



Update on Bronchopulmonary Dysplasia: Severe BPD



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**PULMONARY DISEASE FOLLOWING RESPIRATOR THERAPY OF
HYALINE-MEMBRANE DISEASE***

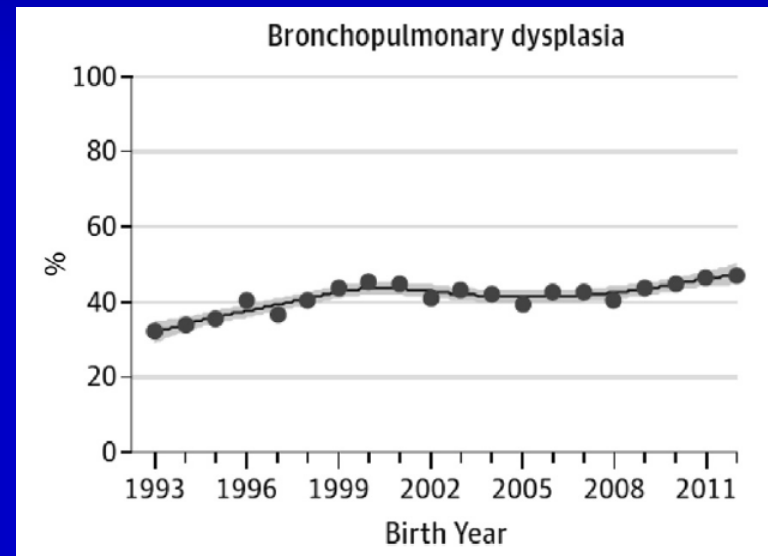
Bronchopulmonary Dysplasia

WILLIAM H. NORTHWAY, JR., M.D.,† ROBERT C. ROSAN, M.D.,‡ AND DAVID Y. PORTER, M.D.§

Incidence

- 2 - 3/1000 live births
- ~1.5% of all newborn births
- 20% of preterms < 30 weeks and <1500 g

- 6%	1251 - 1500 g
- 14%	1001 - 1250 g
- 33%	751 - 1000 g
- 46%	500 - 750 g



Fanaroff AA et al. Am J Obstet Gynecol
196:147.e1; 2007

From: Stoll BJ et al. JAMA 314:1044; 2015

"Severe" BPD—How to Define?

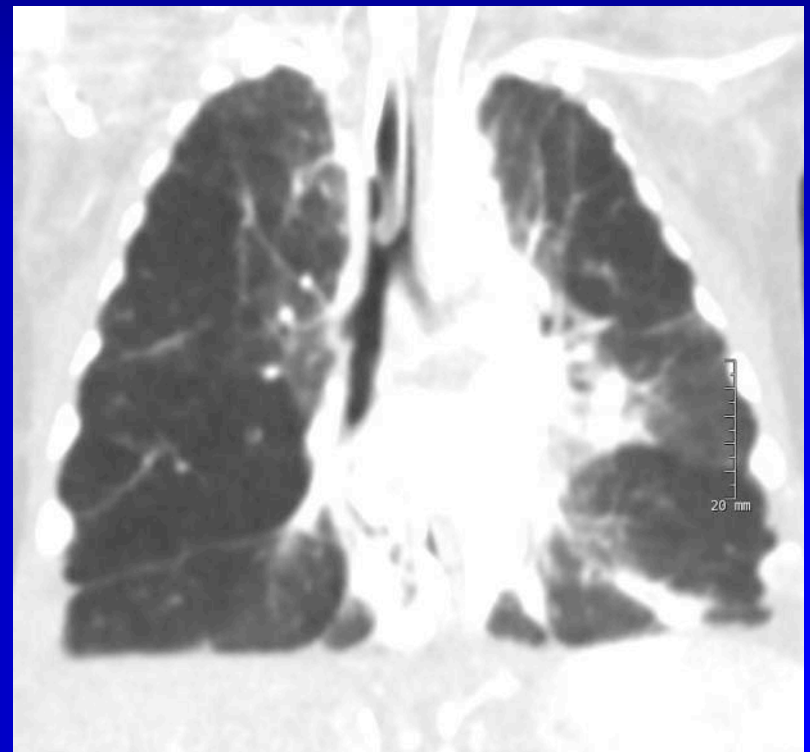
Treatment with Supplemental O₂
for at least 28 days PLUS:

	At 36 wk PMA or at D/C	Relative Incidence	Postdischarge Mortality
Mild	RA	30.3%	1.5%
Moderate	< 30% O ₂	30.2%	2.0%
Severe (Type 1)	≥ 30% O ₂ or nCPAP/HFNC	16.4%	4.8%
Severe (Type 2)	Mechanical ventilation		

From: Abman SH et al. J Pediatr 181:12; 2017

Prevalence of sBPD

- "Snapshot" 12/17/13
- NIH criteria at 36 wks PMA
 - $FiO_2 \geq 0.30$ and/or
 - PPV
- 8 NICUs
 - 710 neonates
 - 351 (49%) <32 wks
 - 128 (36.5%) sBPD
 - 62% PPV at 28 d PMA
 - 41% PPV by 36 wk PMA



"Classic" vs. "New" BPD

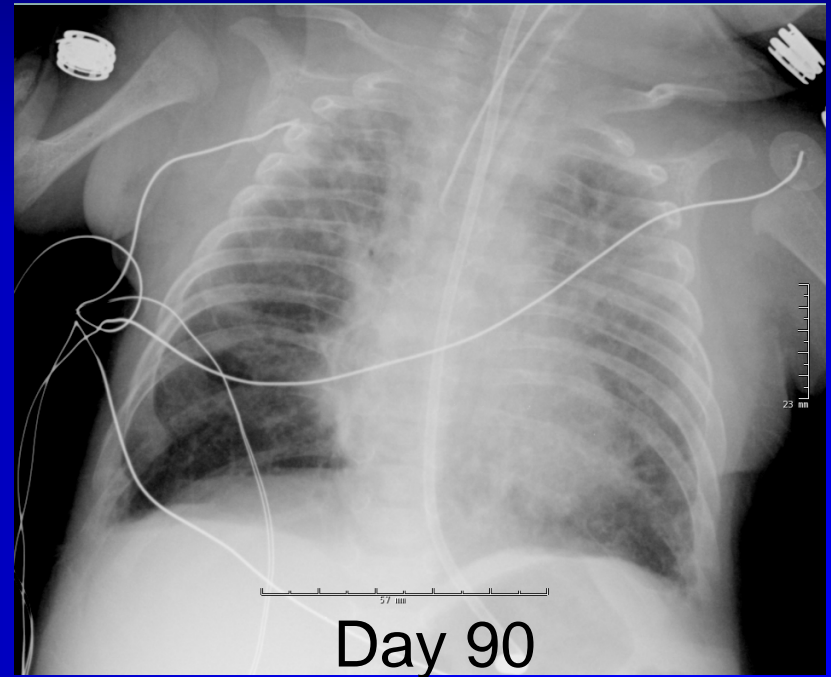
Classic

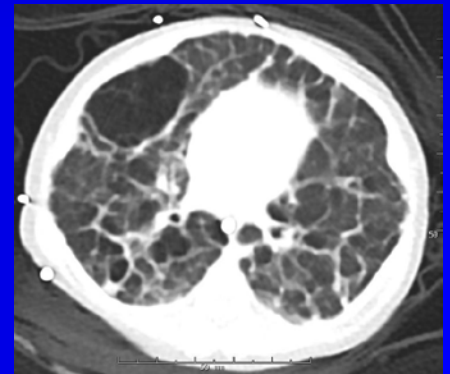
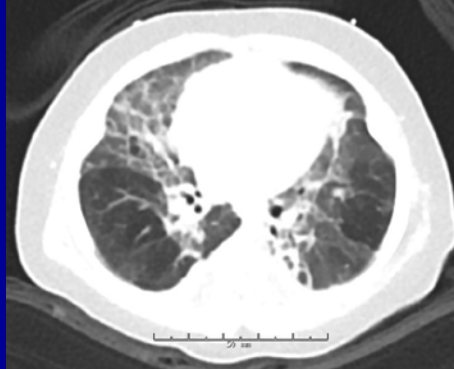
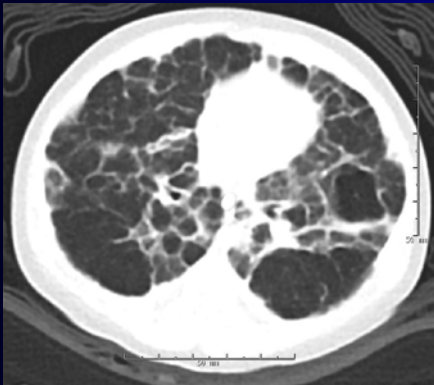
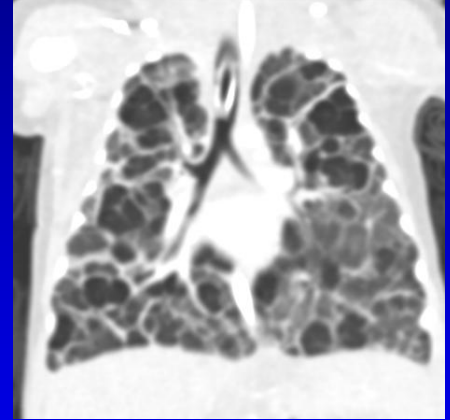
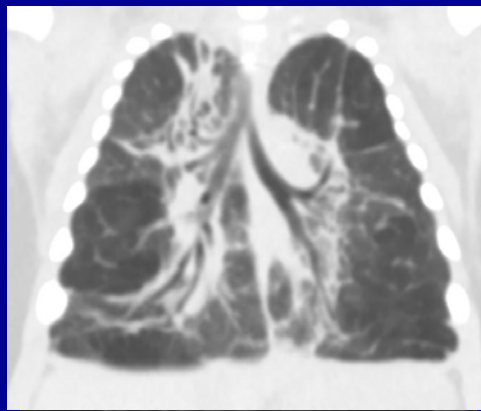
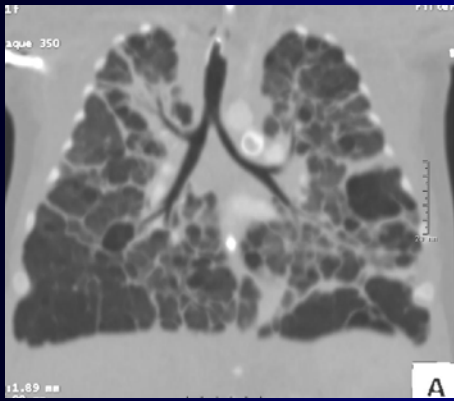
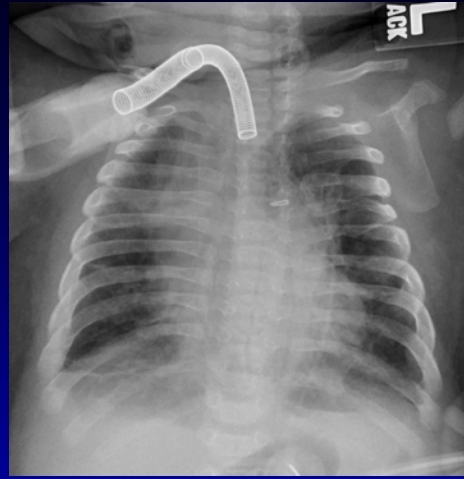
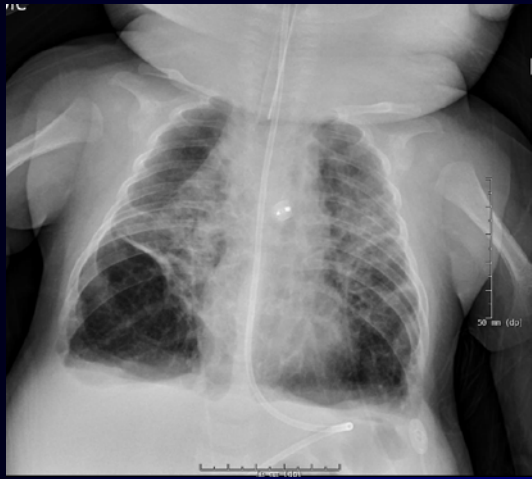
- Airways
 - Inflammation
 - Fibrosis
 - Smooth muscle hypertrophy
- Alternating zones of overdistension and atelectasis

New

- Arrest of acinar development
 - (airspace & arteries)
- ↓ airway epithelial disease
- ↓ severe vascular disease
- ↓ interstitial fibrosis

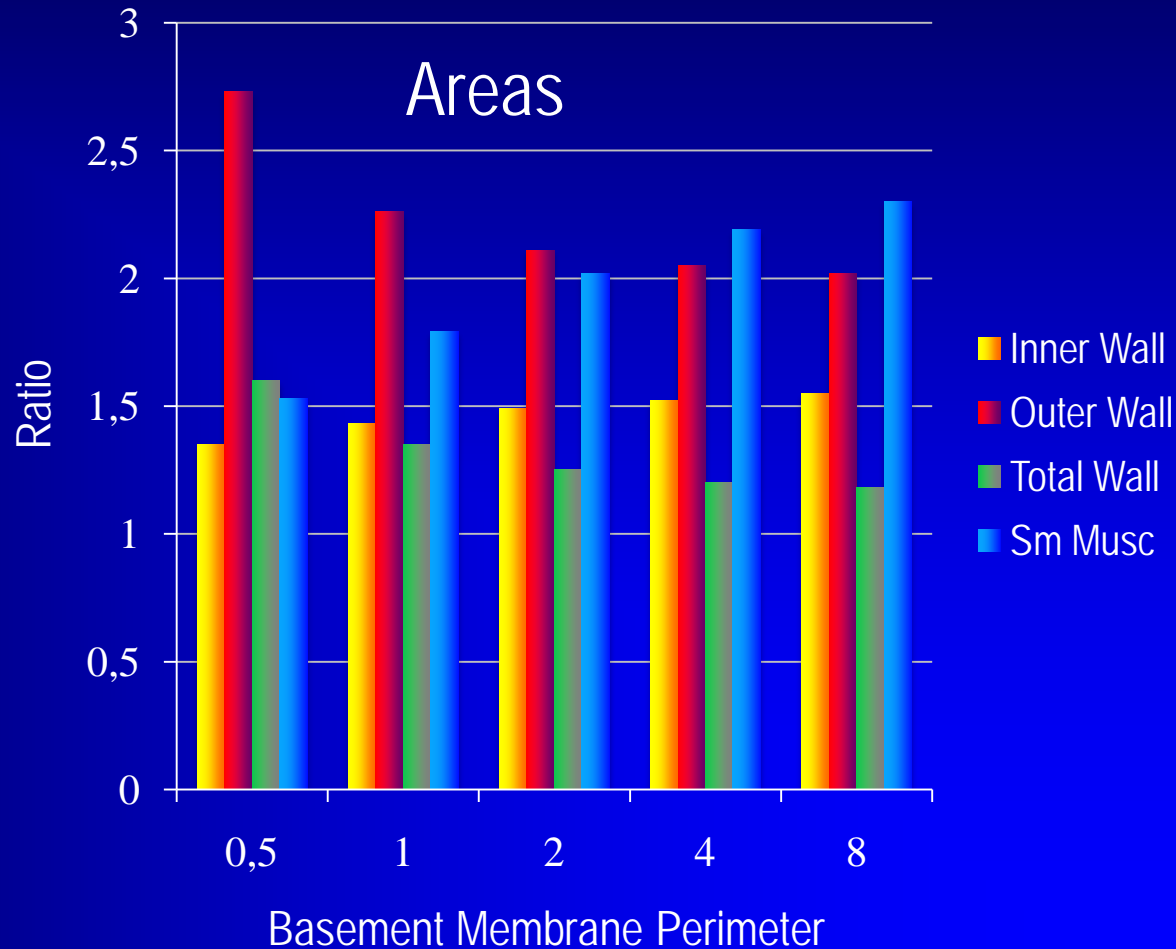
Old vs. New Severe BPD





Airway Wall Structure in Severe BPD

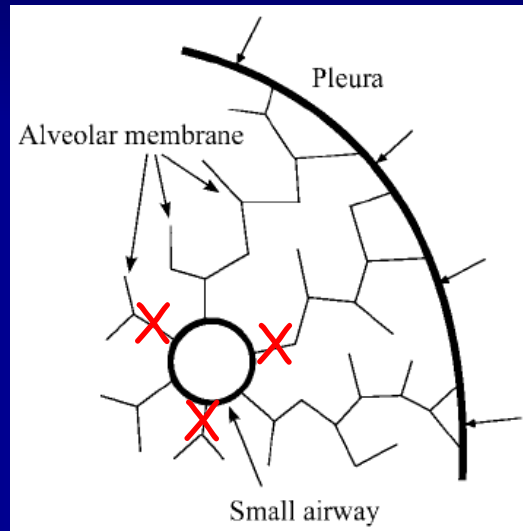
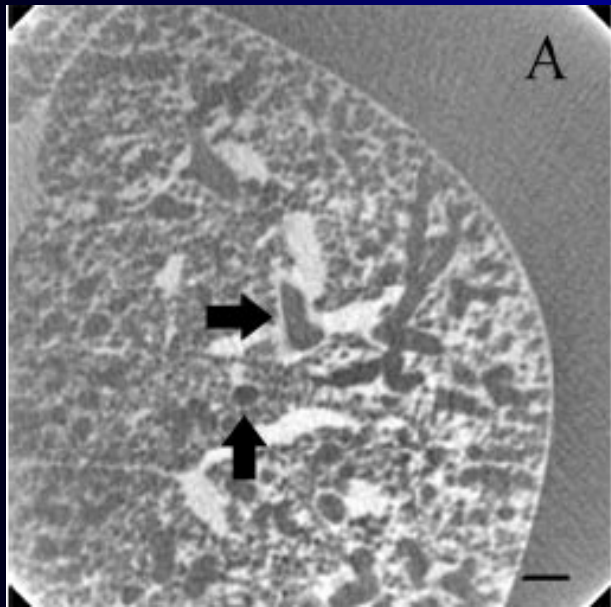
- BPD vs SIDS
 - N = 5 / 11
 - 75 / 176 airways
- GA 23.8-34.7 wks
- PCA 30.8wk-22mo



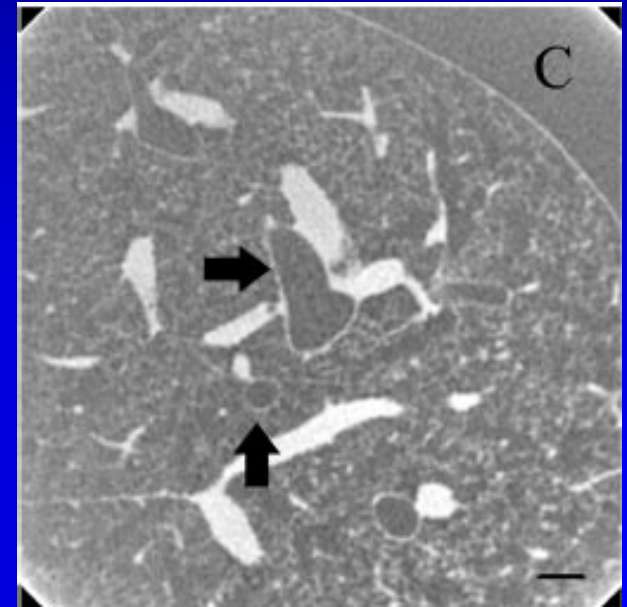
From: Tiddens HAWM et al.
Pediatr Pulmonol 43:1206; 2008

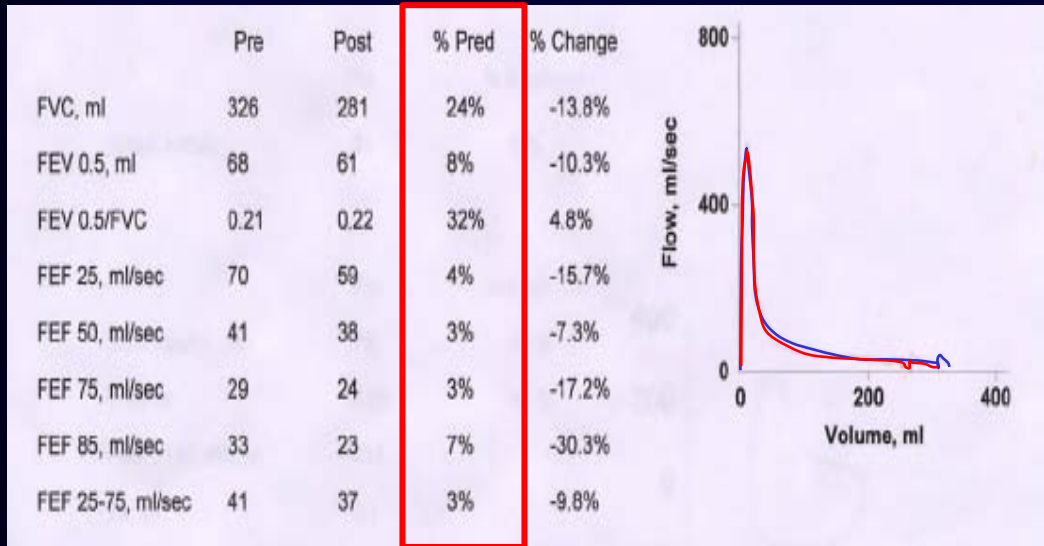
Small Airway Size and Alveolar Wall Attachments

FRC

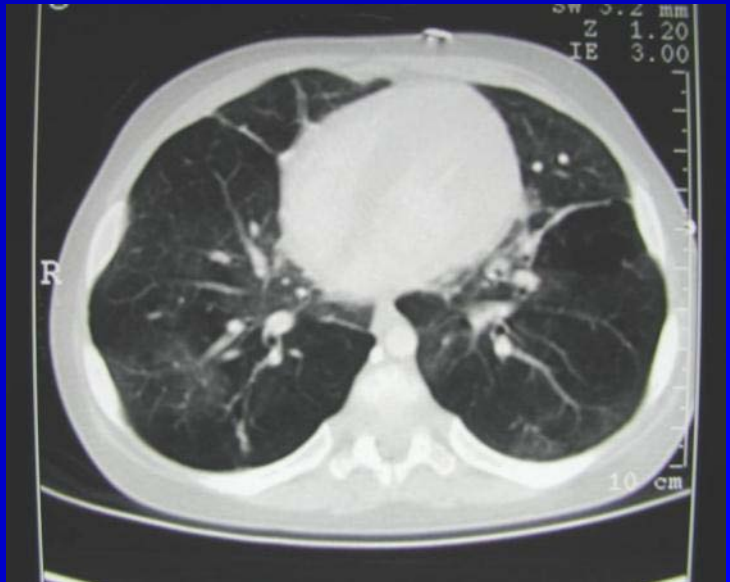
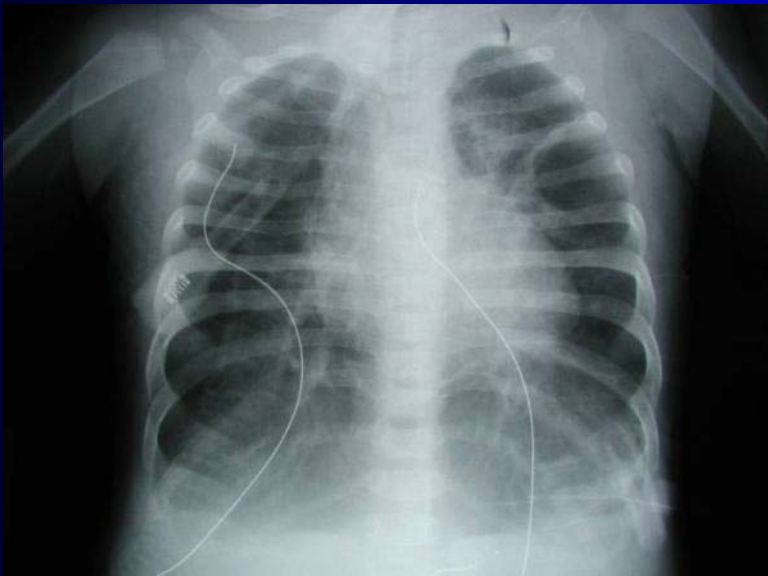


TLC

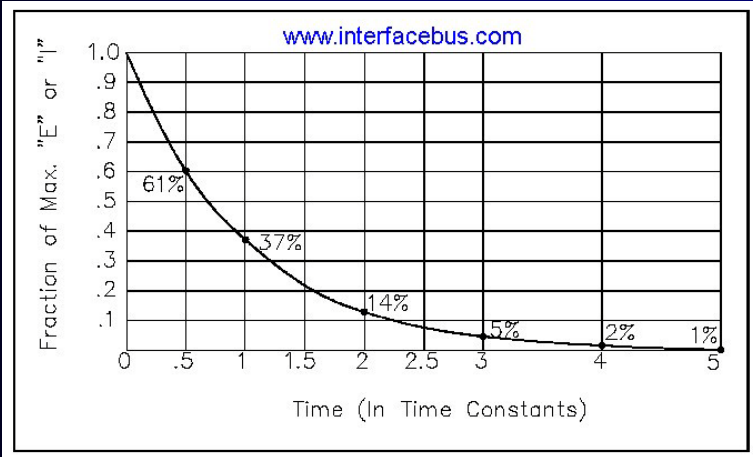




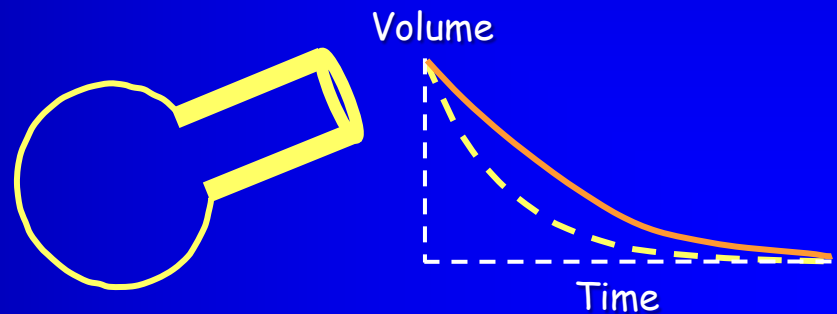
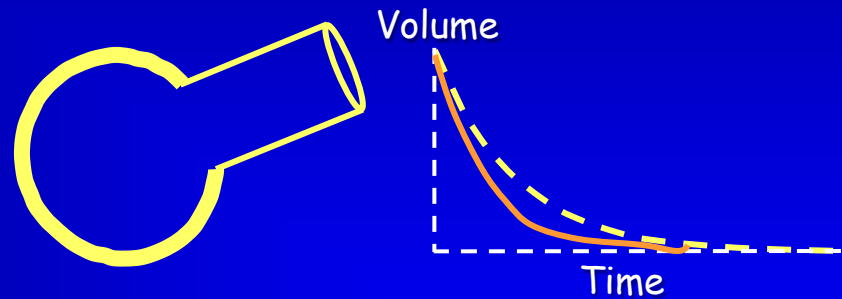
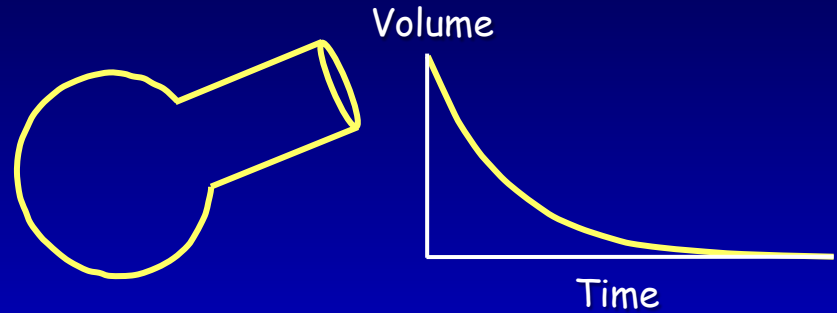
	Pre	Post	% Pred.	% Change
TLC, ml	1991	1913	124%	-3.9%
FVC, ml	258	261	20%	1.2%
ERV, ml	80	128	38%	60%
FRCpleth, ml	1813	1780	338%	-1.8%
RV, ml	1733	1652	560%	-4.7%
RV/TLC	0.87	0.86	414%	-1.1%
FRC/TLC	0.91	0.93		2.2%



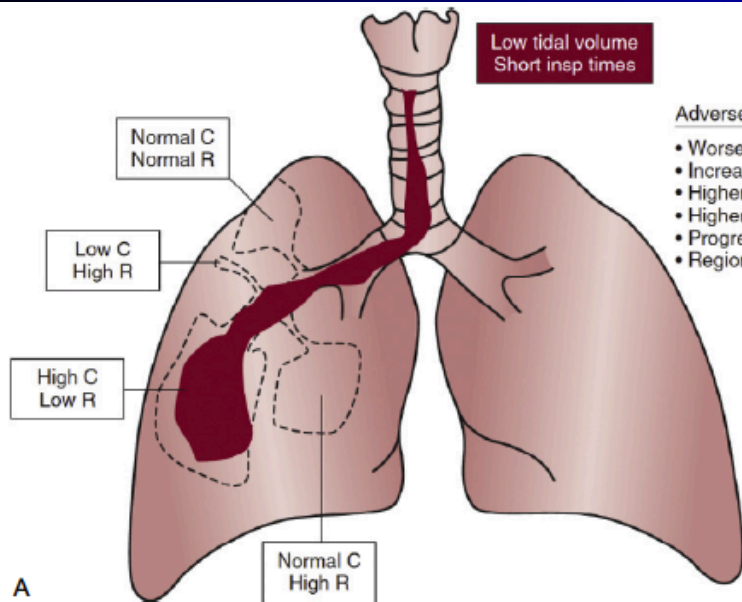
Time Constants



$$T = R \cdot C$$

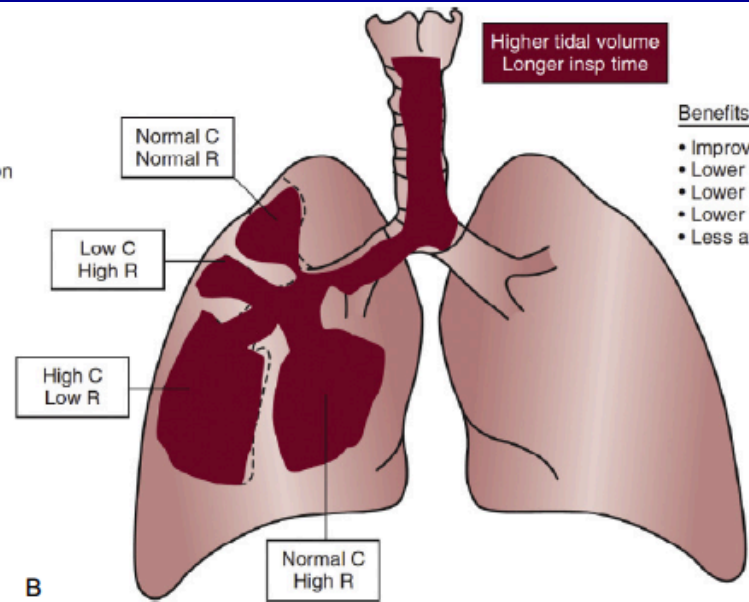


2 (or more) Compartment Model



Adverse effects:

- Worse distribution of gas
- Increased dead space ventilation
- Higher PCO_2
- Higher FiO_2
- Progressive atelectasis
- Regional overdistension



Benefits:

- Improved gas distribution
- Lower V_d/V_t
- Lower PCO_2
- Lower FiO_2
- Less atelectasis

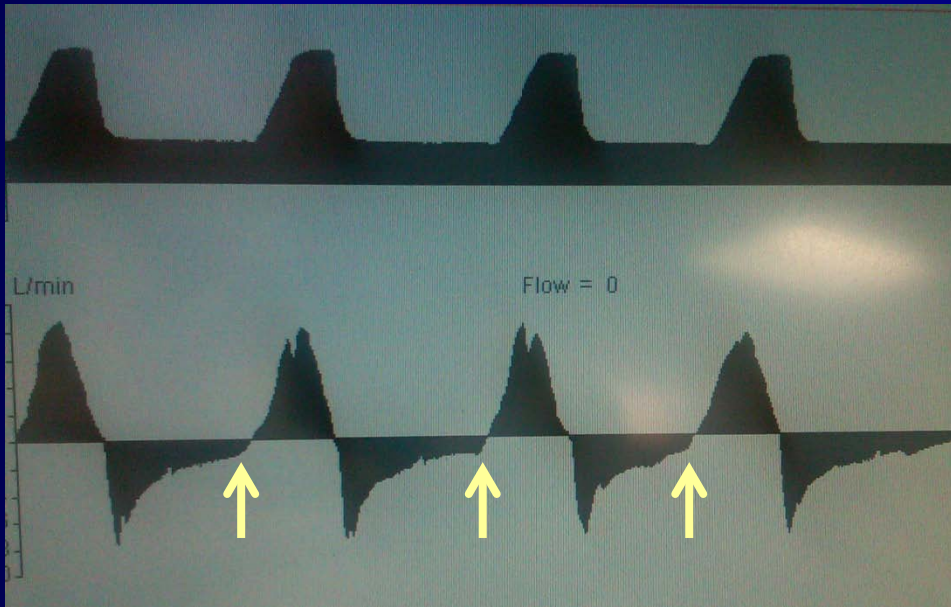
Principles of Ventilator Management in Severe BPD

Ventilator Strategies	Targets
Tracheostomy if long term ventilation required	SpO ₂ 92-95%
Larger tidal volumes (10-12 mL/kg)	Permissive hypercapnia
Slower respiratory rates (10-20)	Allow emptying
Longer inspiratory times (≥ 0.6 sec)	Allow filling
PEEP higher, situationally dependent	

11 mo, 6.9 kg former 24 wks Gestation



- Prolonged steroids, aminophylline
- ASD s/p closure
- PAH
- VC-SIMV
 - Vt 50; Ti 0.5; PEEP 7; PS 20/PEEP; IMV 30
- 7.24/82/34

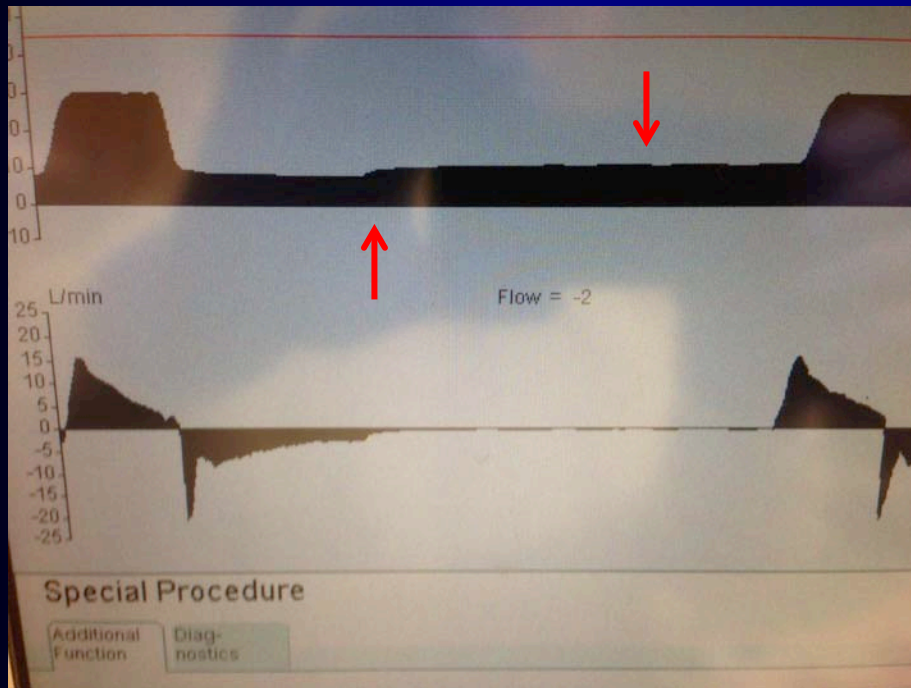


P

\dot{V}

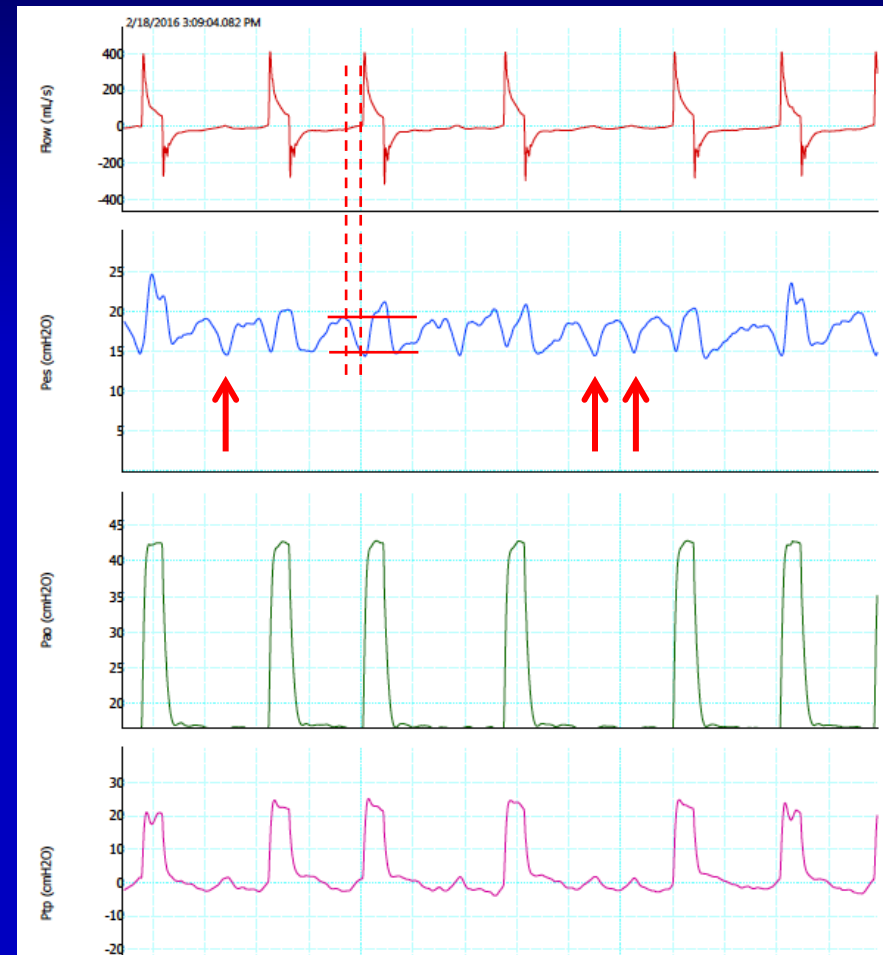
Identification of PEEPi

Paralyzed or Relaxed

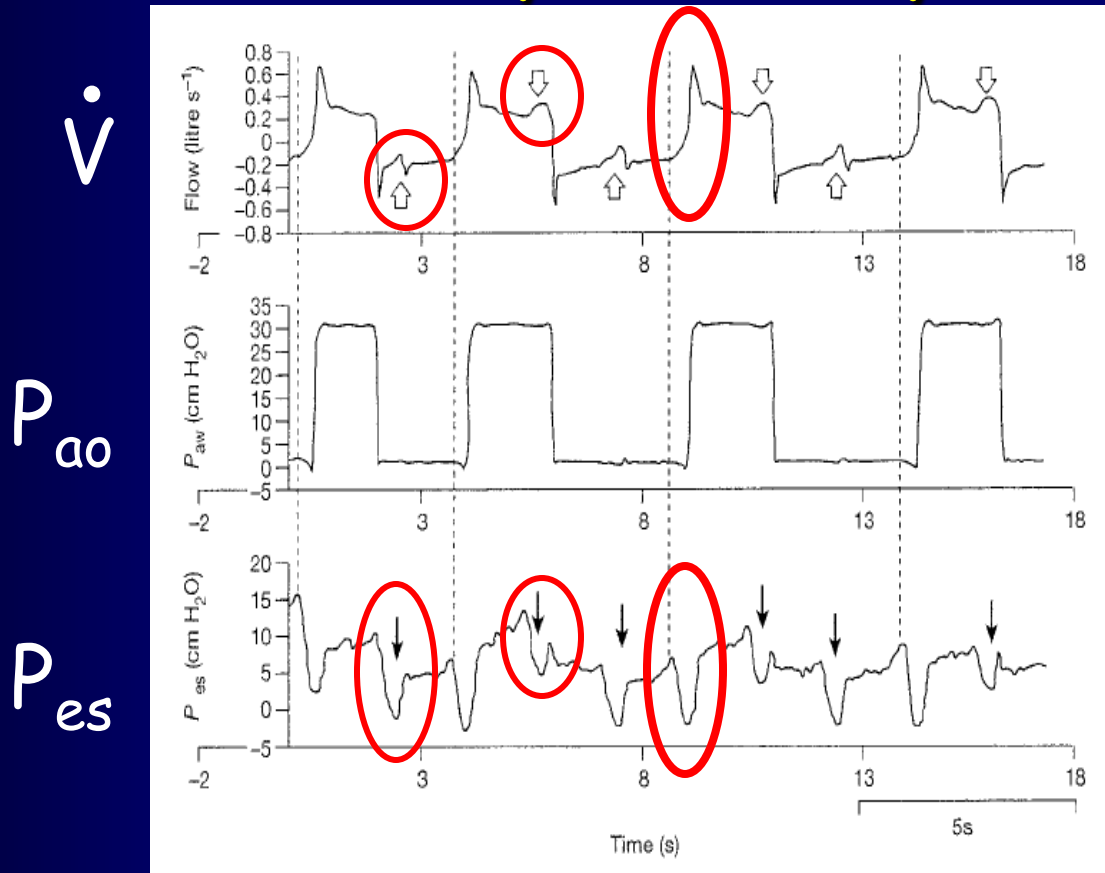


Expiratory Hold Maneuver

Spontaneous Breathing

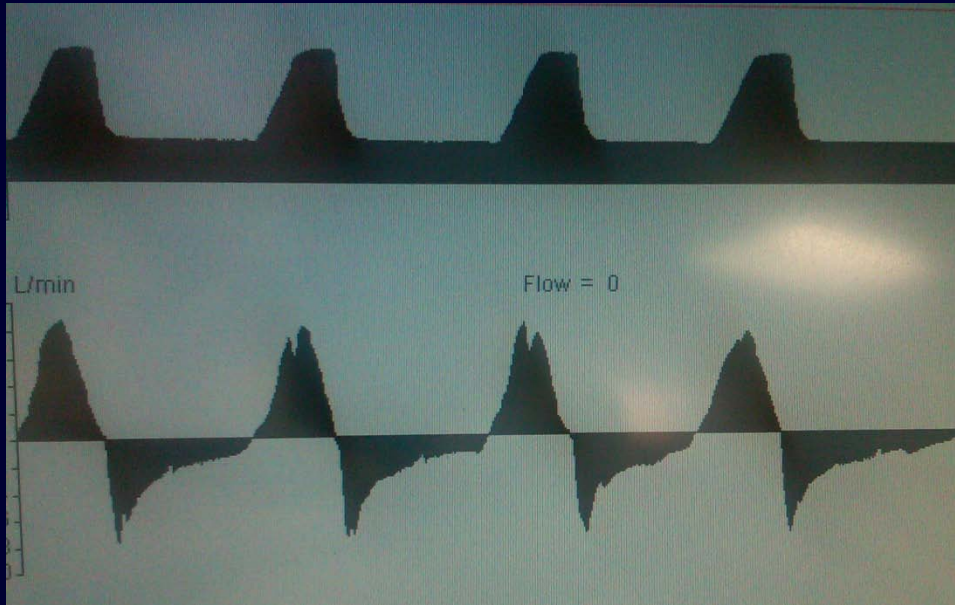


PEEPi and Patient-Ventilator Asynchrony

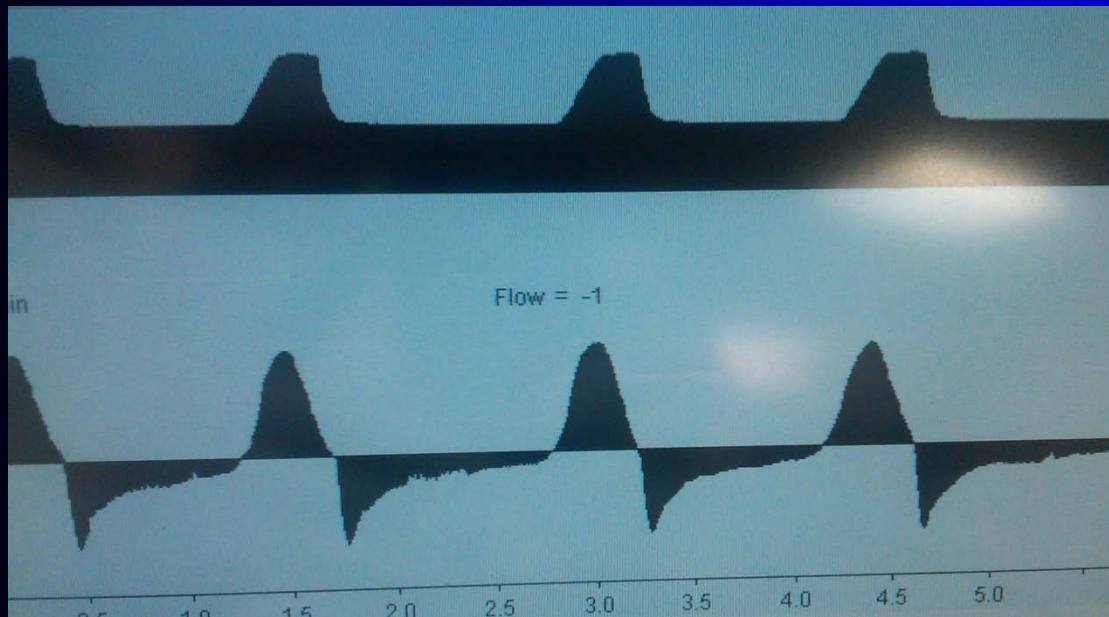




- PEEP increased to 11 cmH₂O
- IMV decreased to 20
- Ti increased to 0.7 sec
- Vt increased to 100mL
- At discharge: 7.42/54/34



PEEP = 7 cmH₂O



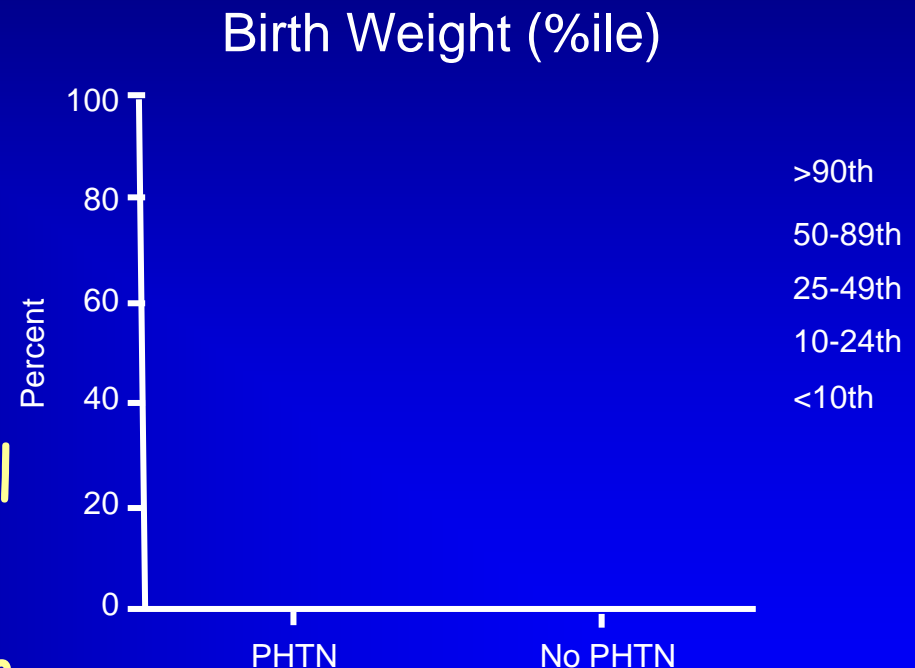
PEEP = 11 cmH₂O

Factors Contributing to Severe BPD

- Undertreated bronchospasm
- Pulmonary hypertension
- Gastroesophageal reflux (aspiration)
- Tracheobronchomalacia/ Small airway obstruction
- Profound pulmonary hypoplasia

Risk Factors for Developing PAH in BPD

- Extremely low GA
- SGA birthweight
- Oligohydramnios
- Prolonged mechanical ventilation
- Prolonged supplemental oxygen
- Antenatal inflammation



Berkelhamer SK et al.

Semin Perinatol 37:124; 2013

Pathophysiology of Vascular Injury

Prenatal Injury

Hypertensive diseases of pregnancy
IUGR
Genetic/Epigenetic factors

Postnatal Injury

Hyperoxia
Mechanical Ventilation
Infection
Acute and Chronic Hypoxemia
Hemodynamics (PDA)



Developing
Lung
Circulation

Abnormal Function

<u>Decreased Growth</u>	<ul style="list-style-type: none">• High vascular tone• Altered vasoreactivity• Impaired metabolic function	<u>Abnormal Structure</u>
<ul style="list-style-type: none">• Angiogenesis• Alveolarization		<ul style="list-style-type: none">• SMC proliferation• Altered extracellular matrix



Decreased Alveolar-Capillary Surface Area for Gas Exchange

Exaggerated Effects of Left-to-Right Shunts

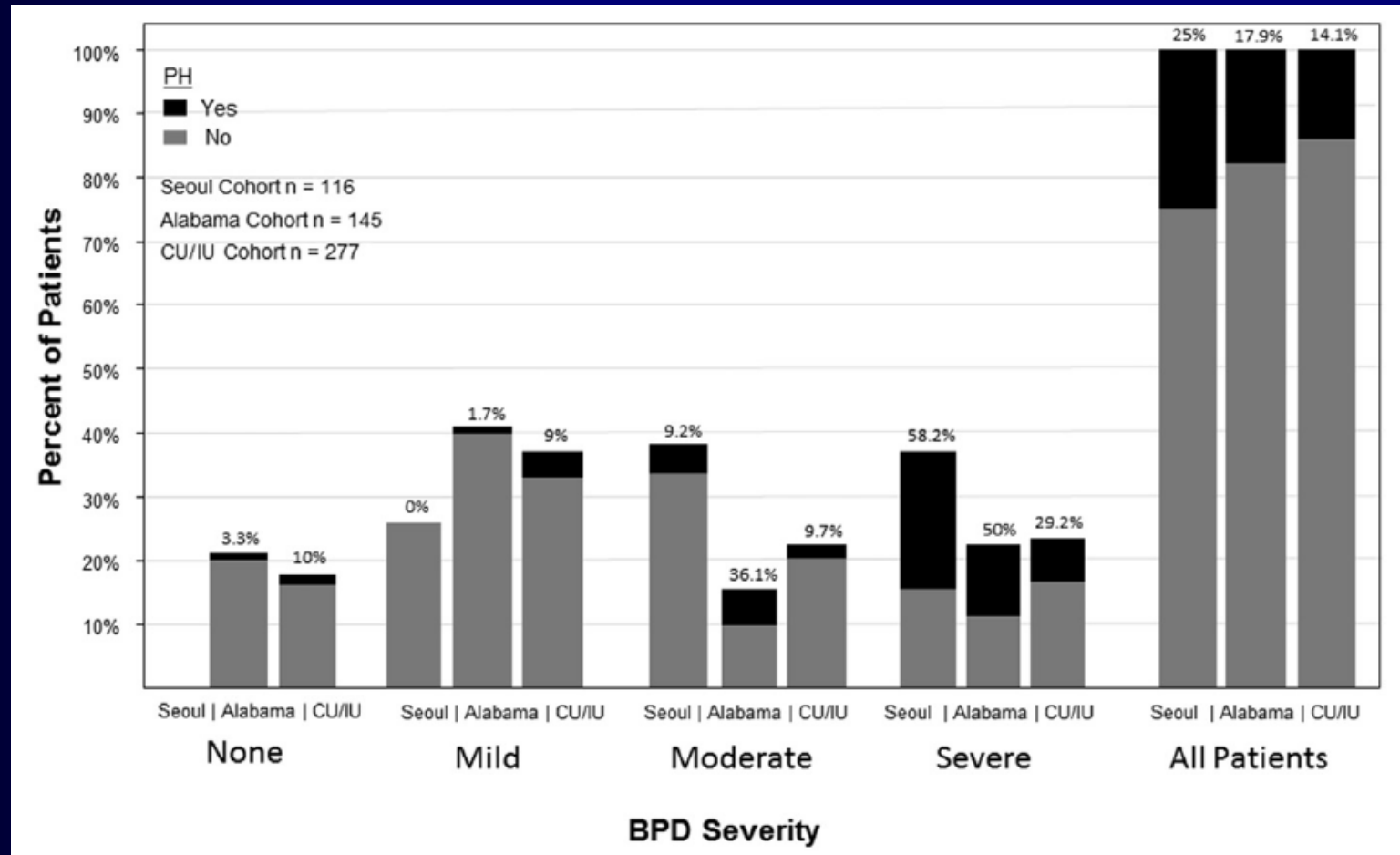
Prolonged Oxygen Therapy

Altered Redistribution of Blood Flow in Response to Infection

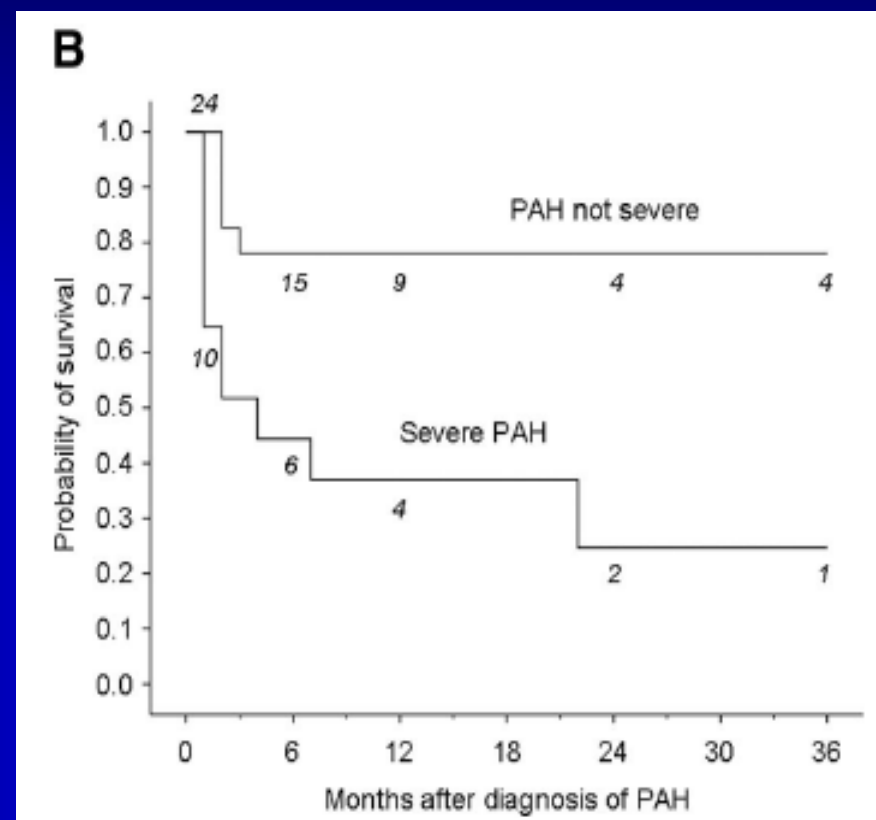
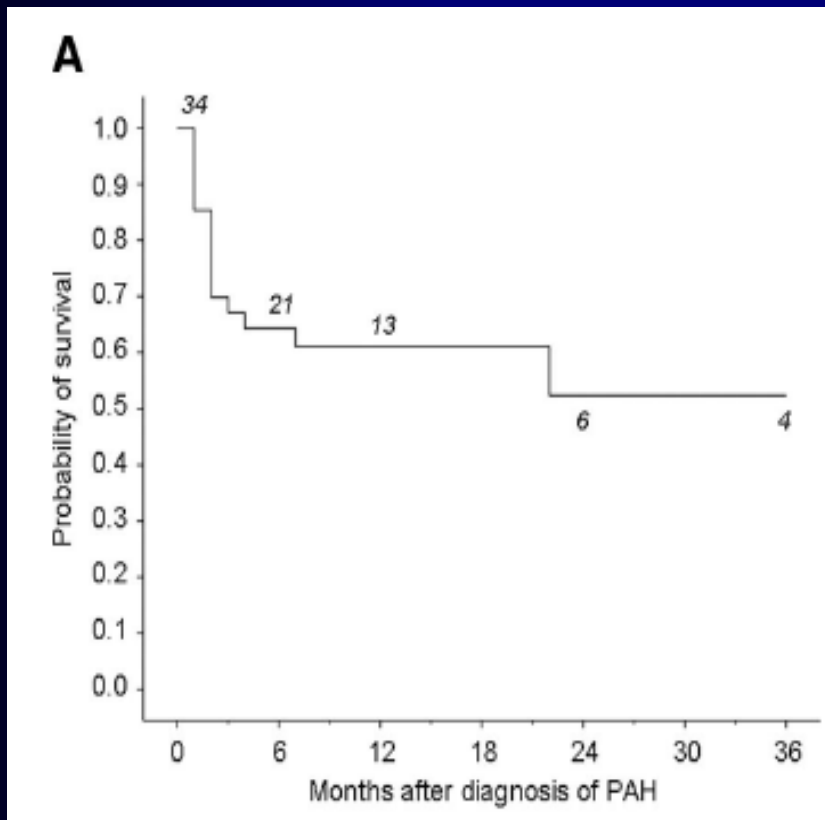
Exercise Intolerance

Pulmonary Hypertension

Pulmonary Hypertension and Severity of BPD

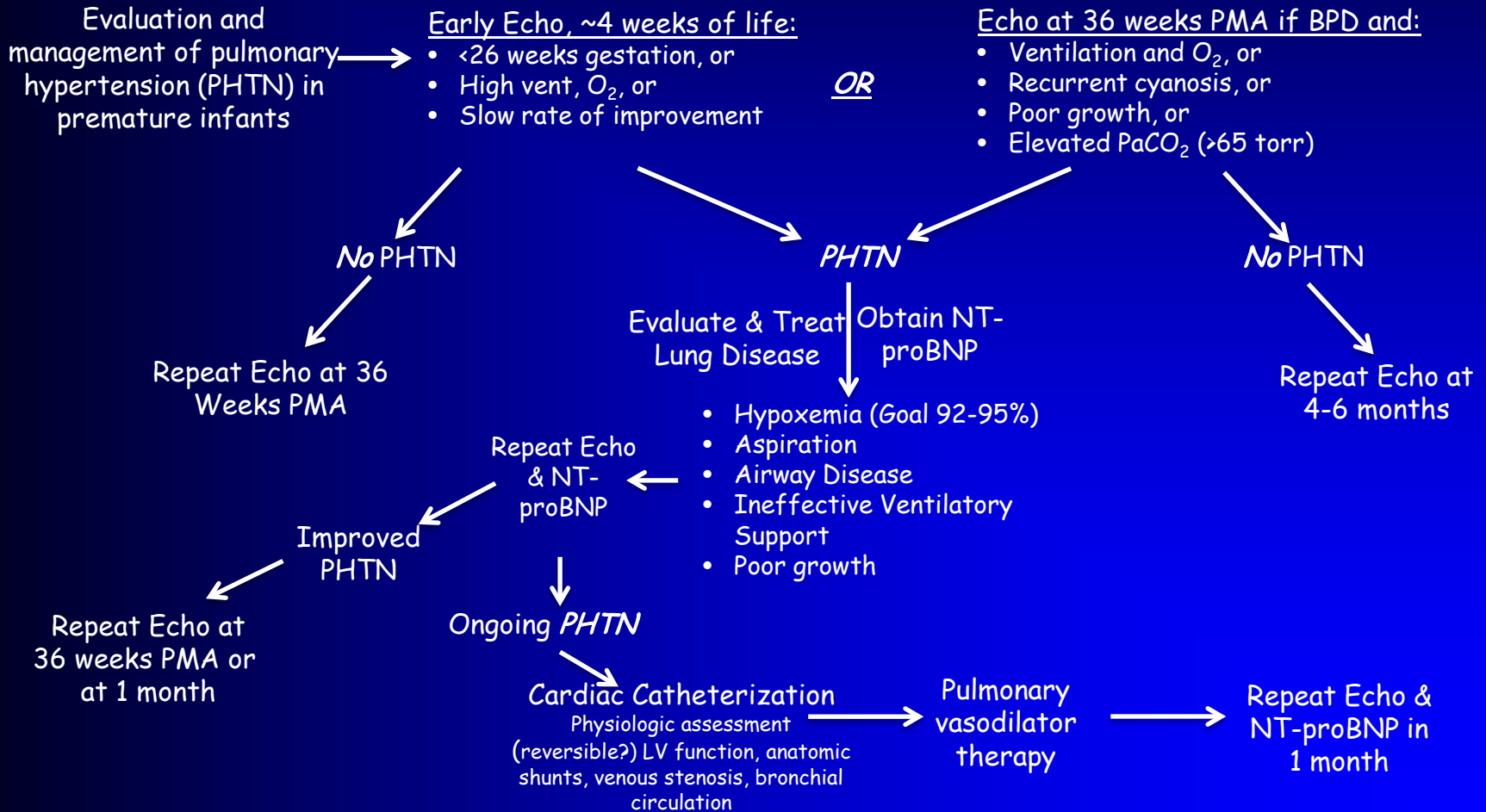


Pulmonary Hypertension and Survival in BPD



Khemani E et al. Pediatrics 120:1260; 2007

Evaluation and Treatment Guidelines for PH in BPD

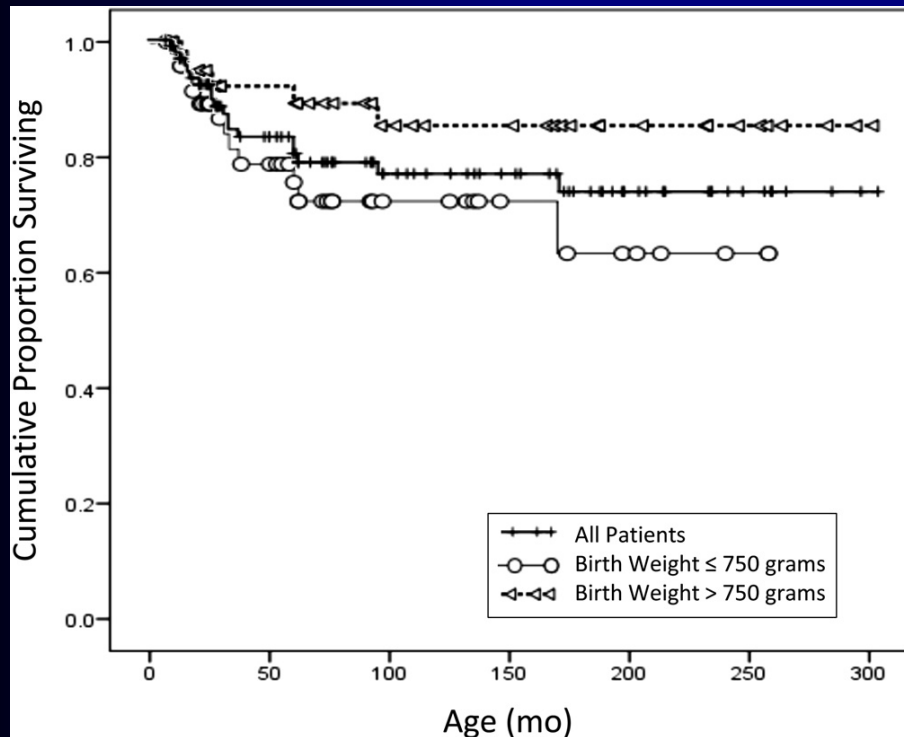


Pharmacotherapy of PH in BPD

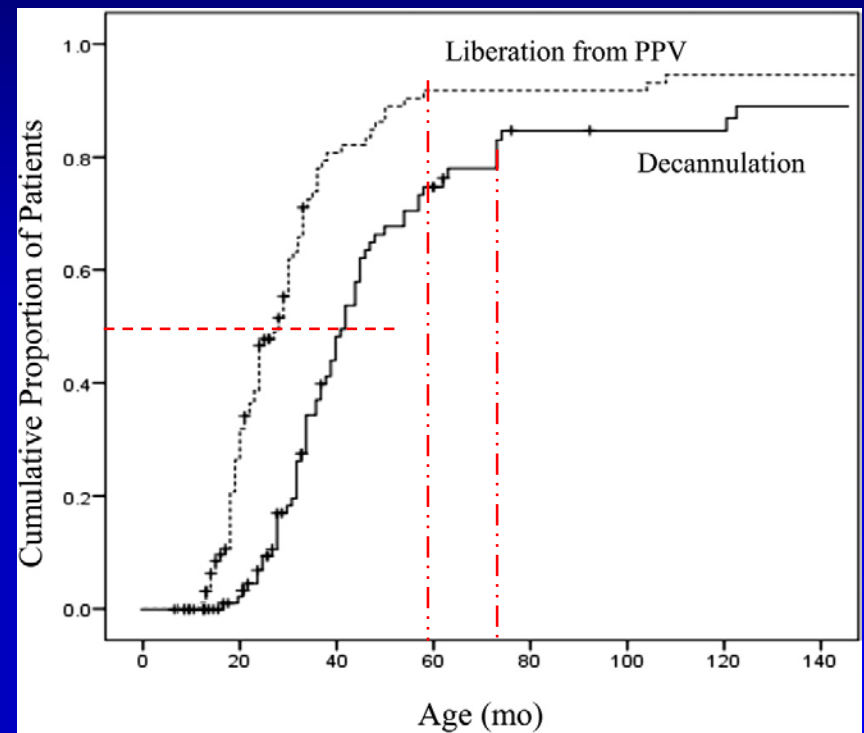
Recommendation	Level of Evidence
Oral sildenafil should be considered for treatment of PH in BPD, especially if iNO is not available	B
IV sildenafil may be considered for treatment of PH in critically ill patients, especially in those with unsatisfactory response to iNO	B
IV prostanoids or inhaled iloprost can be beneficial	B
All infants with proven or suspected PH should receive close follow up, including echocardiography (1/wk initially, 1-2/mo thereafter), lab eval (pro-BNP, BNP, etc) guided by clinical improvement	B
In infants with severe BPD with or without PH, treatment with diuretics can be considered as long as cardiac preload is adequate	B

From: Hilgendorff A et al. Heart 102; ii49; 2016

Outcomes of 102 Ventilator-Dependent Children with BPD



Survival



Liberation

The Functional "Phenotype"

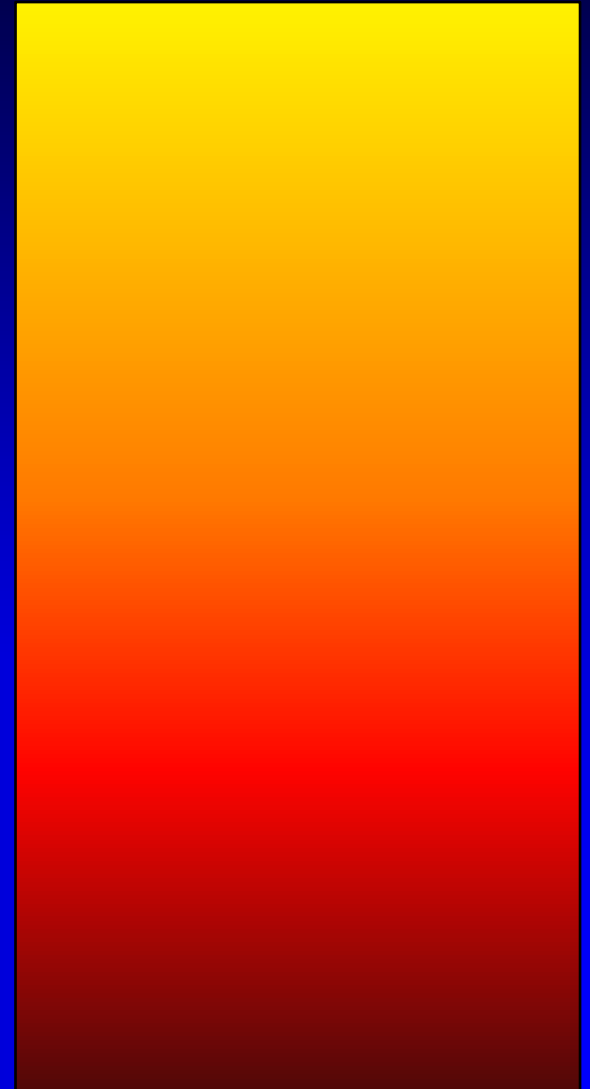
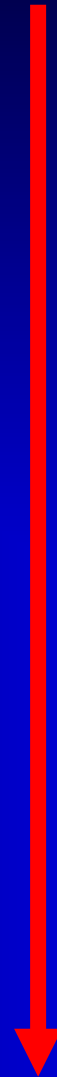
Mild airway reactivity

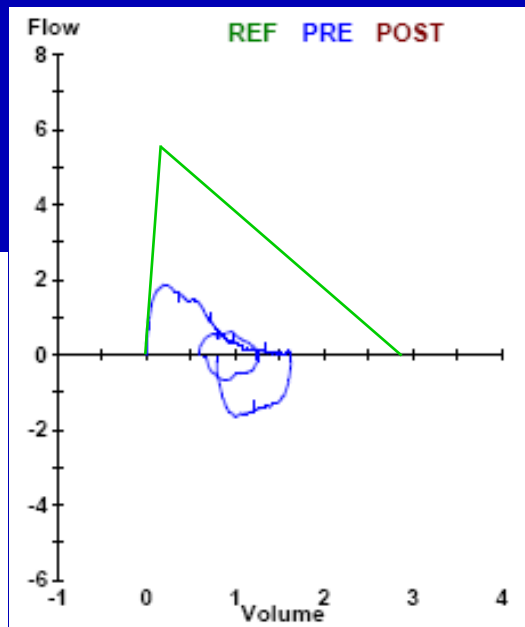
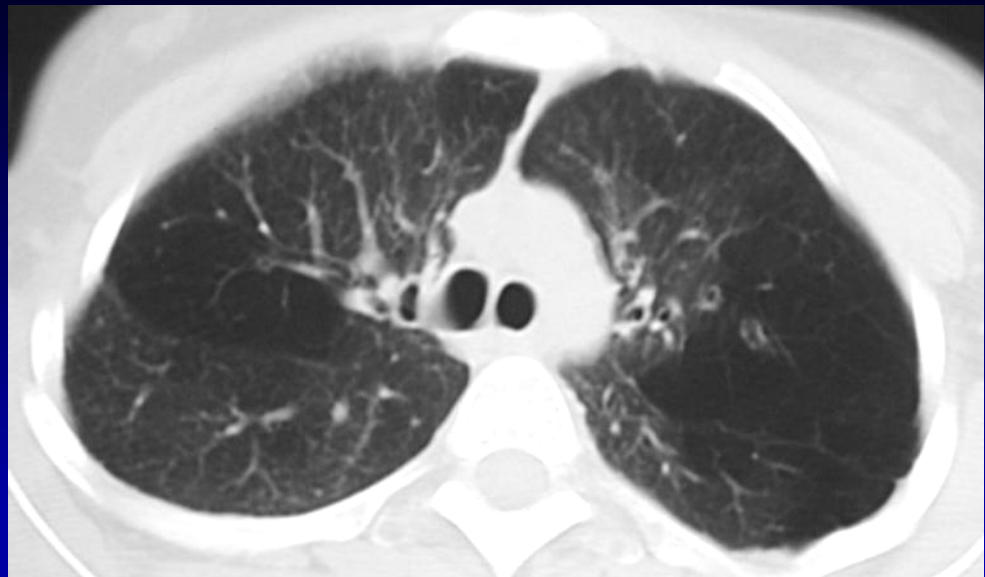
Asthma-like disease

Fixed mild
obstruction/partially
reversible-mild restriction

Moderate
obstructive/partially
reversible-restrictive disease

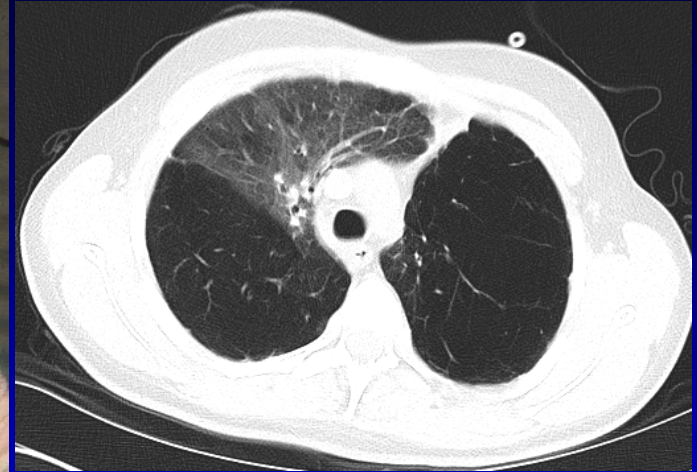
Severe obstructive-restrictive
disease





Spirometry

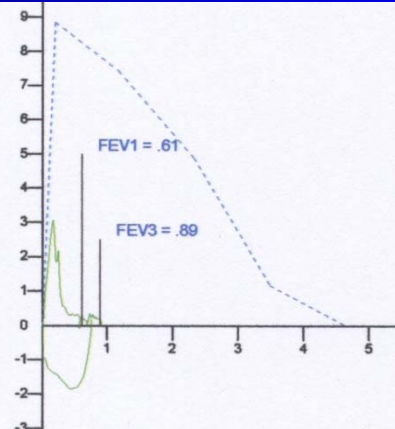
		Ref	Pre Meas	Pre % Ref
FVC	Liters	2.89	1.64	57
FEV1	Liters	2.66	0.98	37
FEV1/FVC	%	92	60	
FEF25-75%	L/sec	3.39	0.41	12
PEF	L/sec	5.65	1.87	33
FEF/FIF50		<1.00	0.44	
FET100%	Sec		8.88	
FEV.5	Liters	2.26	0.75	33



Spirometry (BTPS)

		Ref	Pre	% Ref	Z-score
FVC	L	4.65	1.06	23	-7.54
FEV ₁	L	3.95	0.61	15	-8.30
FEV ₁ / FVC	%	84	58	69	-4.33
FEF ₂₅₋₇₅	L/s	4.40	0.31	7	-5.01
PEFR	L/s	8.85	3.59	41	-4.44
FET	sec		4.84		
FIF50	L/s		2.02		
FEF ₅₀ / FIF50			0.15		
FEV.5	L	2.74	0.47	17	
Back Volume			0.04		

ATS



Summary

- Severe BPD remains a significant problem
- Structural changes favor severe OLD
- Infants with sBPD require unique mechanical ventilation strategies
- sBPD is often associated with PAH
- Long-term burden of disease is yet to be determined

