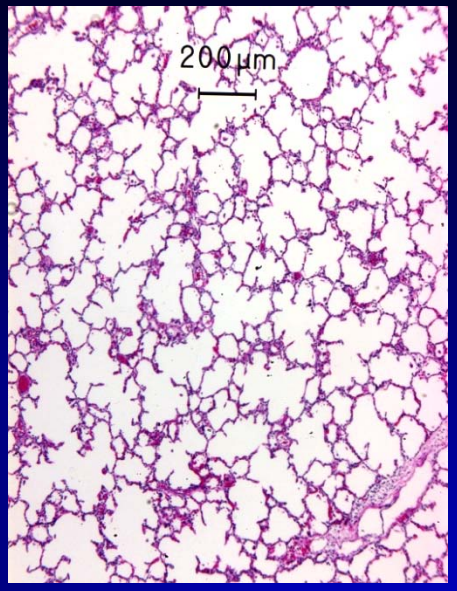
Hypoplasia

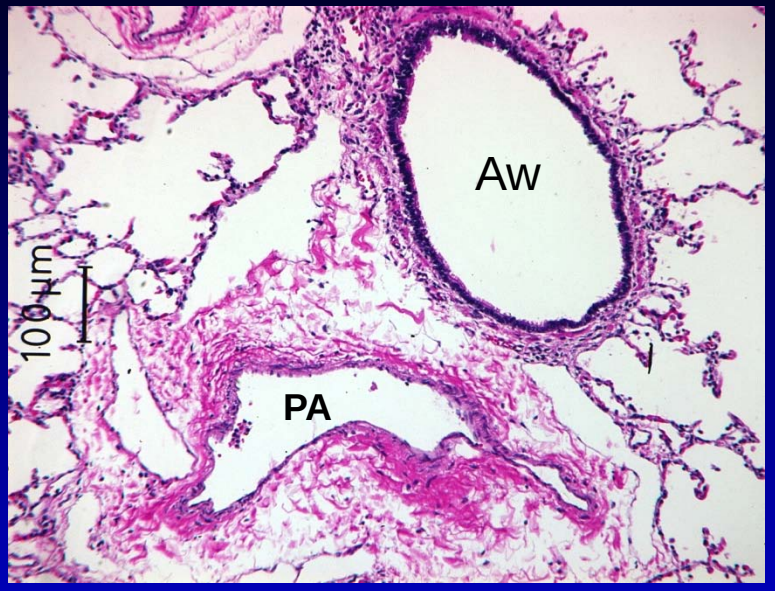
- Smaller and fewer arterioles
- Abnormally developed
  - Excessive smooth muscle
  - Abnormal response to O_2

Hypertension

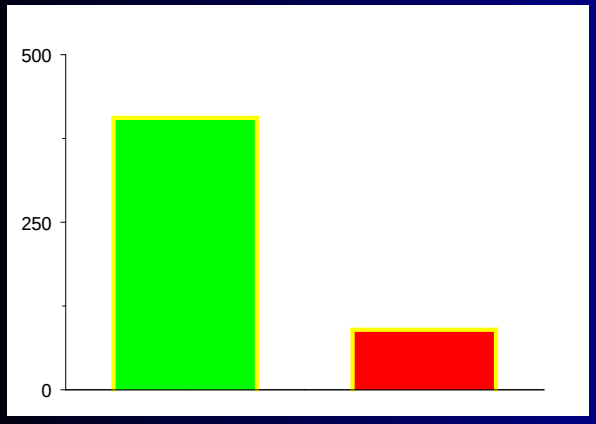
Hislop A and Reid L. Thorax 31:450; 1976

Normal lung, 6 months

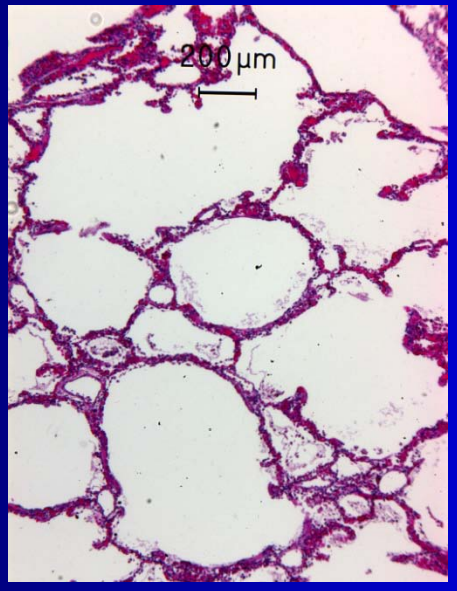


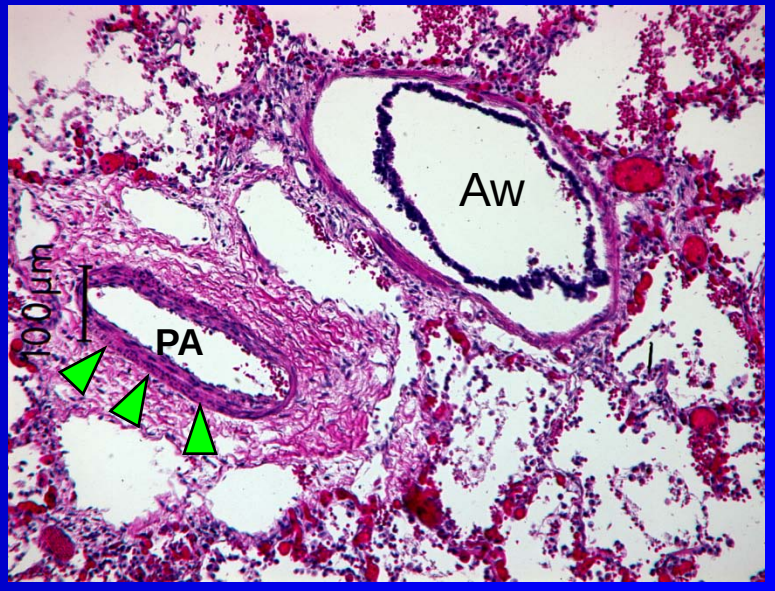


Alveolar surface Density (cm-1)



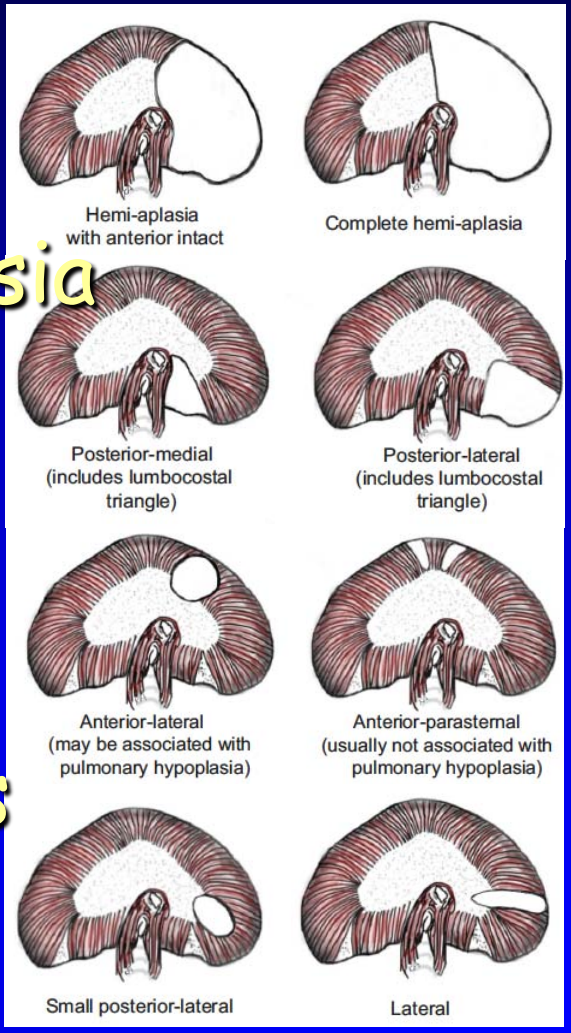
CDH, 7 months





CDH: A Heterogeneous Condition

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



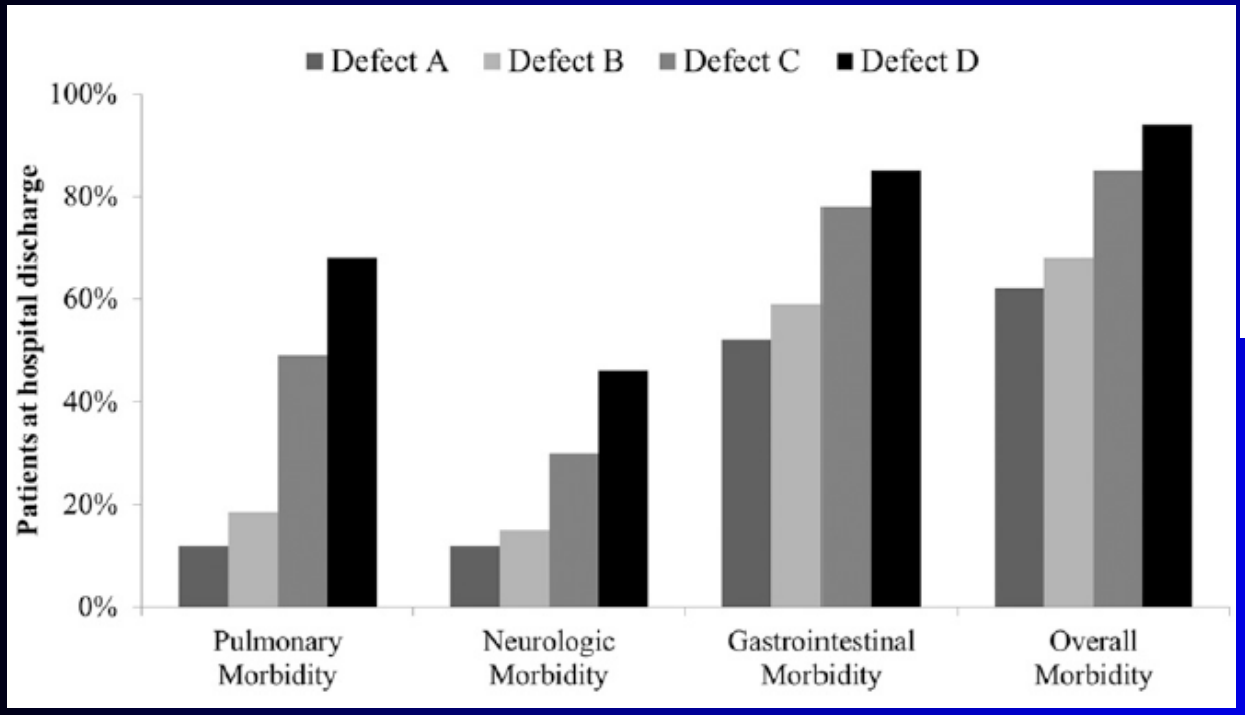
From Kardon G et al.
Dis Model Mech 10:955;2017

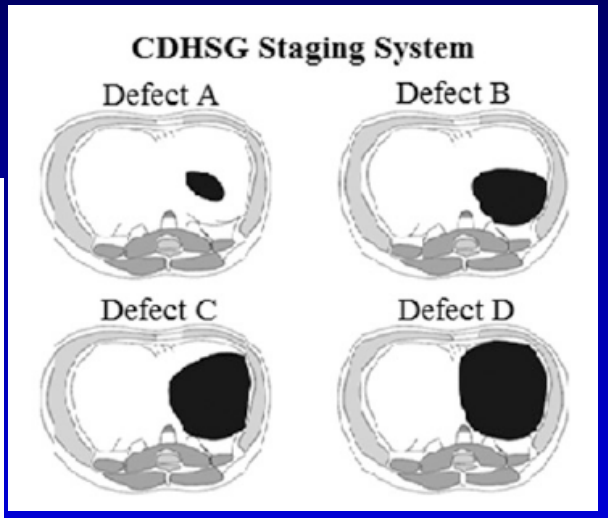
Selected Genetic Mouse Models of Abnormal Diaphragm Development

Model	Diaphragm Defect	Human Correlate
C-Met	Amuscular	Unknown
COUP-TFII (*Nkx 3.2* conditional model)	Posterior hernia (no sac)	Cytogenetic hotspot 15q26.1-26.2 (D1H1, OMIM #142340) (syndromic)
Fog2 (*Zfpm2*$^{lil/lil}$)	Posterior hernia (sac), muscle patterning defect	*de novo* mutation (non-syndromic)
Gab 1	Amuscular	Unknown
Gata4 $^{+/-}$	Central hernia (sac)	Suspected, cytogenetic hotspot 8p23.1
LOX	Central rupture	Unknown
MyoD	Thin, not functional	Unknown
Mogen	Amuscular	Unknown
MyoR/Capsulin	Posterior hernia (?sac)	Unknown
Pax3 (Splotch)	Amuscular	Unknown
RARα/RARβ2 (retinoic acid receptors)	Compound receptor nulls have posterior hernias	Unknown, suspected
Slit3	Central midline hernia (sac)	Unknown
Wt1	Posterior hernia	Syndromic

Adapted from Ackerman KG and Greer JJ. Am J Med Genet Part C Semin Med Genet 145C:109–116; 2007

Morbidity at Discharge and Defect Size



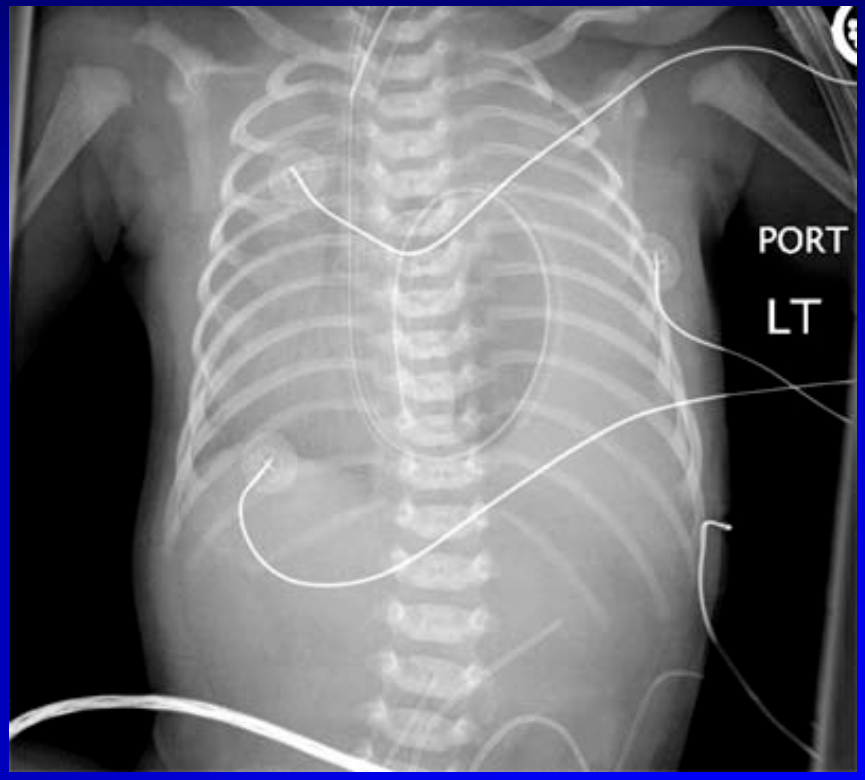


Putnam LR et al. Pediatrics 138:e20162043; 2016

Pulmonary Hypoplasia in CDH: A Two-Hit Hypothesis

- Space occupying lesion
- Embryopathy
- **Combination**

- ?Accelerated (catch-up) growth?



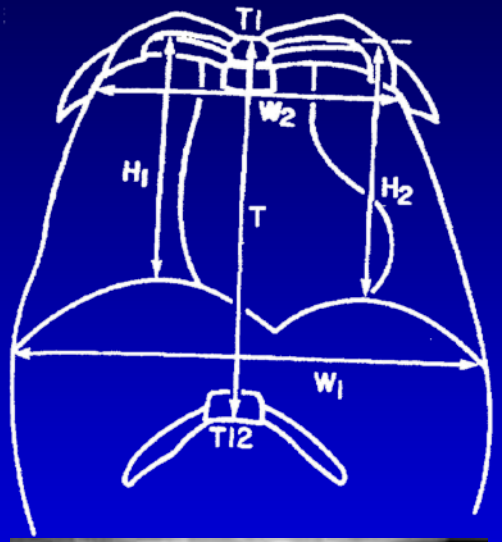
Giant Omphalocele

- Omphalocele 1 in 6,000 live births
  - Small, giant, ruptured
  - Giant contains most of liver
  - High incidence of respiratory insufficiency

Chest Shape in Newborns with Abdominal Wall Defects

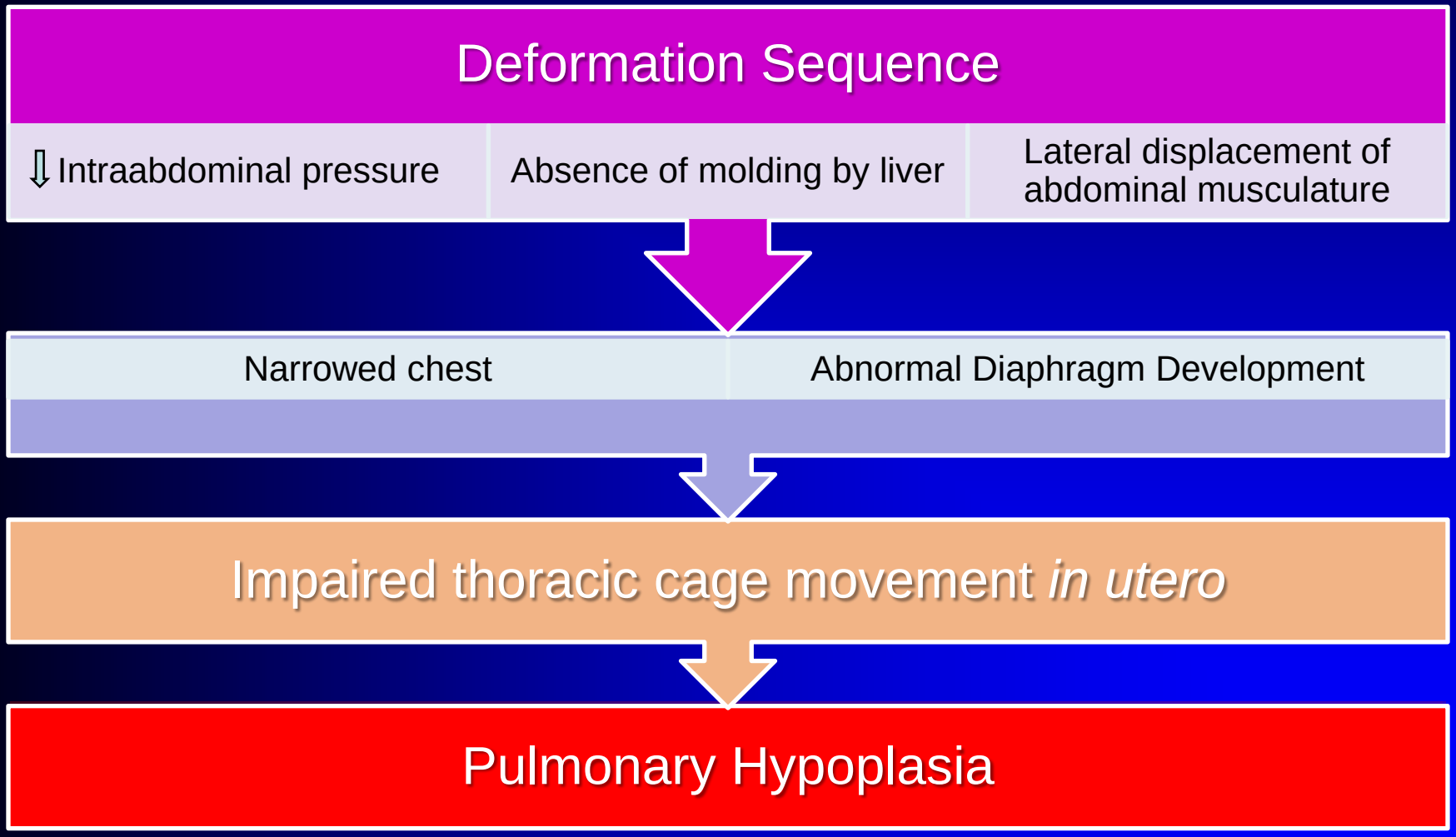
	Gastroschesis	Small Omphalocele	Giant Omphalocele
BW (g)	2515 ± 573	3393 ± 949†	2863 ± 566
GA (weeks)	37.4 ± 3.1	38.9 ± 3.8	38.3 ± 2.6
W1/T	1.12 ± 0.08	1.13 ± 0.06	0.97 ± 0.07†
W2/T	0.71 ± 0.06	0.71 ± 0.07	0.65 ± 0.06†
(H1+H2)/2T	0.68 ± 0.09	0.69 ± 0.06	0.74 ± 0.08
(Ac – Ah)/T	2.55 ± 0.61	2.70 ± 0.51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

†P < 0.001
‡P < 0.05



Hershenson MB et al. J Pediatr Surg 20:348; 1985

Purported Mechanism of Pulmonary Hypoplasia in GO



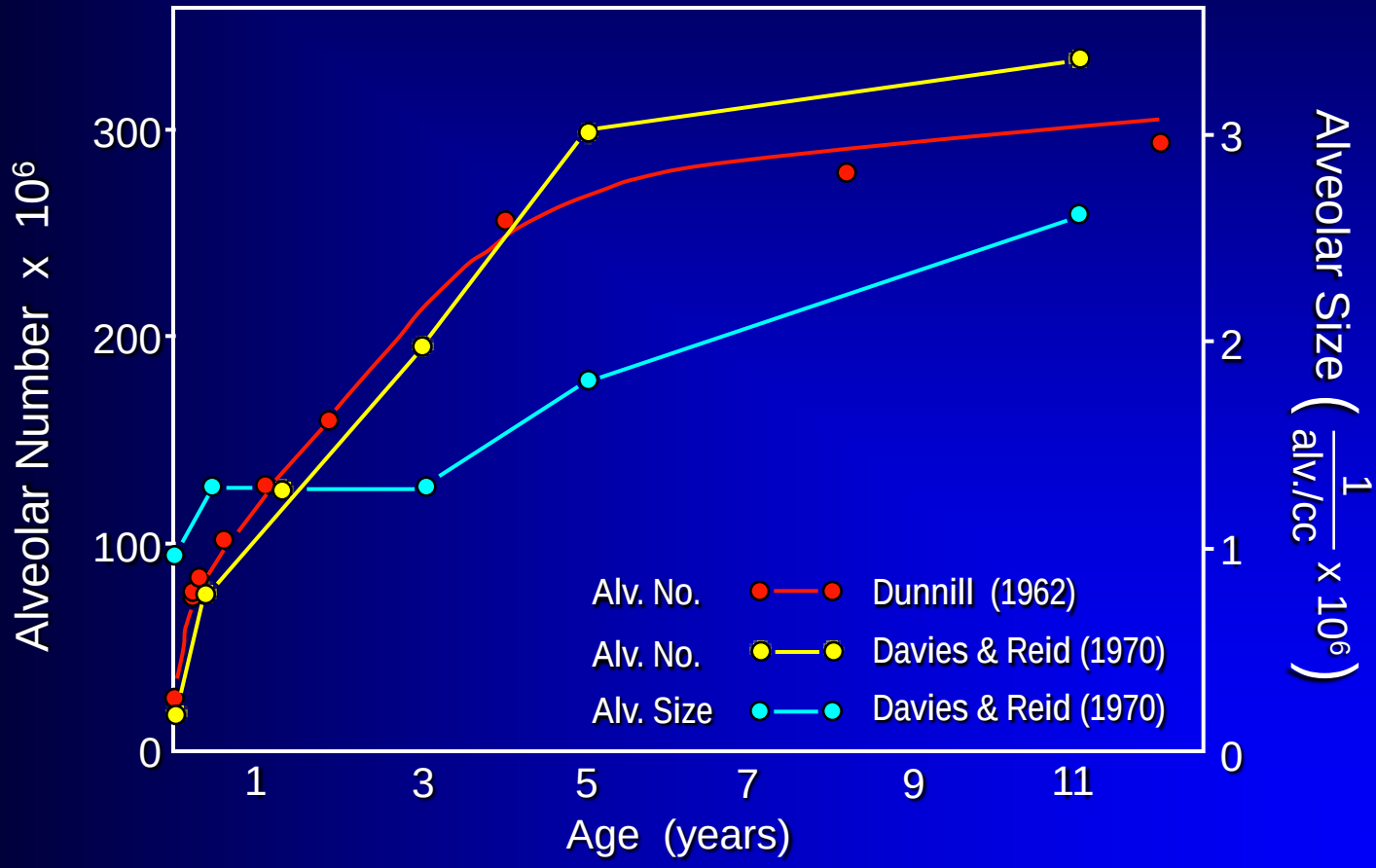

Left
X-Table
50 mm (dp)
50 mm (dp)

Pulmonary Hypertension in GO

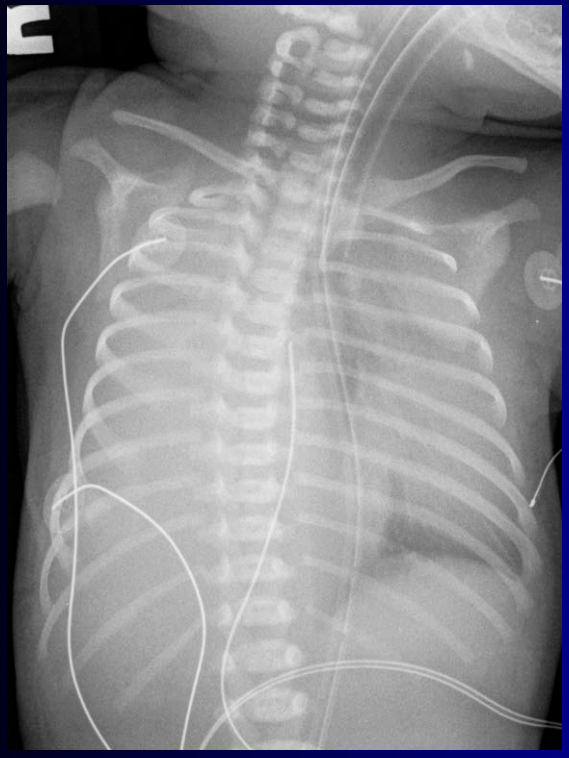
- N = 54
  - 34 without PH
  - 20 with PH
    - 9 required long term therapy (sildenafil)
- PH associated with
  - Duration of mechanical ventilation
  - Requirement for tracheostomy
  - Need for bronchodilators
  - Supplemental O_2 at time of NICU discharge

Partridge EA et al J Pediatr Surg 49: 1767; 2014

Postnatal Alveolar Development



Reid LM. Br J Dis Chest 78:12; 1984



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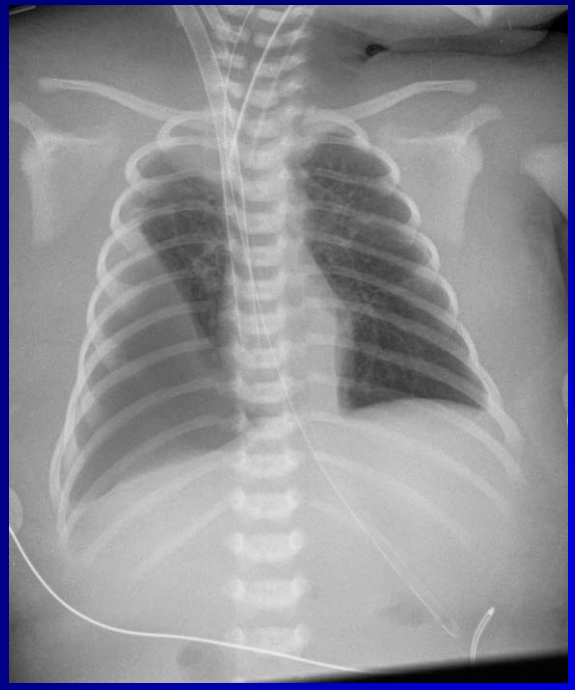

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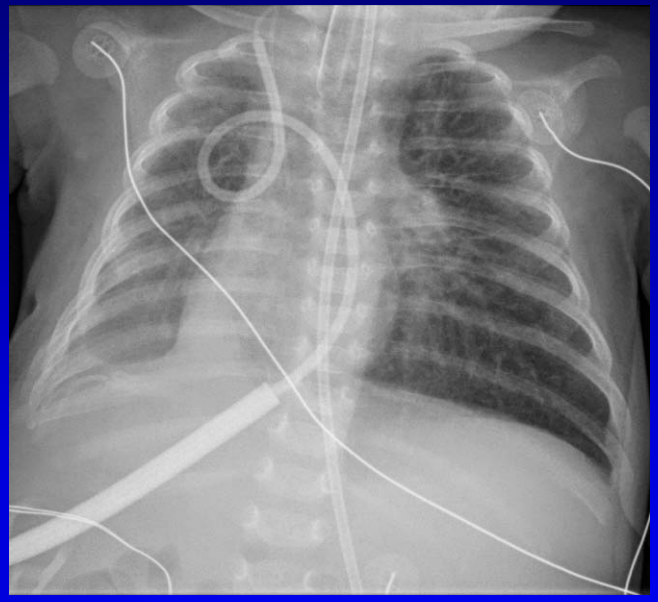
POD #2



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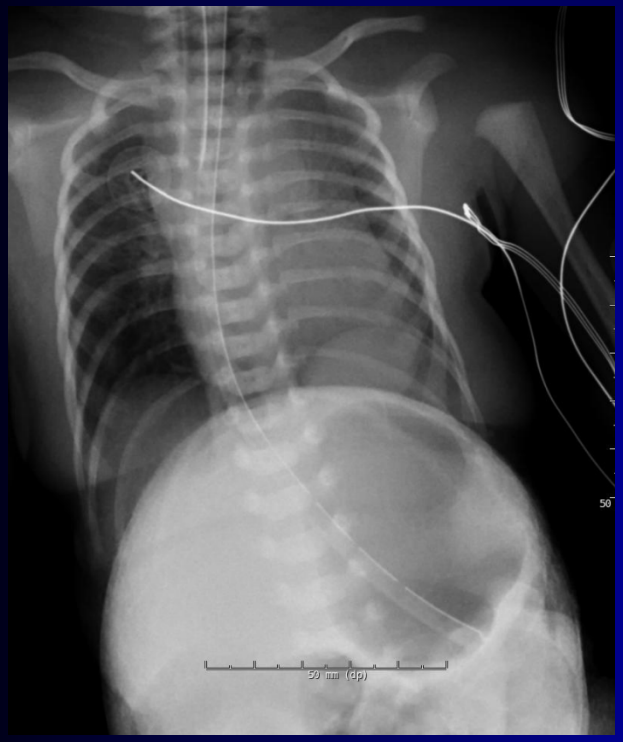
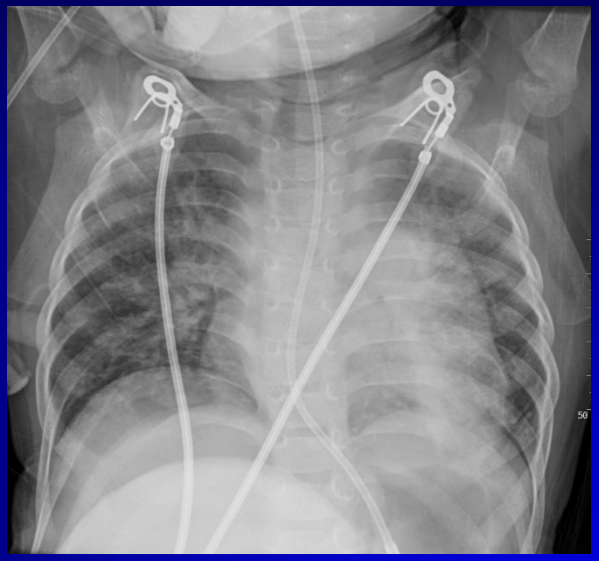
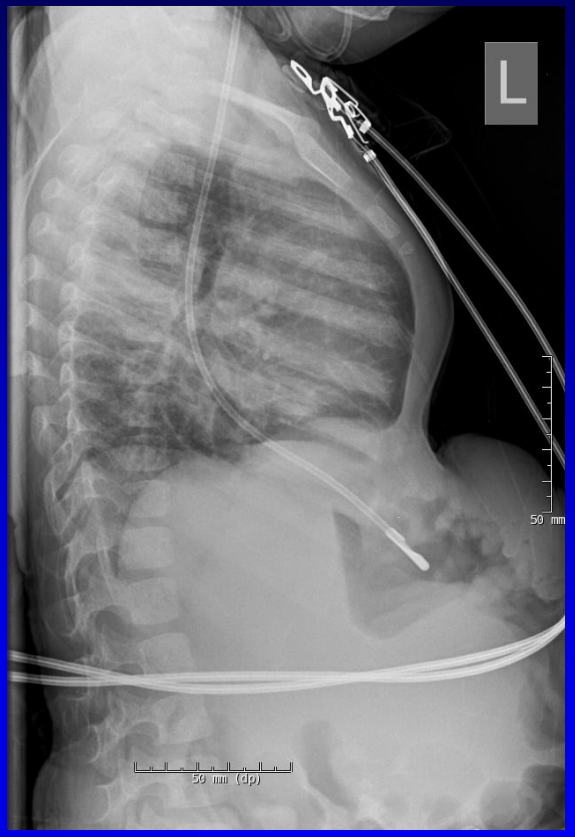




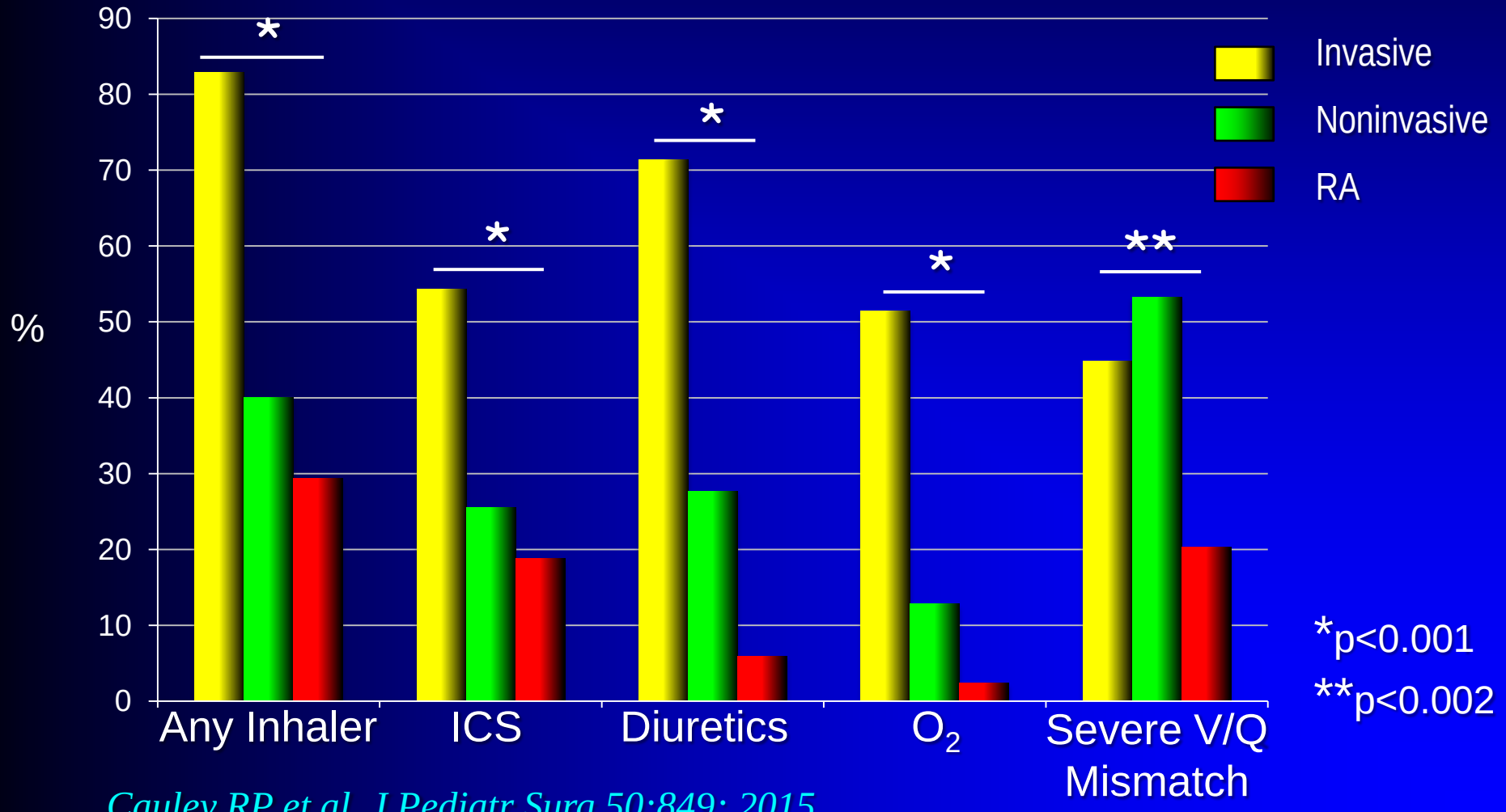


1 day old

2.5 yrs old

Pulmonary Outcomes at 1 Yr

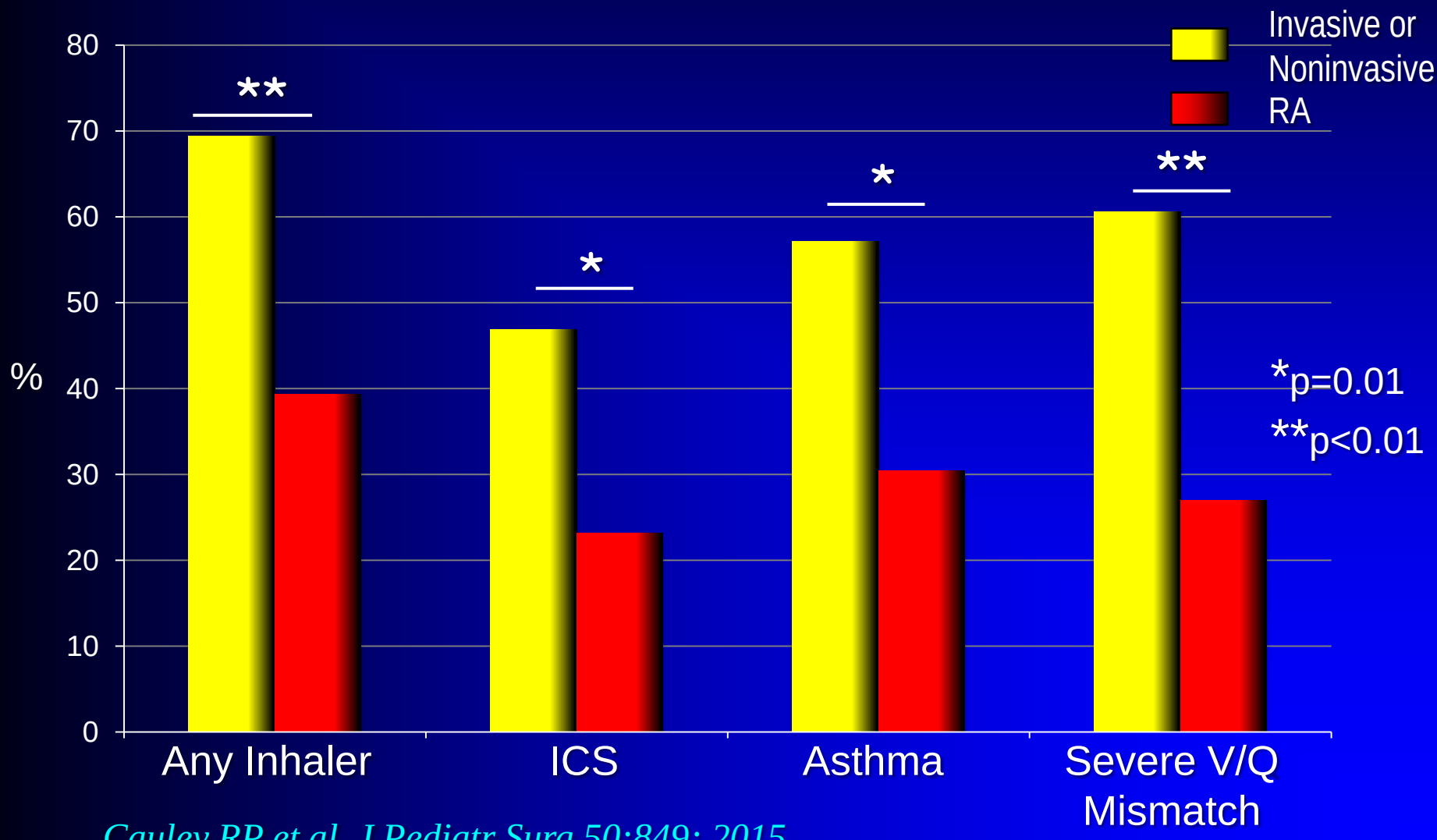
vs Support at 30d



Cauley RP et al. J Pediatr Surg 50:849; 2015

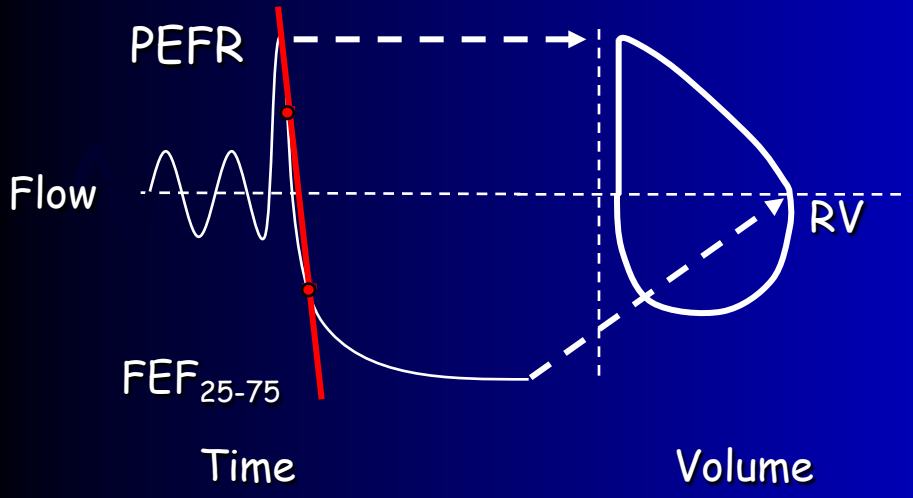
Pulmonary Outcomes at 5 Yr

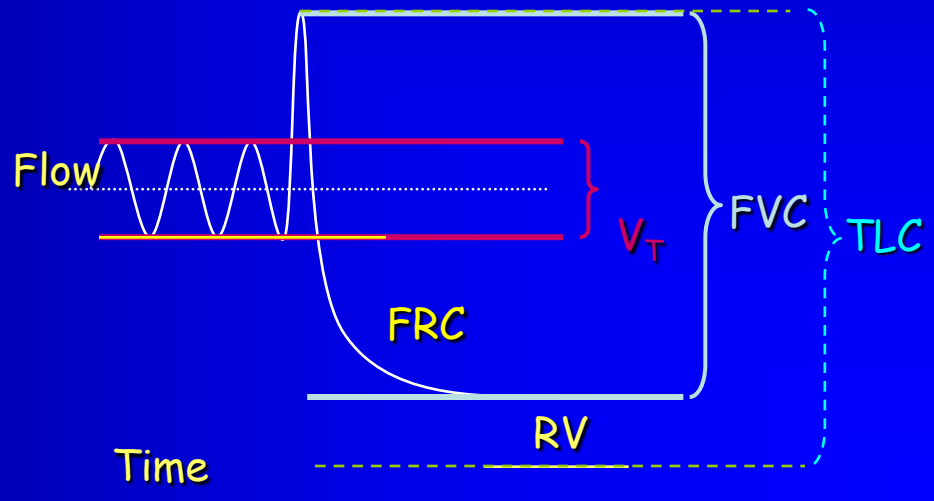
vs Support at 30d



Cauley RP et al. J Pediatr Surg 50:849; 2015

Standard Lung Function Testing



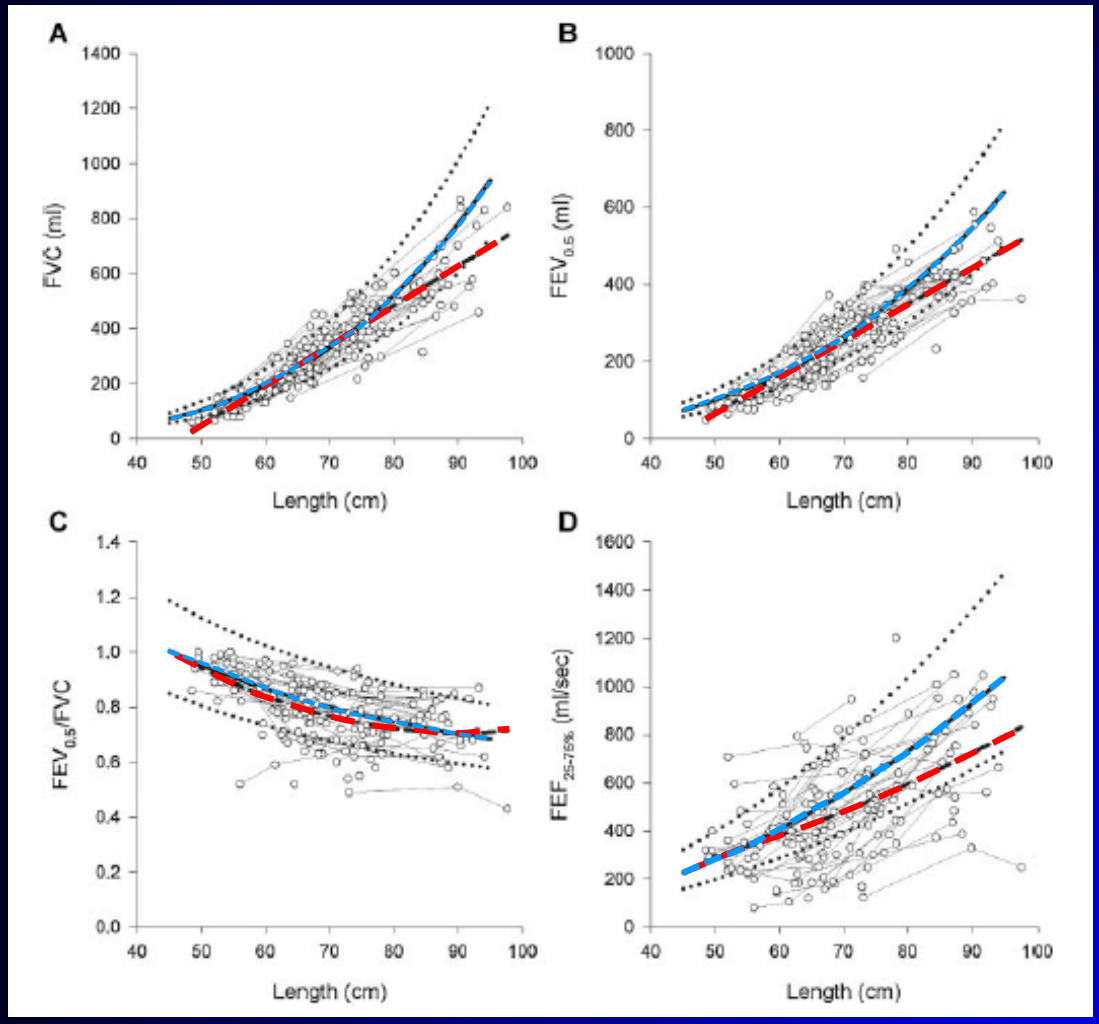


CDH Study Population

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

Panitch HB et al. Pediatr Pulmonol 50:896; 2015

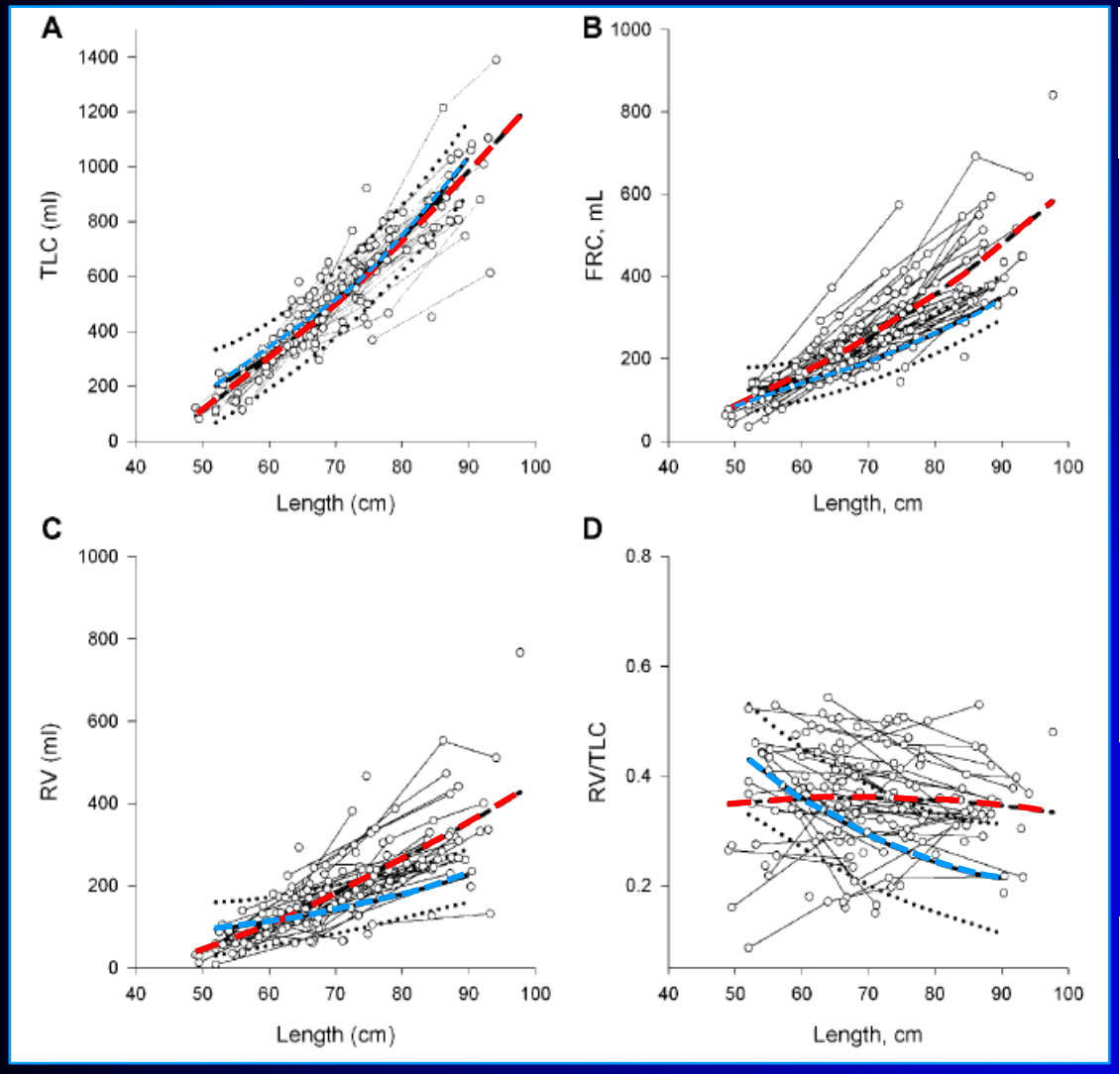
Spirometry



- FVC and forced flows were lower than normal
- $FEV_{0.5}/FVC$ slightly reduced
  - 23 with $FEV_{0.5}/FVC$ < -1.645 Z scores

Panitch HB et al. Pediatr Pulmonol 50:896; 2015

Lung Volumes

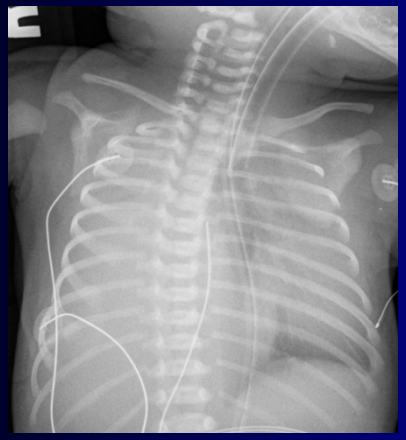


Z scores	First study (n = 98)
Fractional lung volumes	
TLC	0.439 ± 1.685*
FRC	3.901 ± 3.087***
RV	2.350 ± 2.521***
RV/TLC	0.780 ± 2.336**
	Second study (n = 43)
TLC	0.154 ± 2.657
FRC	6.381 ± 4.337***
RV	4.523 ± 4.150***
RV/TLC	1.611 ± 2.180***
	Change in Z score from 1st to 2nd study (*P*-value)
TLC	−0.427 ± 2.445 (0.283)
FRC	2.870 ± 4.344 (<0.001)
RV	1.922 ± 3.079 (<0.001)
RV/TLC	−0.190 ± 1.851 (0.525)

Panitch HB et al. Pediatr Pulmonol 50:896; 2015

Change in Lung Function with Growth

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



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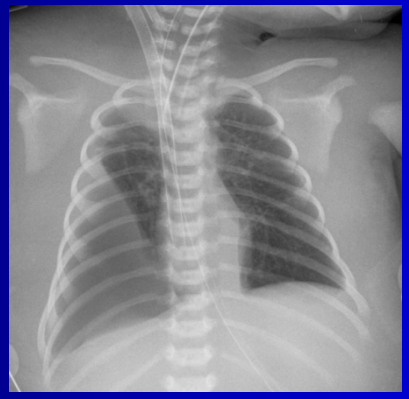

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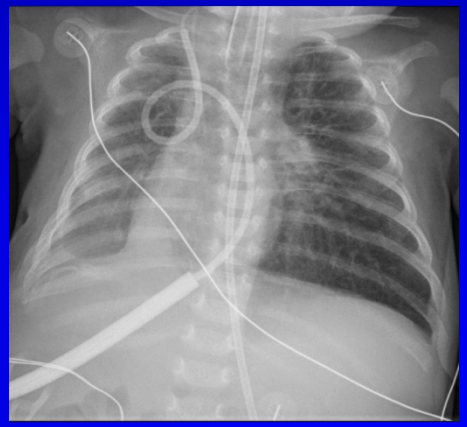

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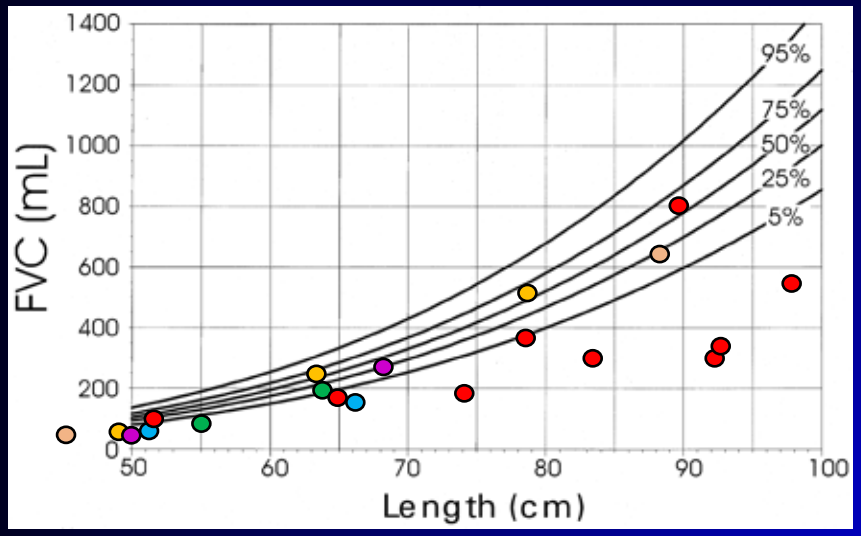
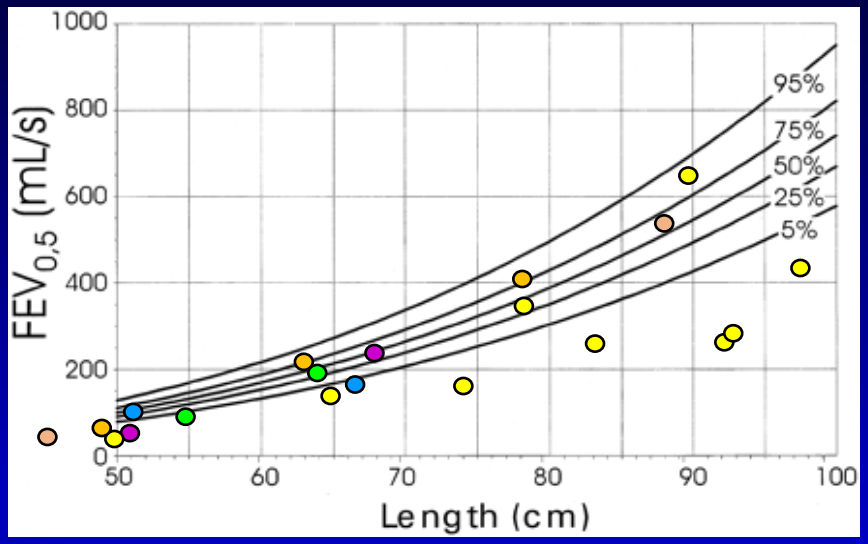
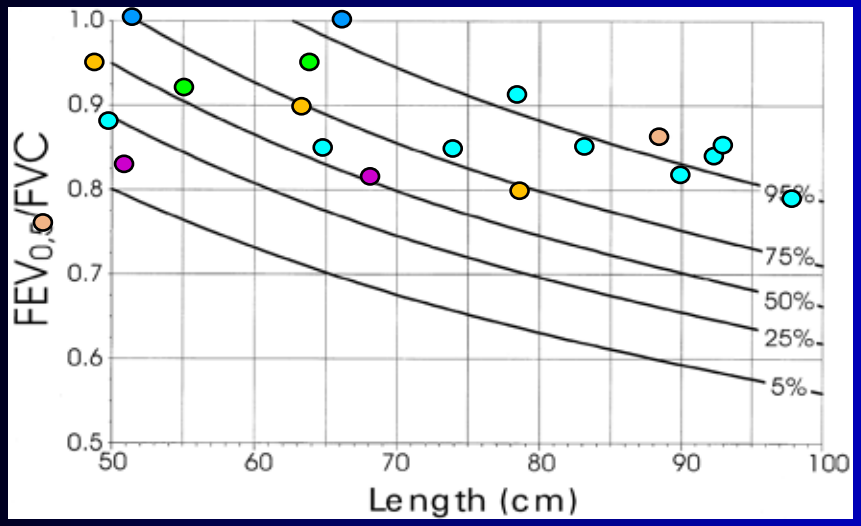
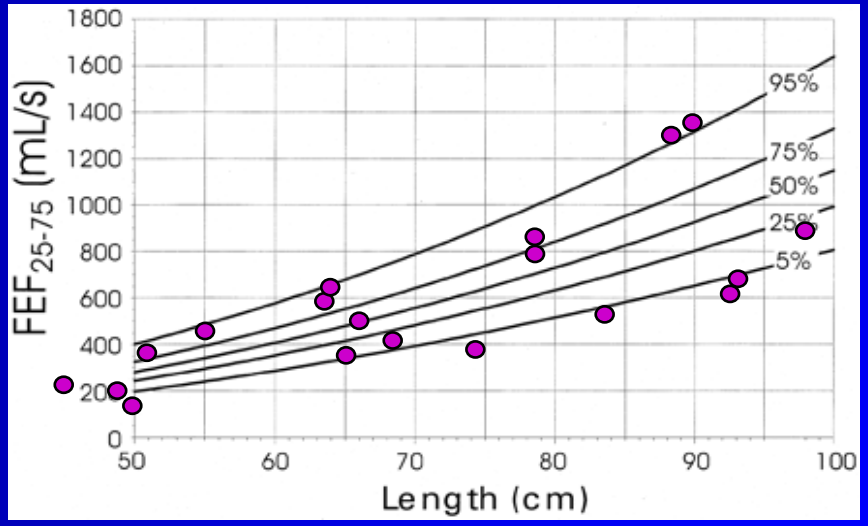
Panitch HB et al. Pediatr Pulmonol 50:896; 2015

Forced Expiratory Flows: GO



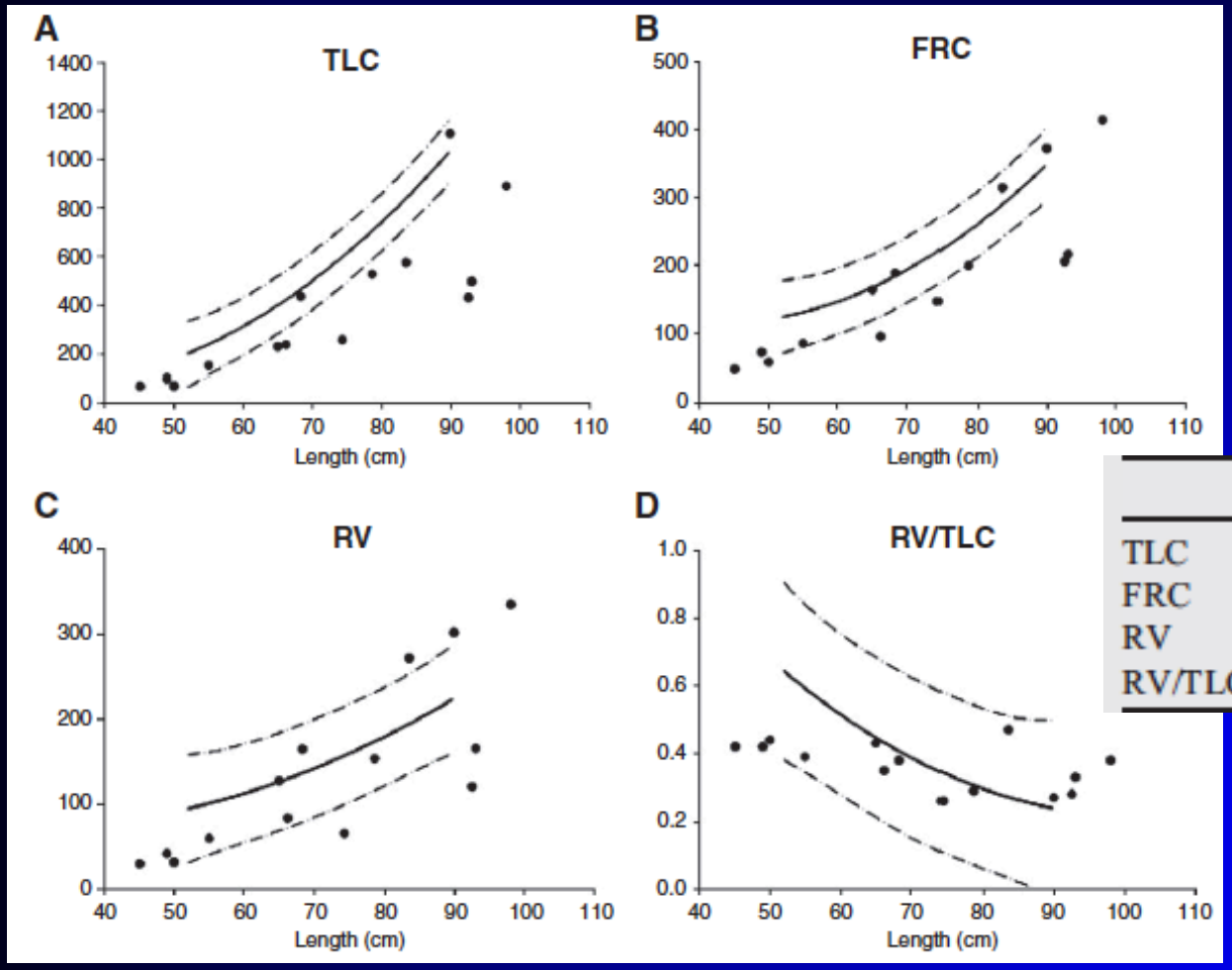






Danzer E et al. J Pediatr Surg 47:1811; 2012

Lung Volumes: GO

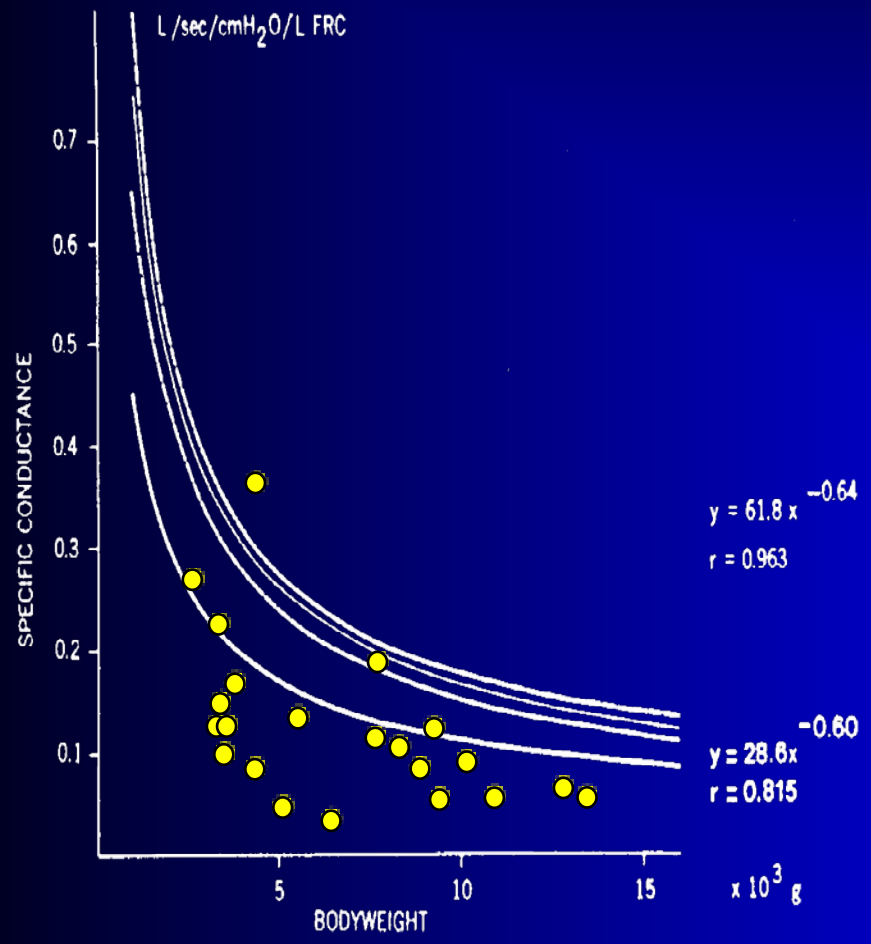


	% Predicted [a]	*P* value [b]
TLC	63.9 ± 19.6 (38-107)	**<.001**
FRC	74.1 ± 22.6 (41.0-106)	.21
RV	81.9 ± 37.0 (35-138)	.34
RV/TLC	127.1 ± 35.1 (84-200)	.48

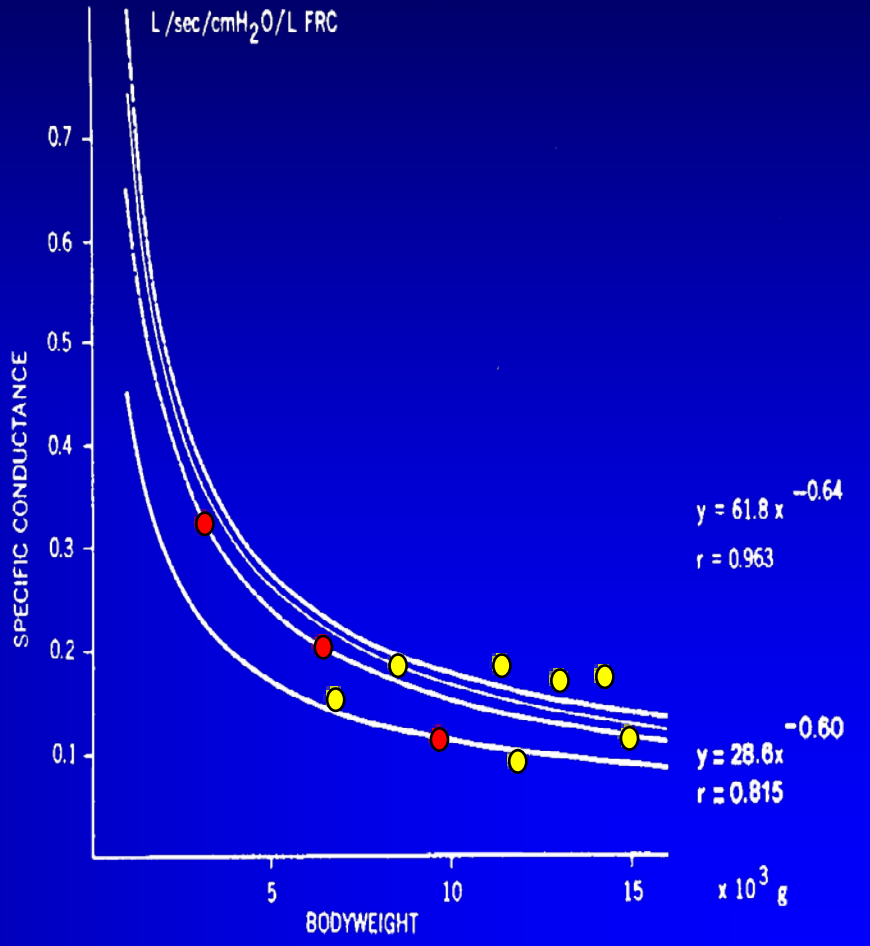
Danzer E et al. J Pediatr Surg 47:1811; 2012

Specific Conductance

CDH

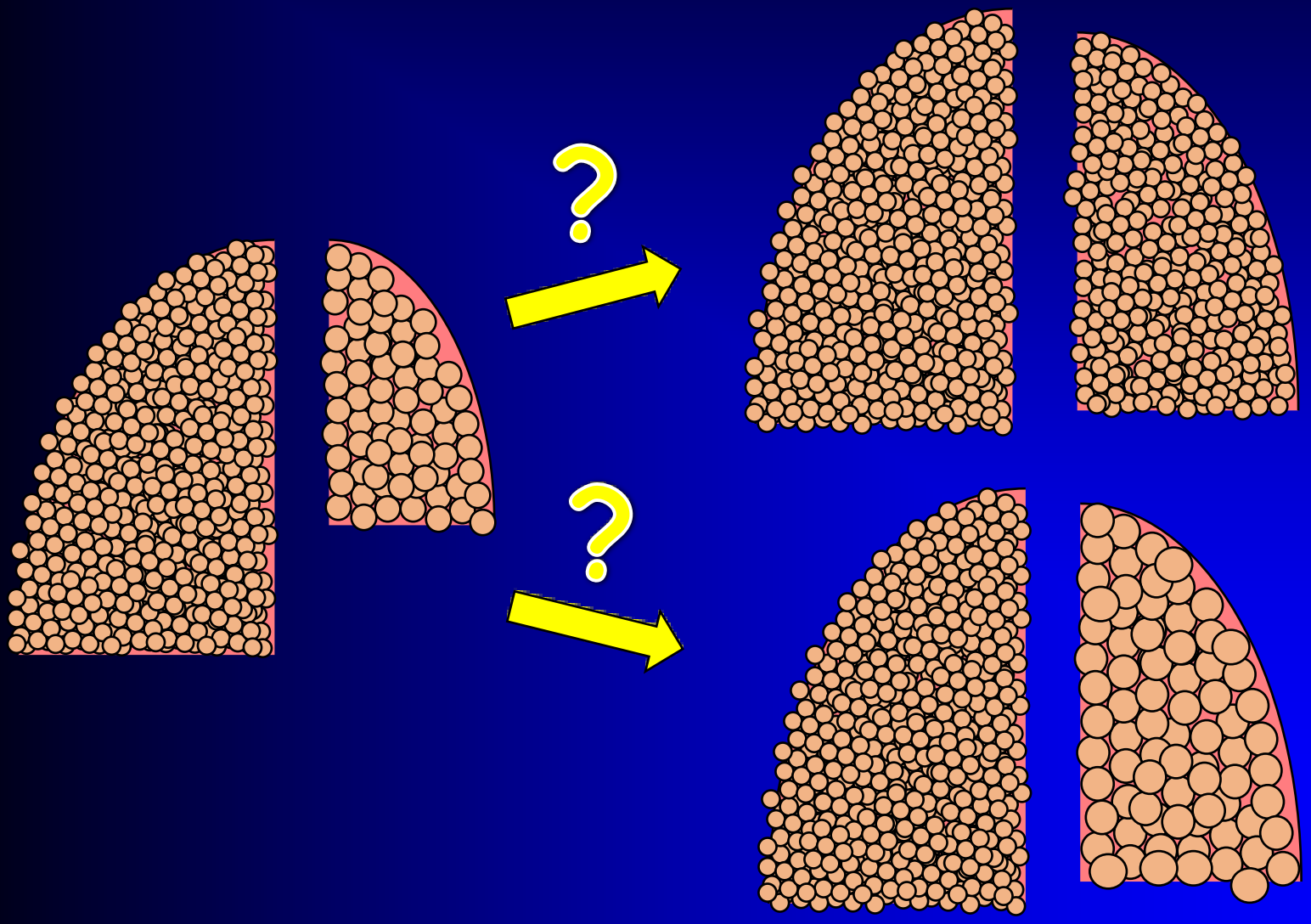


GO



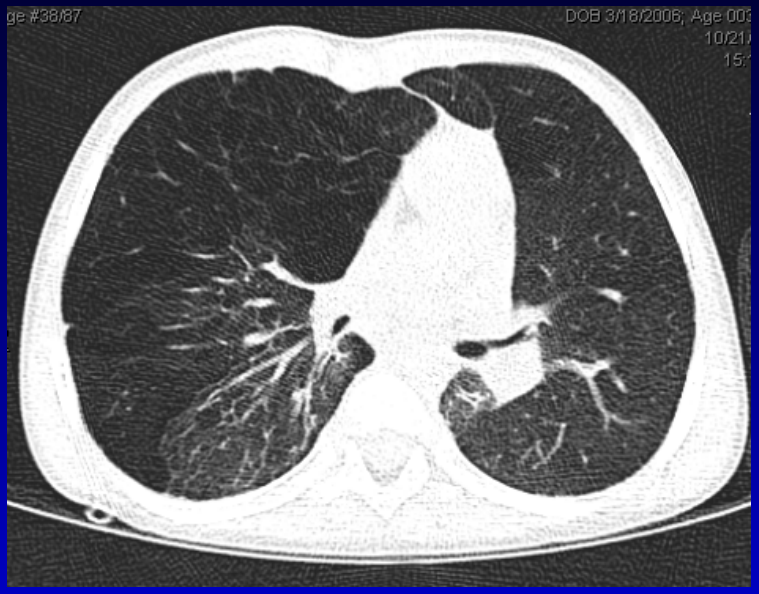
Gerhardt T et al. J Pediatr 110:448; 1987

Subsequent Lung Growth



Expiratory

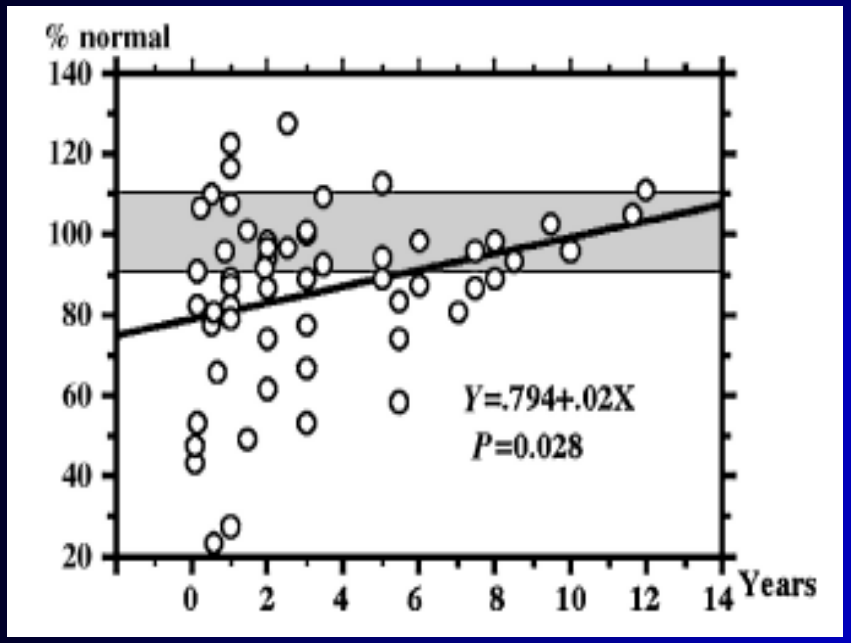
Inspiratory



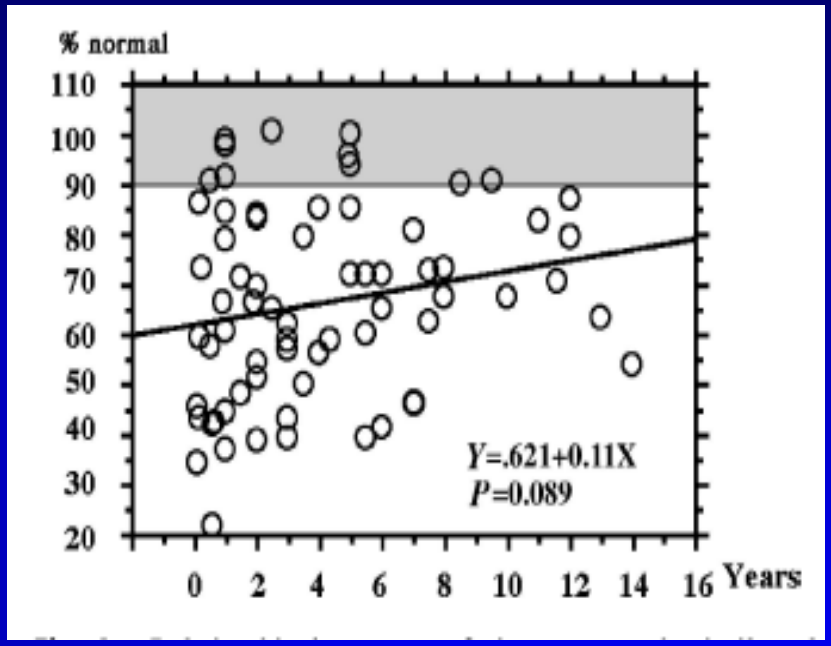
R=962 mL
L=792 mL

TLC= 1596 mL
(Δ=9%)

Long-Term Pulmonary Follow-up



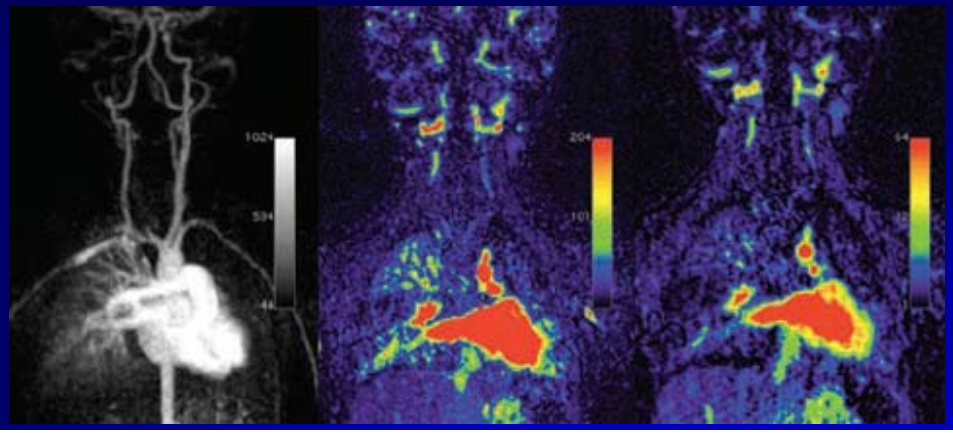
Ipsilateral Ventilation

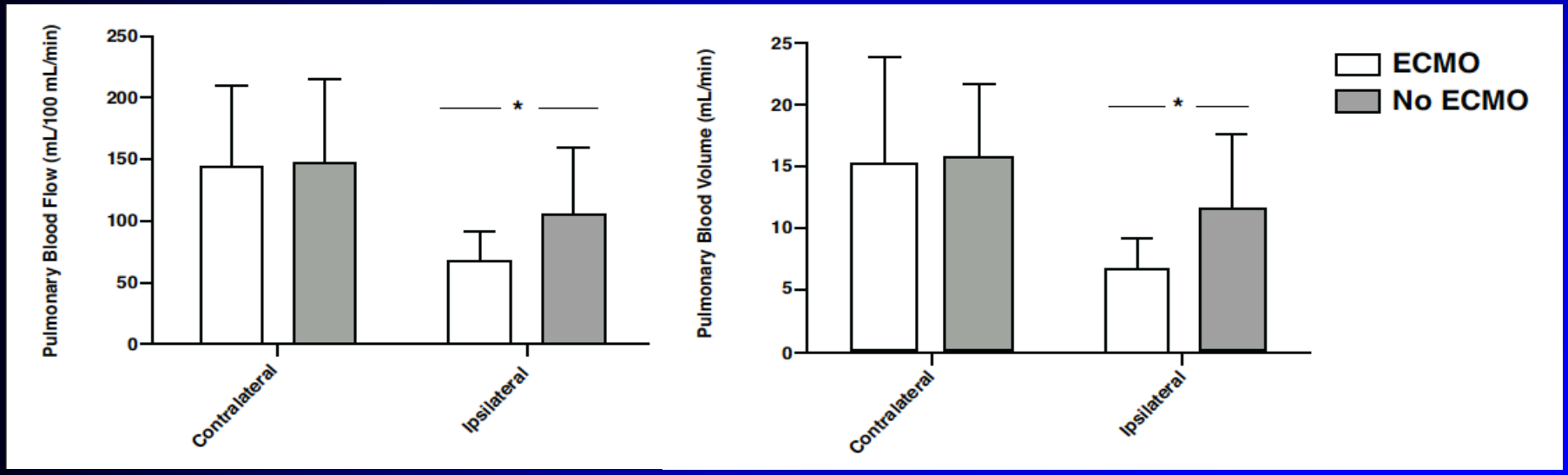


Ipsilateral Perfusion

Kamata S et al. J Pediatr Surg 40:1833; 2005

Pulmonary Blood Flow at 2 Years





Pulmonary Blood Flow

Pulmonary Blood Volume

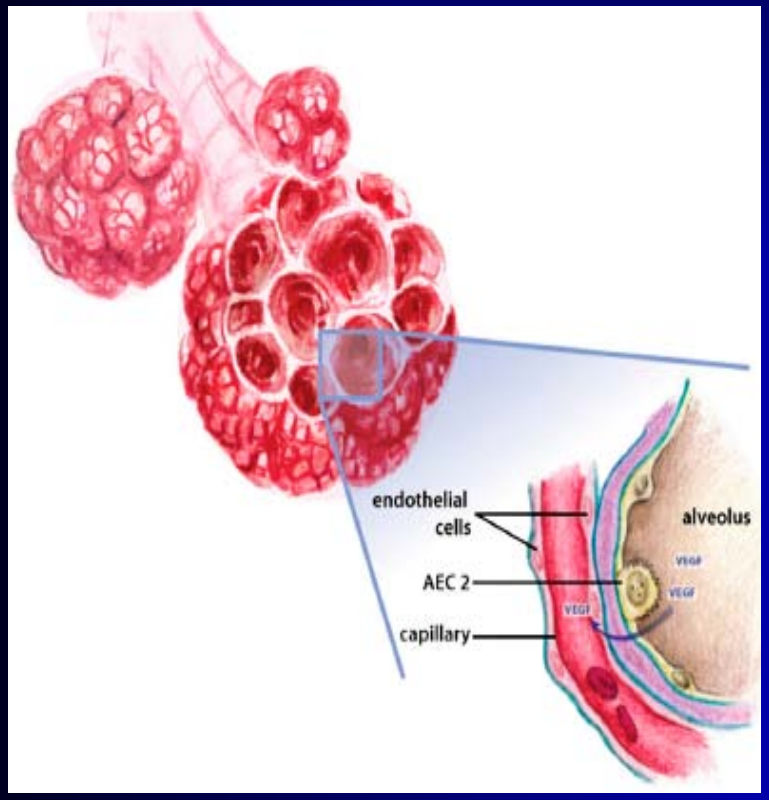
From: Weis M et al. AJR 206:1315; 2016

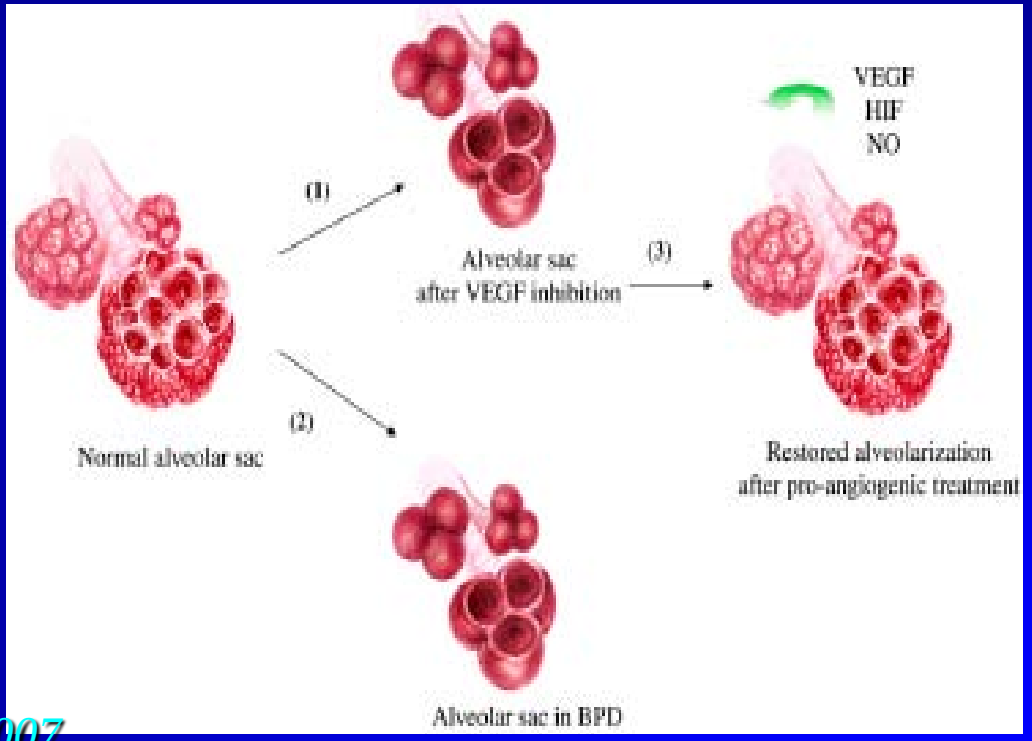
"New BPD": Arrested Alveolar Development

Normal Thin septae Uniform fibrosis

Agrons GA et al. RadioGraphics 25:1047; 2005

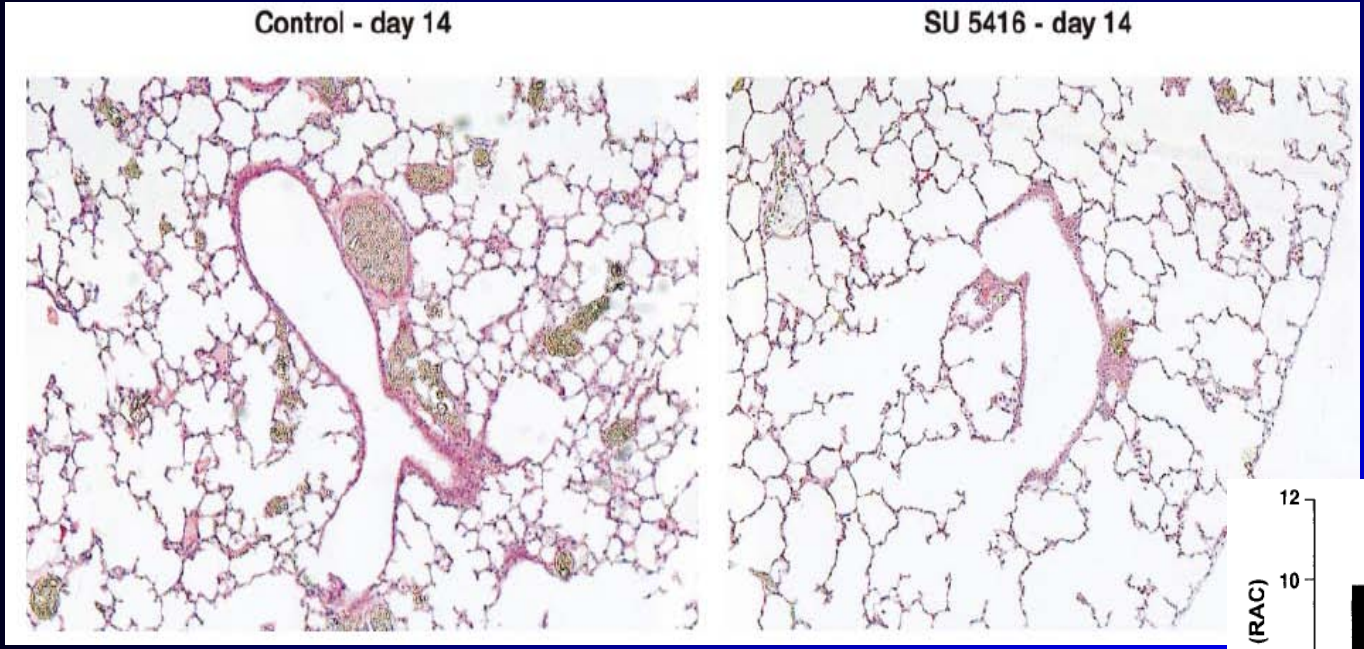
Vascular Growth Factors and Alveolarization

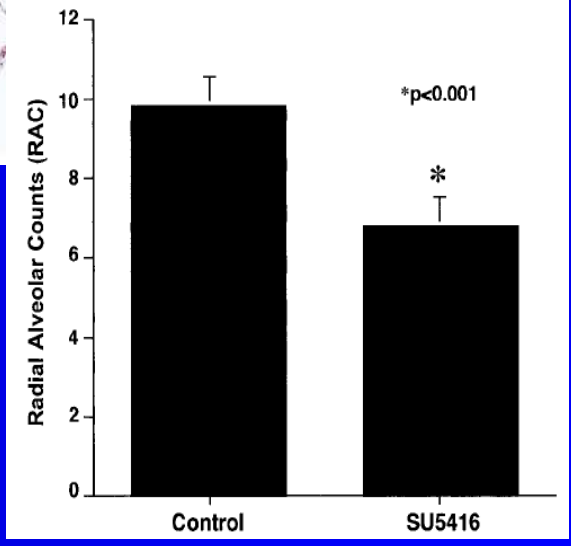




Thebaud B and Abman S.
Am J Respir Crit Care Med 175:978; 2007

Alveolar Development and Angiogenesis

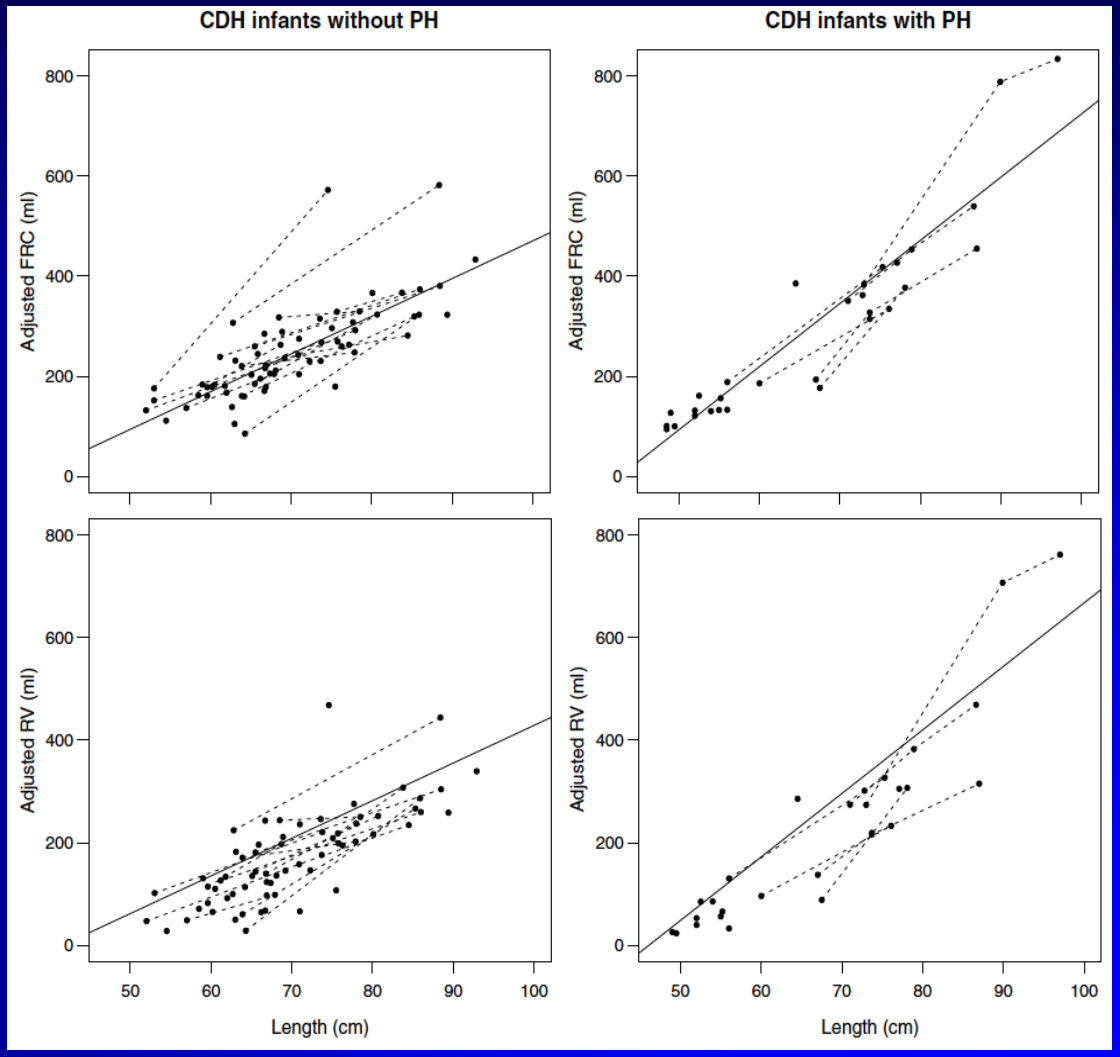




Jakkula M et al.
Am J Physiol Lung Cell Physiol 279:L600; 2000

Change in FRC and RV Over Time

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



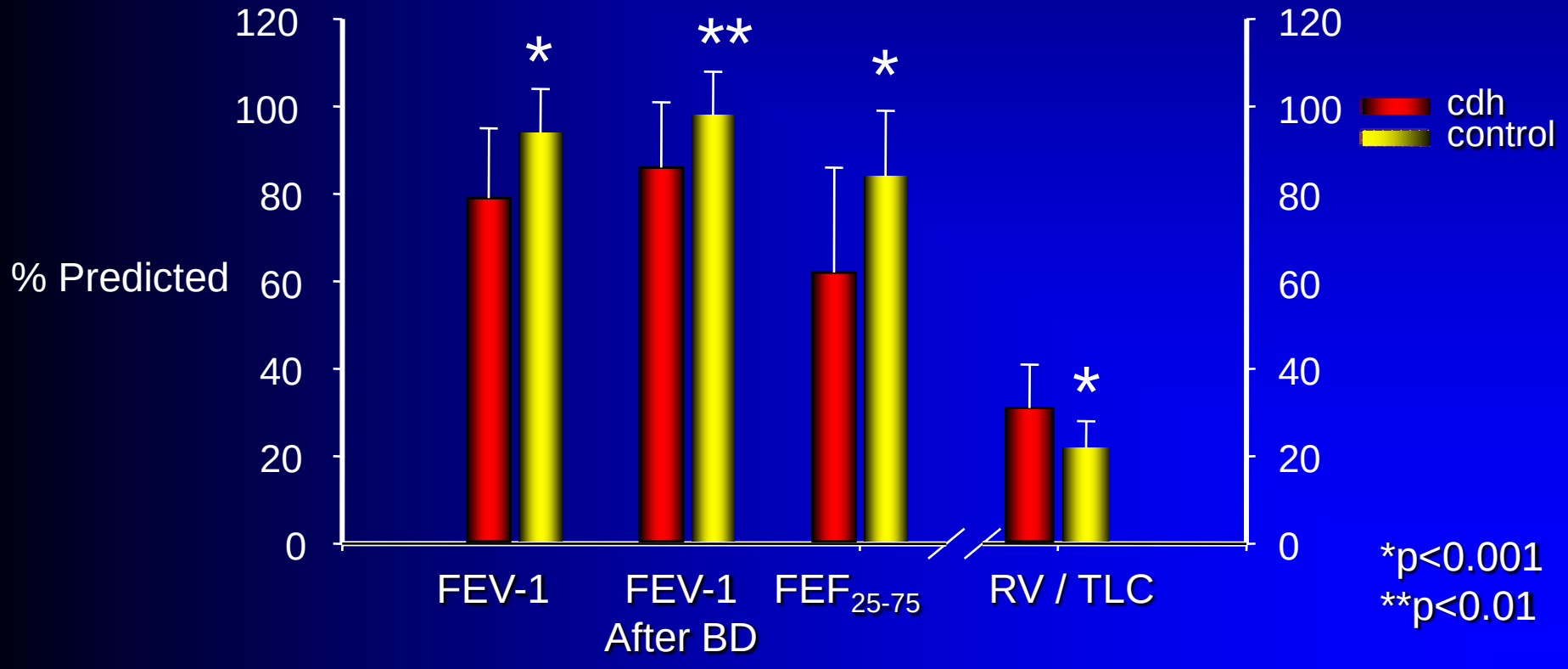
Healy F et al.
Pediatr Pulmonol 50:672; 2015

PAH and Lung Function

- Presence of PAH resulted in
  - Normal TLC but
  - Elevated RV and FRC
  - Elevated RV/TLC and FRC/TLC
  - Lower forced expiratory flows
  - Lower sGrs
- Persistence of PAH correlated with greater changes

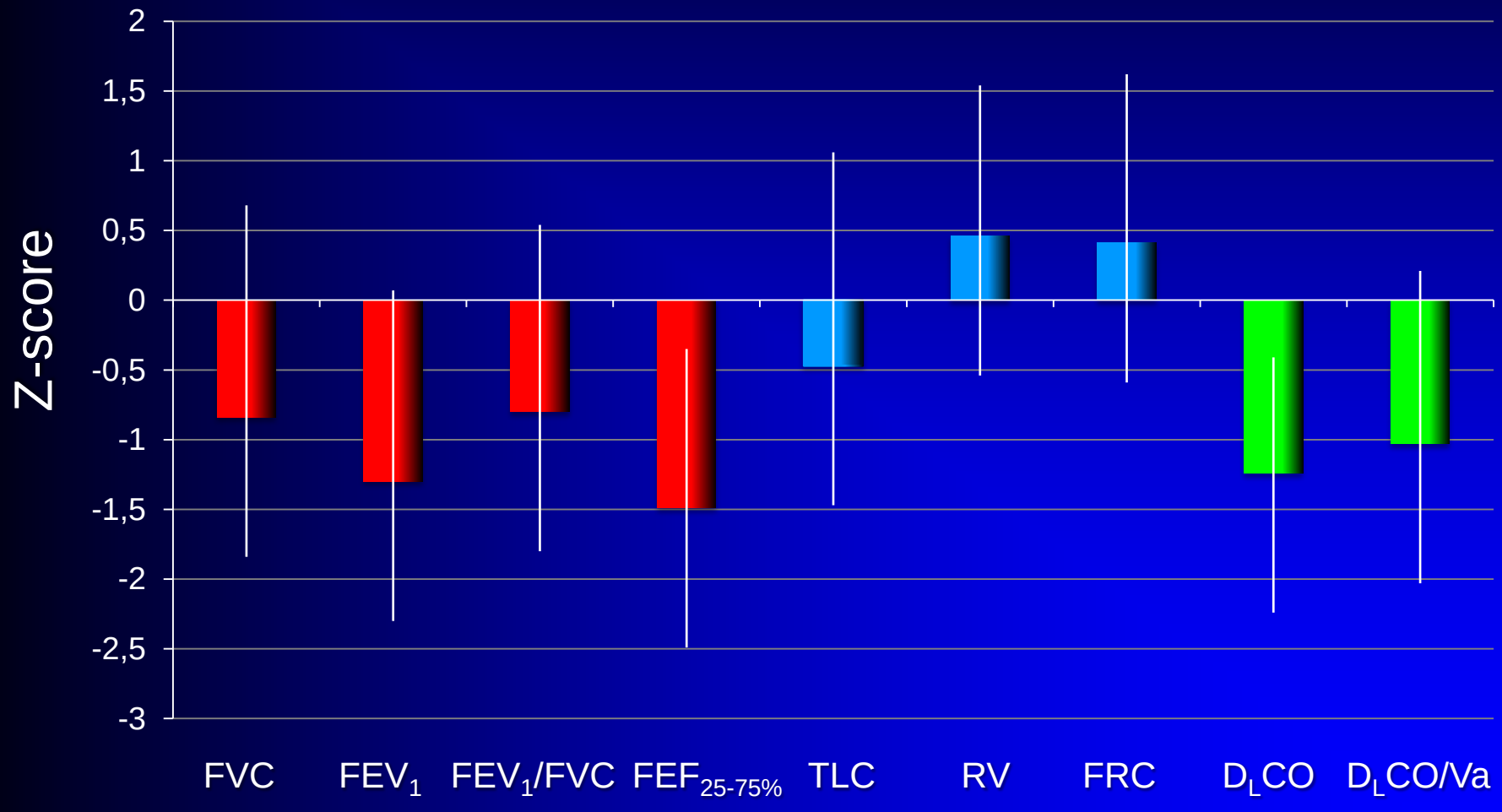
Long-Term Follow-up

- 26 CDH (10.2 - 16.9 yrs, $\bar{X}$ = 13.2 yrs) vs. age- and gender-matched controls



Trachsel D et al. Pediatr Pulmonol 39:433; 2005

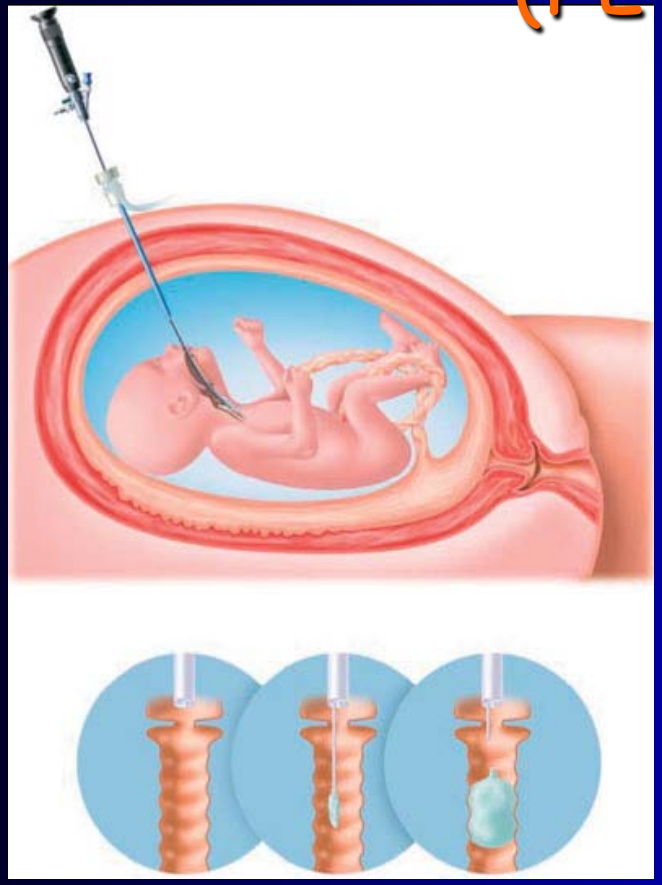
CDH Adult Survivors

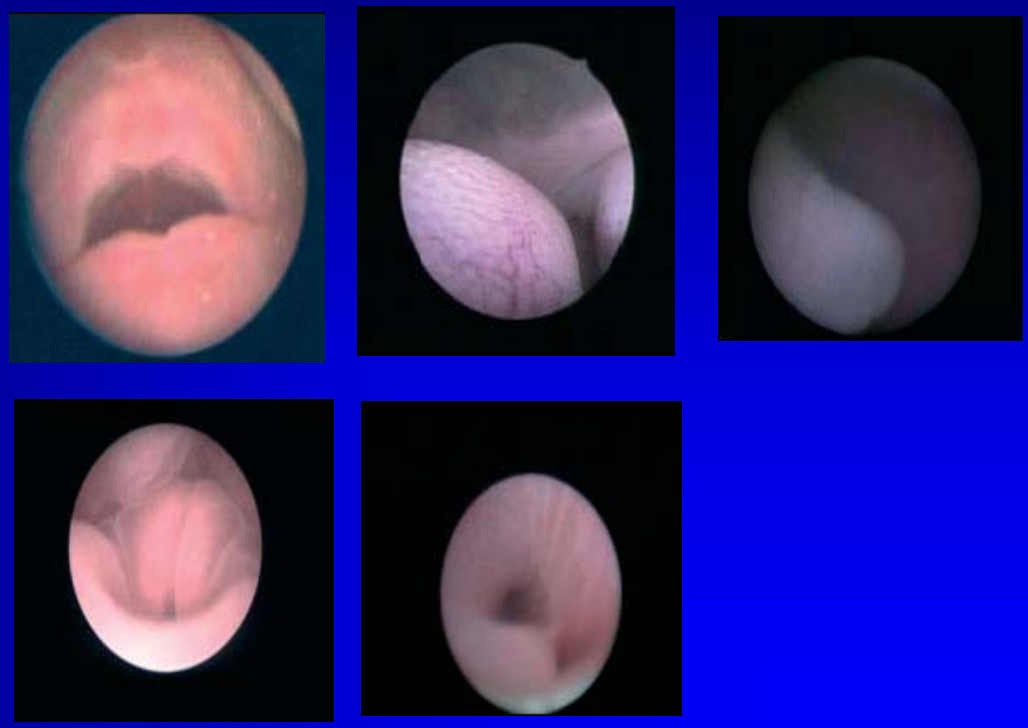


Peetsold MG et al. Pediatr Pulmonol 42:325; 2007

How Will New Therapies Change Outcomes?

Fetal Endoluminal Tracheal Occlusion (FETO) for CDH

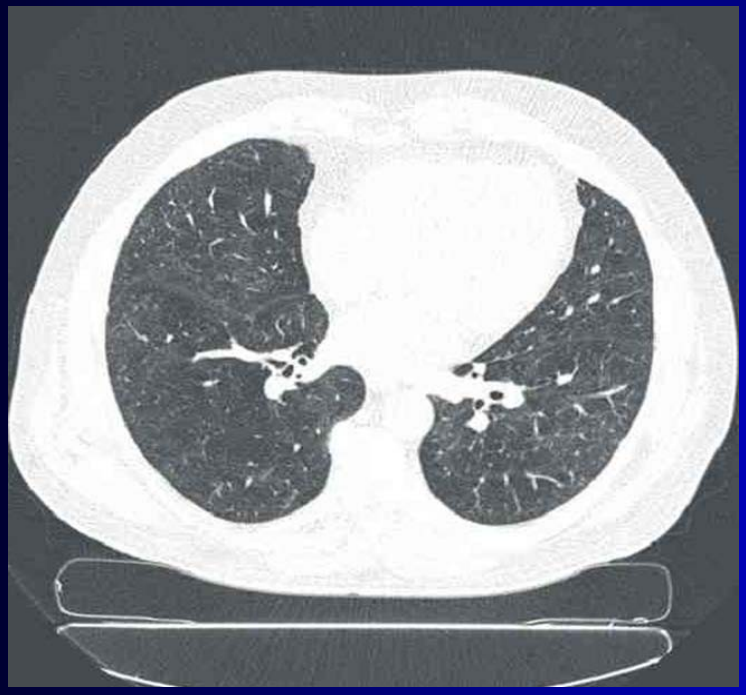




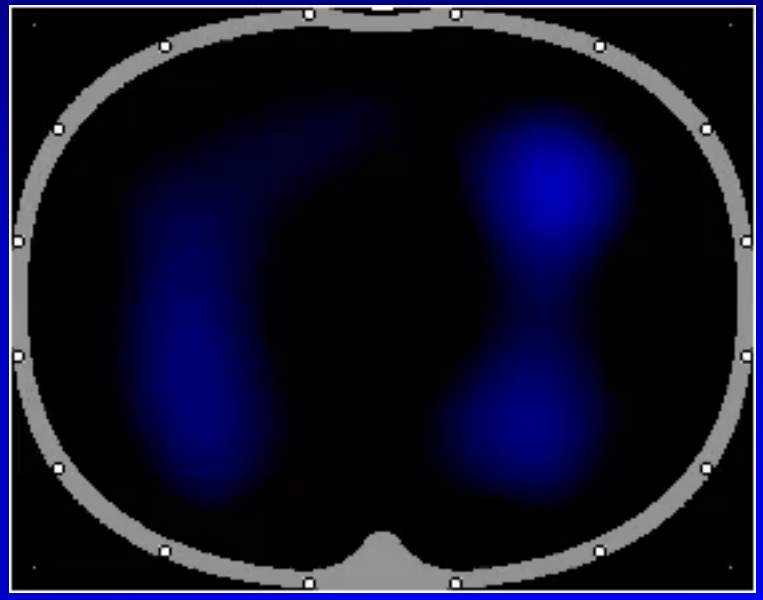
Deprest J et al. Ultrasound Obstet Gynecol 24:121; 2004

Next Steps: EIT

1. Healthy lung

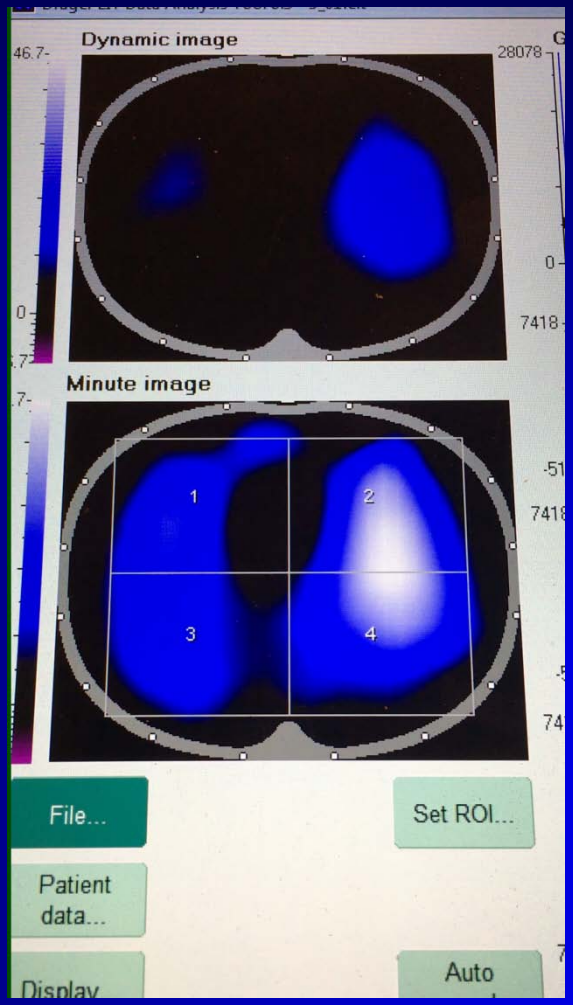


Lung imaging: Air content

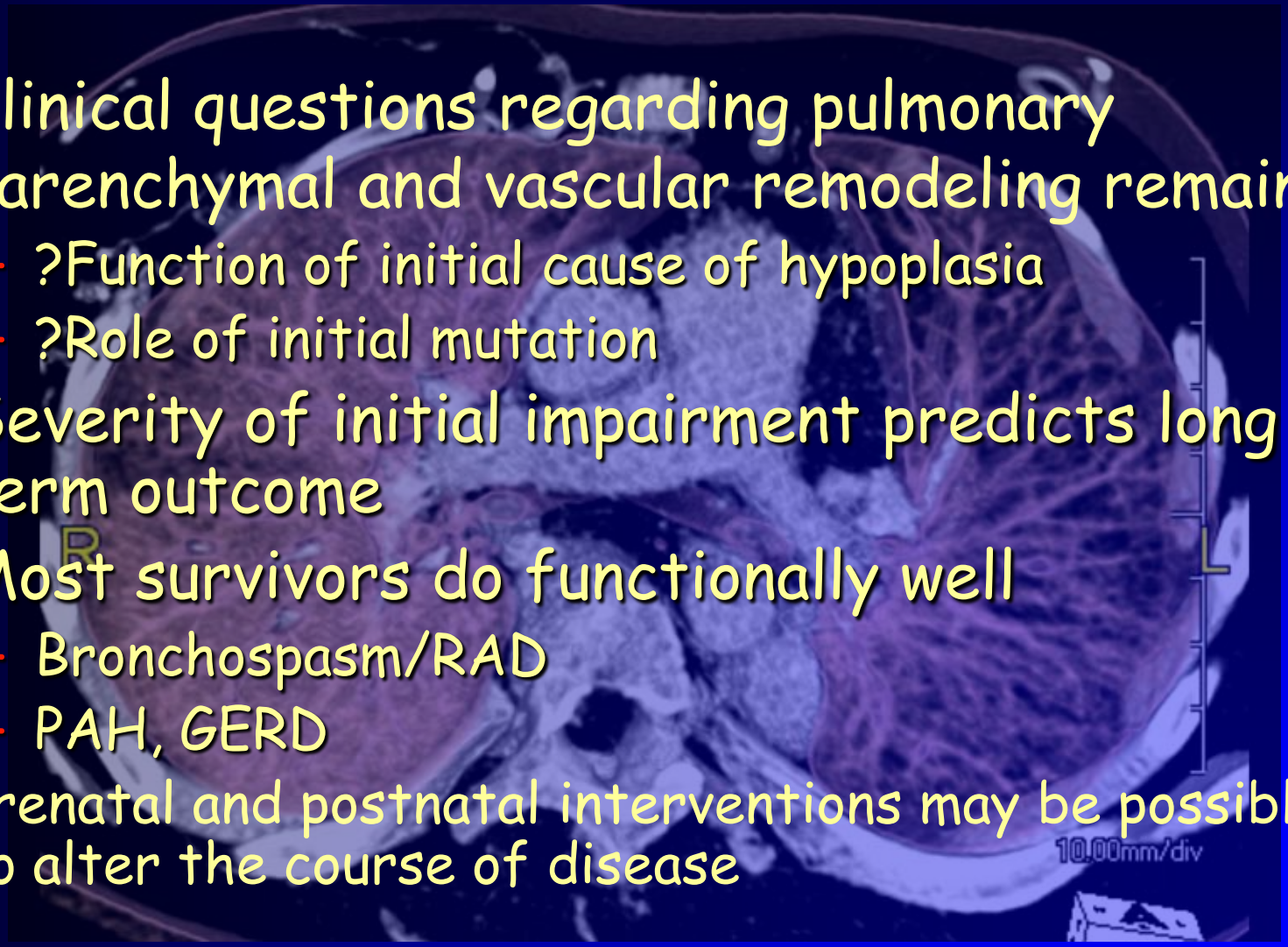


Lung function imaging: Change of air content

Left CDH, Supine



Summary



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

Effect of PAH on Lung Function

	Adjusted mean in no PH group (SE)[1]	Difference between PH and no PH groups (SE)	*P* value
Lung volumes			
TLC z-score	−0.506 (0.327)	1.070 (0.698)	0.1310
FRC z-score	1.703 (0.465)	3.672 (1.052)	0.0009
RV z-score	−0.264 (0.414)	3.709 (1.050)	0.0008
FRC/TLC z-score	1.079 (0.252)	1.534 (0.564)	0.0086
RV/TLC z-score	−1.790 (0.363)	1.843 (0.731)	0.0145
Forced flows			
ln(FVC) z-score	−0.014 (0.222)	−0.597 (0.493)	0.2306
ln(FEV0.5) z-score	−0.005 (0.225)	−1.345 (0.506)	0.0101
ln(FEV0.5/FVC) z-score	0.052 (0.238)	−1.369 (0.601)	0.0265
ln(FEF25–75) z-score	0.307 (0.277)	−2.046 (0.619)	0.0016
Tidal mechanics			
ln(sCrs) (ln(1/cm H_2O))	−2.876 (0.074)	−0.360 (0.203)	0.0827
Crs/kg (ml/(cm H_2O.kg))	1.369 (0.056)	−0.050 (0.172)	0.7730
ln(sGrs) (ln[1/(cmH_2O.sec)])	−1.791 (0.057)	−0.513 (0.170)	0.0042

SE, standard error of mean.
[1]Adjusted for gender, ECMO use in the neonatal period and age at time of IPFT.

Healy F et al. Pediatr Pulmonol 50:672; 2015