Pulmonary Hypertension in Neonates and Infants: Towards Personalized Medicine

Olivier Danhaive, MD

University of California San Francisco

GA: 37 weeks - Cesarean section

Birth weight 1,950 g - Apgar 6-8-8

Tachypnea + hypoxemia at 10 min

Arterial blood gas: pH 7.28 / PaCO2 45 / PaO2 35 / BE -4.5

30 min: HFNC 2L - FiO2 50%

6 h: CPAP 6cm – FiO2 60%

8 h: Intubation – Surfactant - SIMV – FiO2 70%

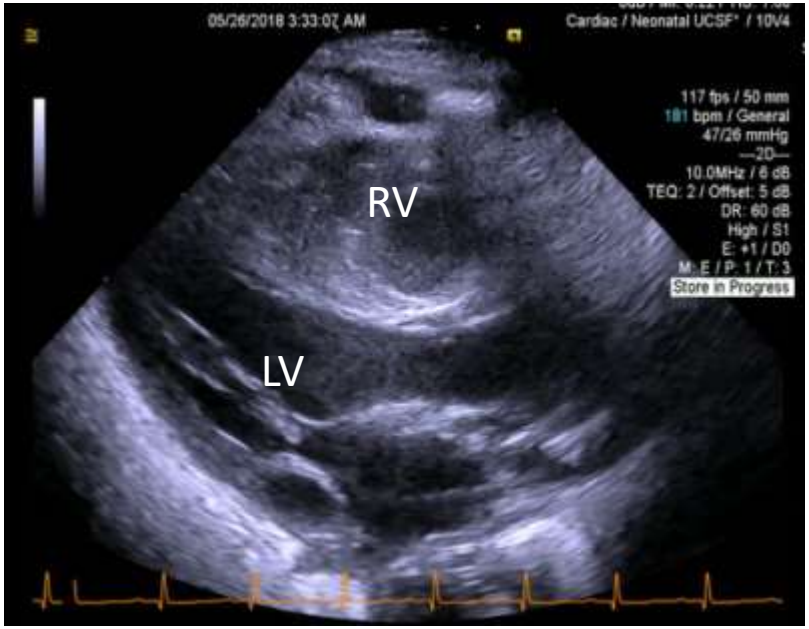
10 h: HFOV - FiO2 100%

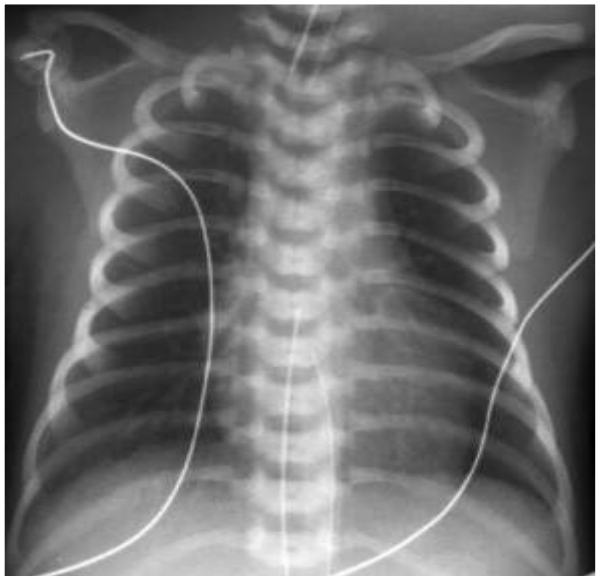
12h: Echocardiography: **Pulmonary hypertension**

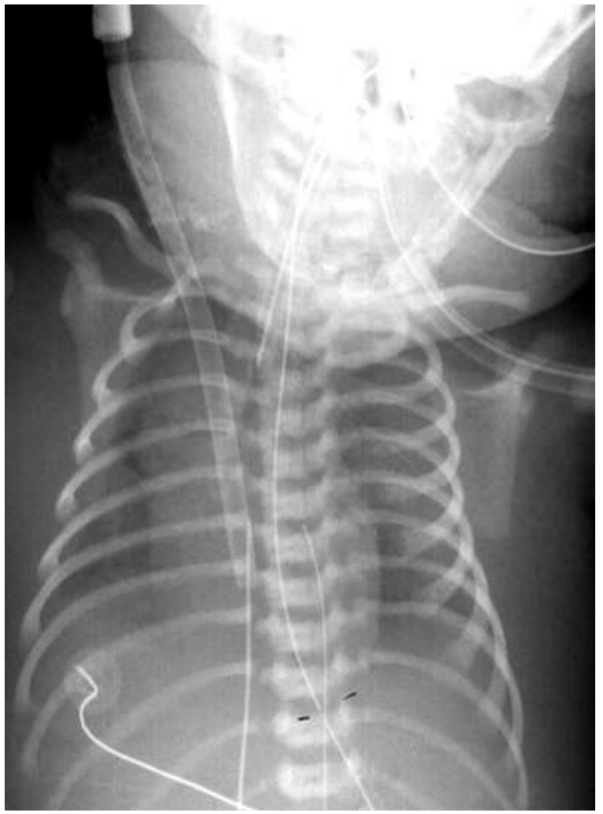
13 h: iNO - 20ppm

20 h: ECMO x 5 days

12 days: extubated to CPAP - discharged home at 1 month

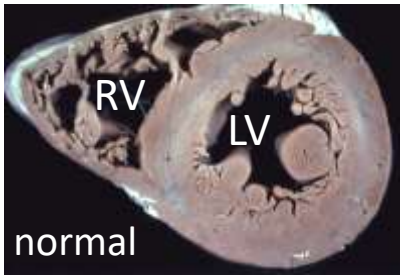


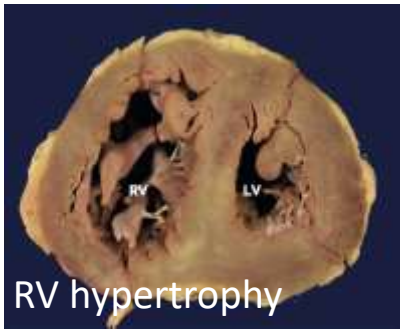


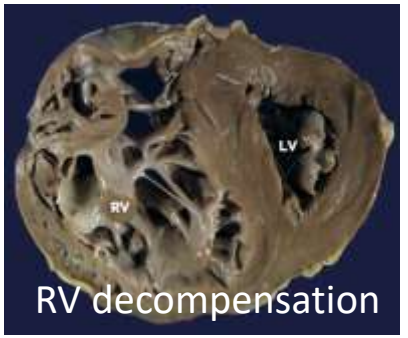


Diagnosis of pulmonary hypertension:

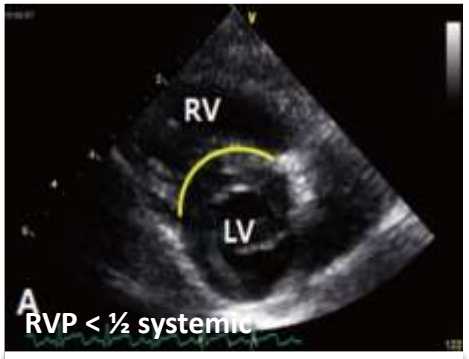
Mean pulmonary arterial pressure ≥25 mmHg

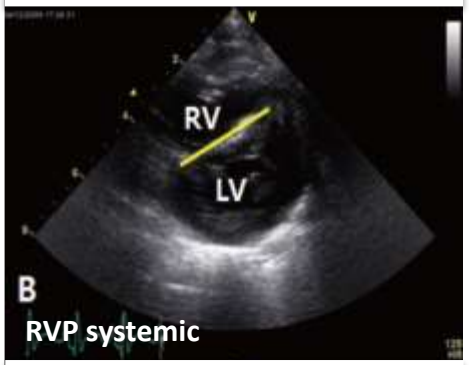


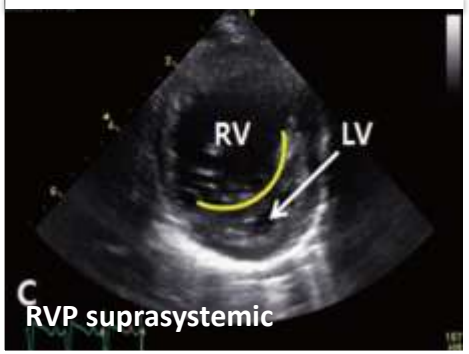


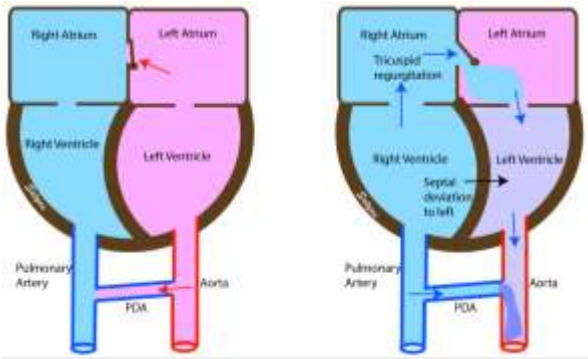


IV septum shape (2D)

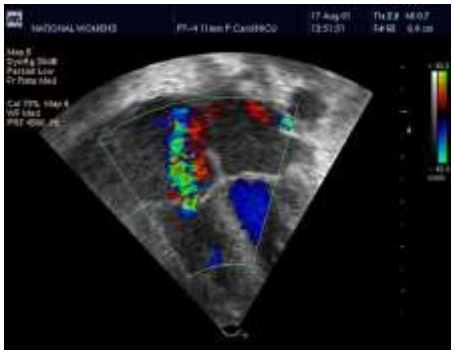


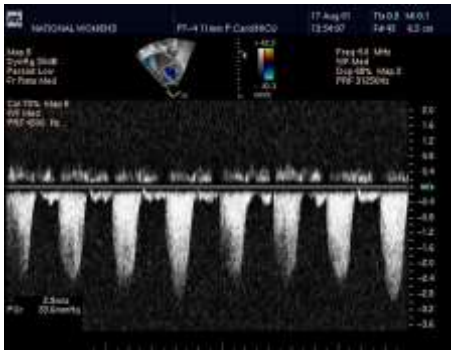


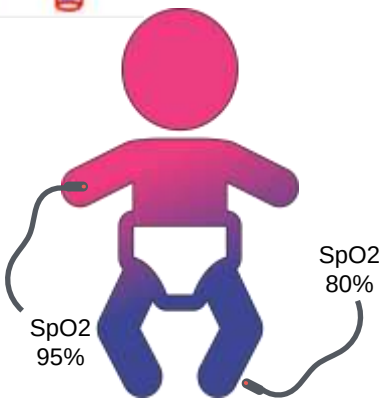




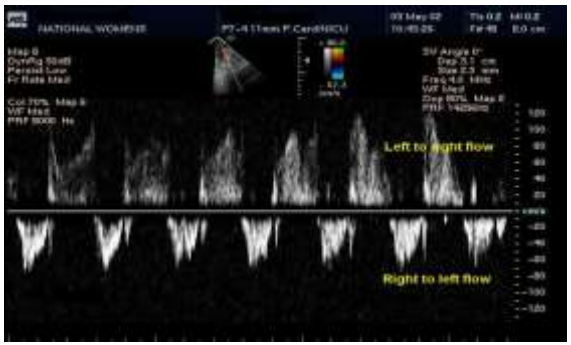
Tricuspid regurgitation







PDA flow



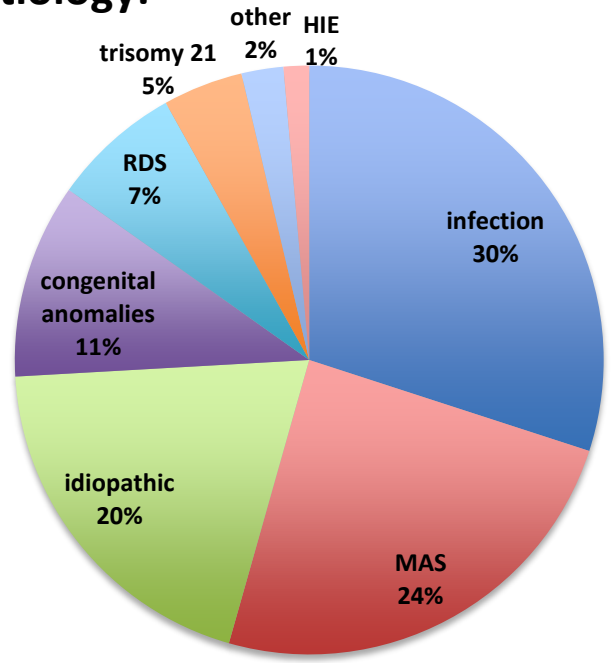
Kim GB. Korean J Pediatr 2010;53:688-93

Persistent Pulmonary Hypertension of the Newborn in Late Preterm and Term Infants in California

Martina A. Steurer, MD, MAS,[a,b] Laura L. Jelliffe-Pawlowski, PhD, MS,[b,c] Rebecca J. Baer, MPH,[c,d] J. Colin Partridge, MD, MPH,[a] Elizabeth E. Rogers, MD,[a] Roberta L. Keller, MD[a]

PEDIATRICS Volume 139, number 1, January 2017

Etiology:



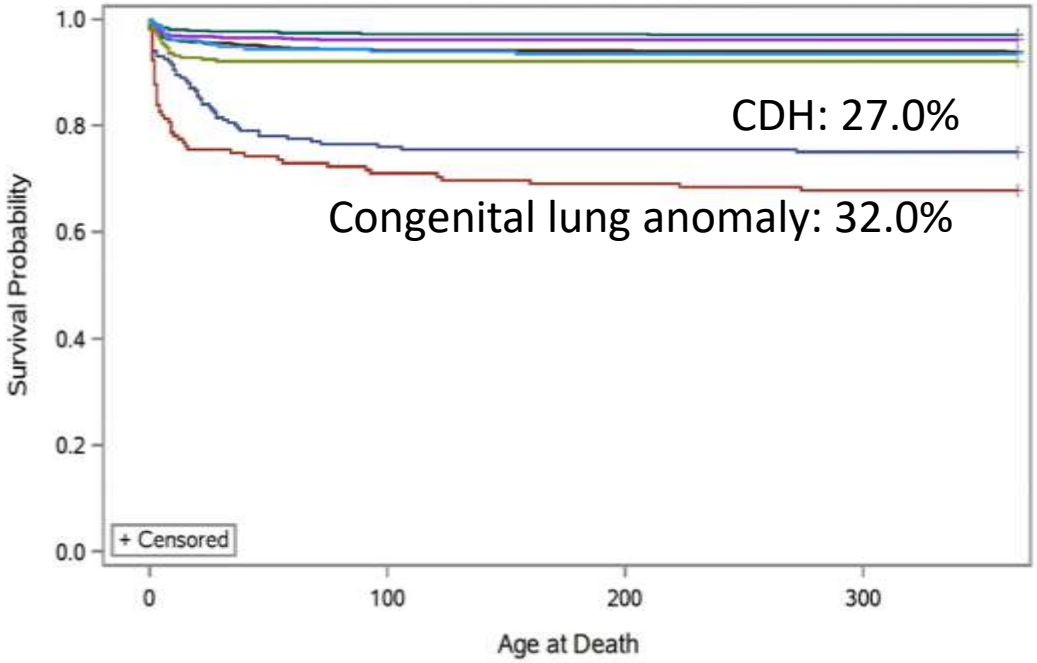
Prediction:

3277 cases / 1.781.156 live births 2007-2011
Incidence 1.8 ‰

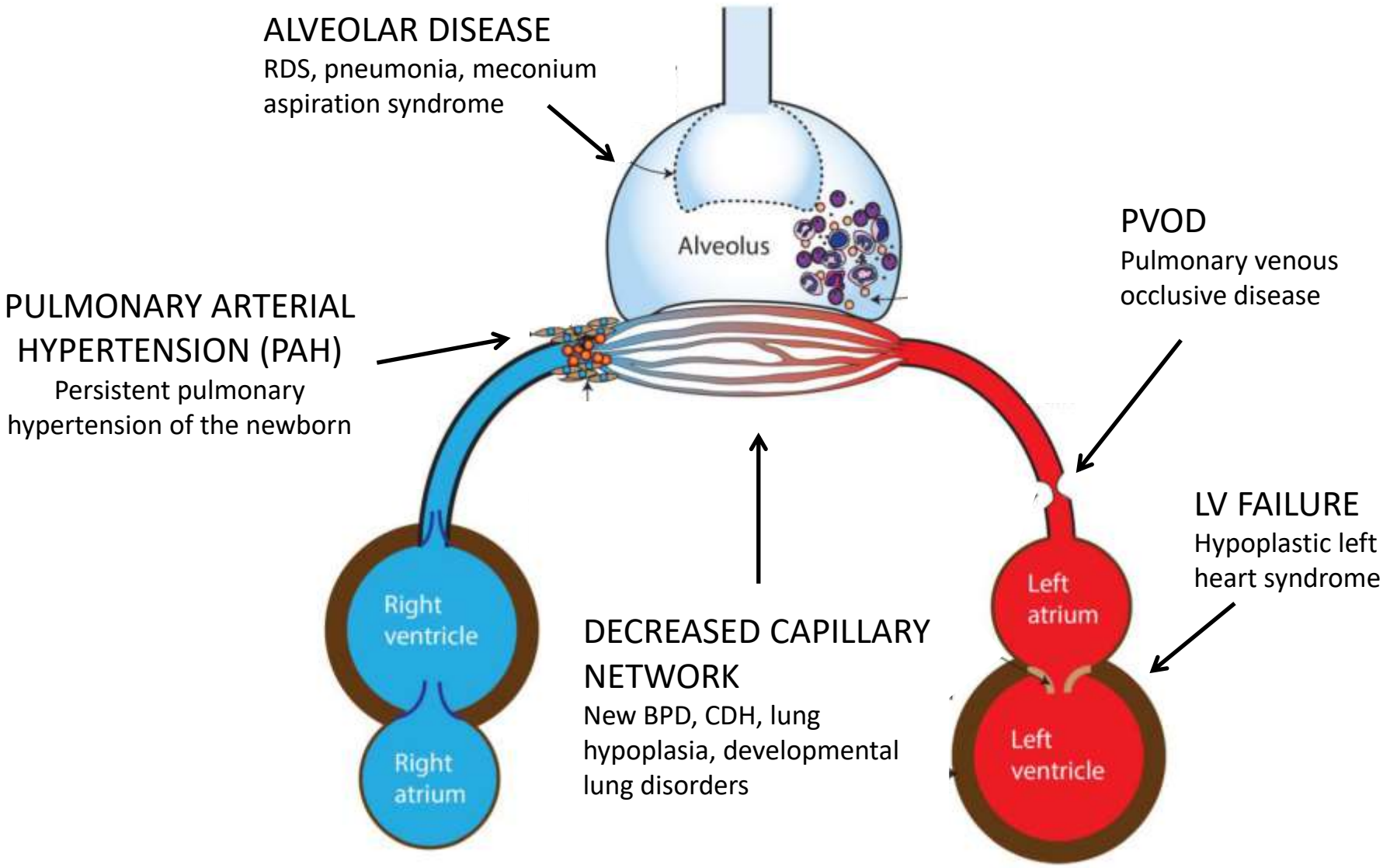
Risk factors:

- C-section: ↗ 2.8x
- Late prematurity 34-36w: ↗ 3.7x
- Post-term >41w: ↗ 1.5x
- LGA: ↗ 1.8x
- SGA: ↗ 1.6x
- Oligohydramnios: ↗ 1.4x
- Maternal diabetes: ↗ 2.8x
- Drug use: ↗ 1.3x
- Smoking: ↗ 1.3x
- Chorioamnionitis: ↗ 2.3x
- Female gender: ↙ 0.8x
- Black race: ↗ 1.3x

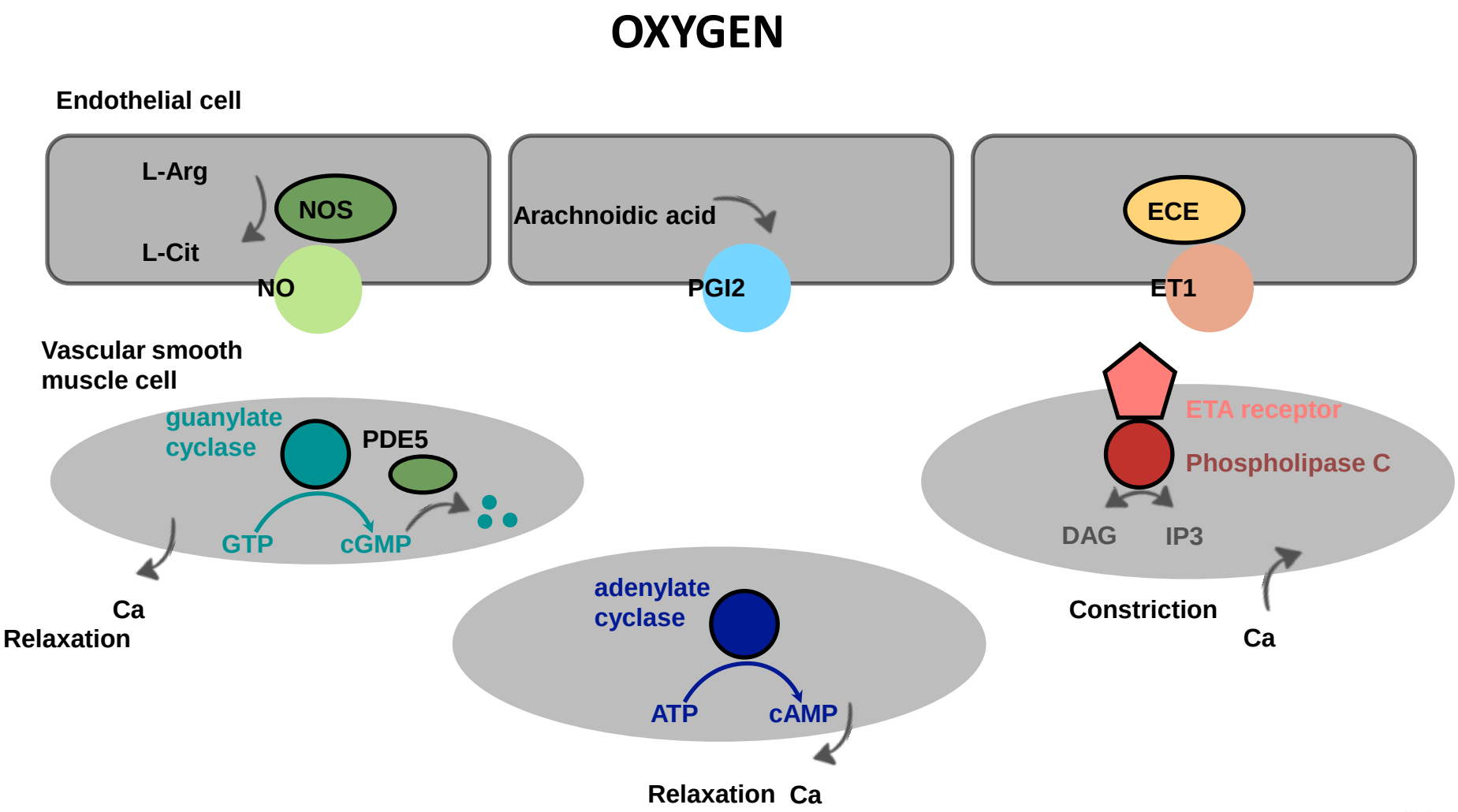
One-year mortality: 7.6%



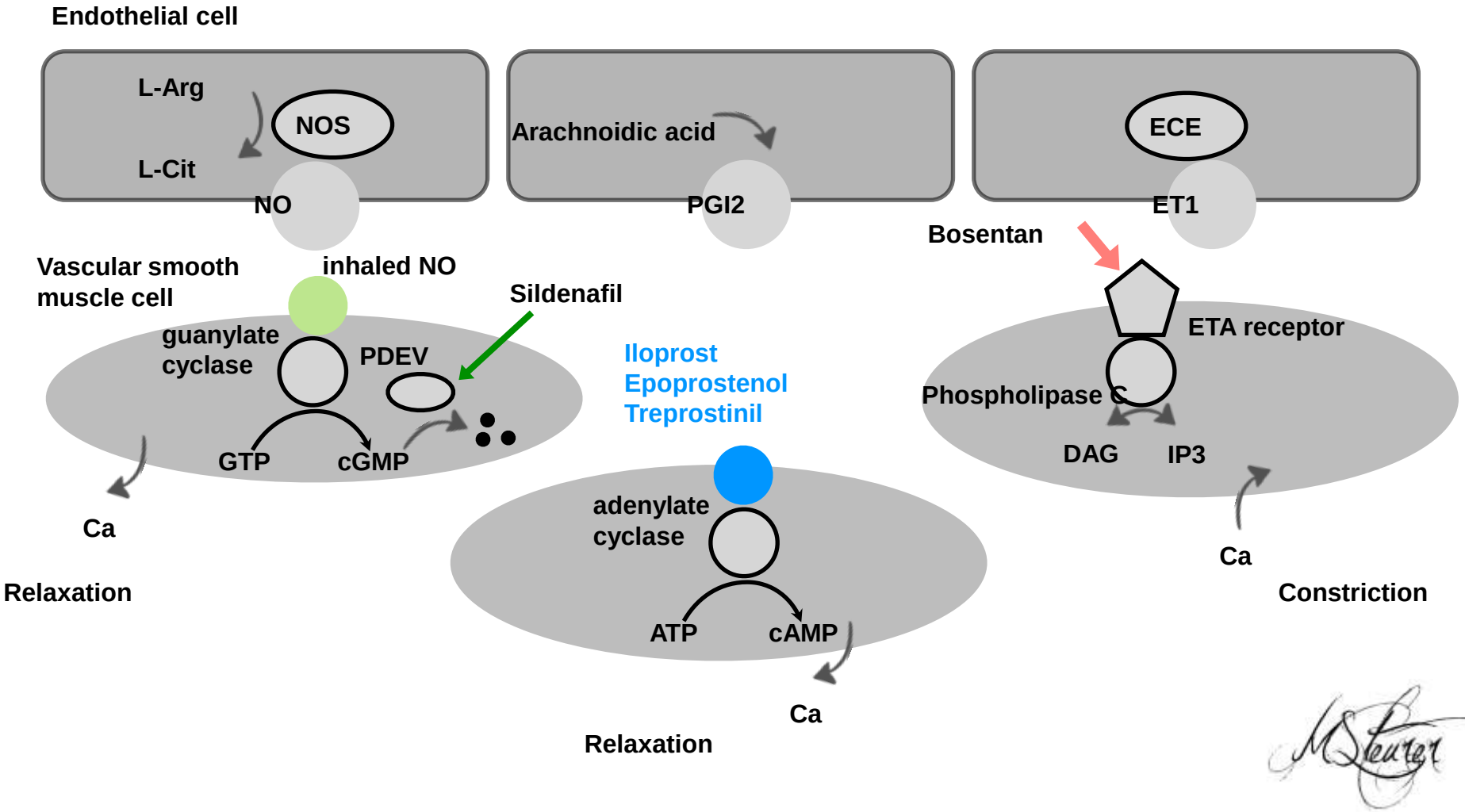
Basic mechanisms of pulmonary hypertension in newborns



Mediators of pulmonary vascular tone



Pulmonary hypertension: Treatment concepts

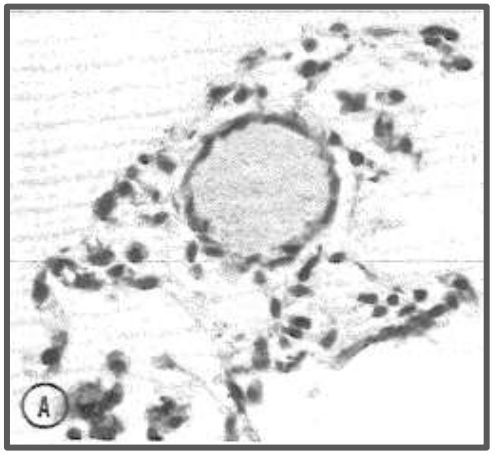


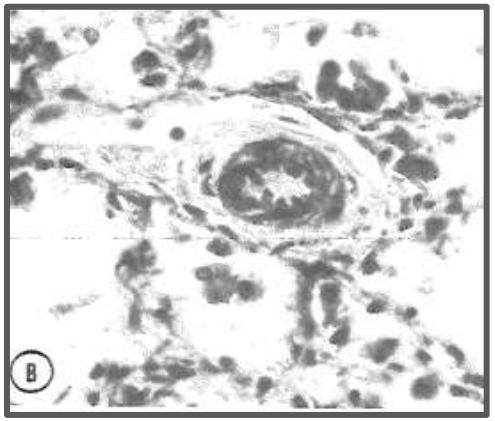
Why do some infants fail to respond?

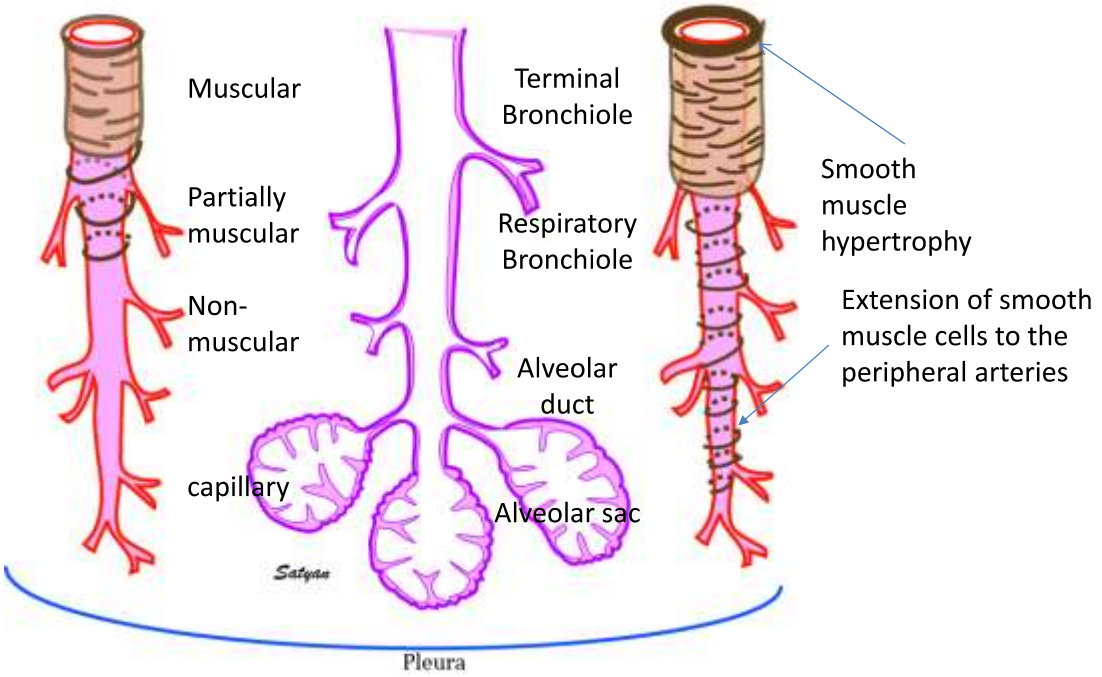
Pulmonary vascular disease in fatal meconium aspiration

Murphy, Vawter, and Reid
The Journal of Pediatrics
May 1984

11 newborns 37-41 weeks – meconium aspiration syndrome
- 10 died of PPHN
- 1 died of hypoxic ischemic encephalopathy – no PPHN



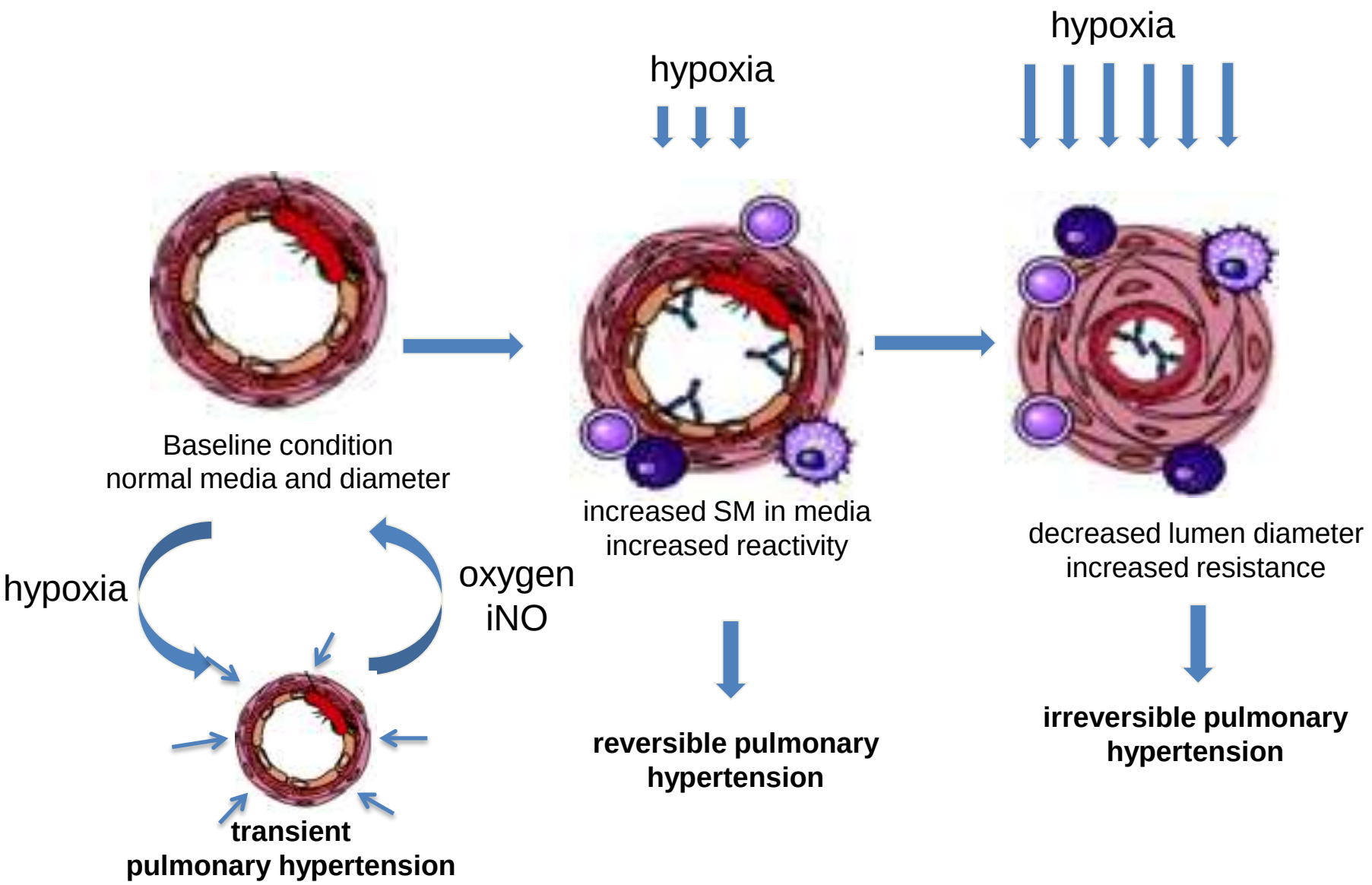




The persistent pulmonary hypertension associated with fatal meconium aspiration may be the result of a structurally abnormal pulmonary microcirculation. (J PEDIATR 104:758, 1984)

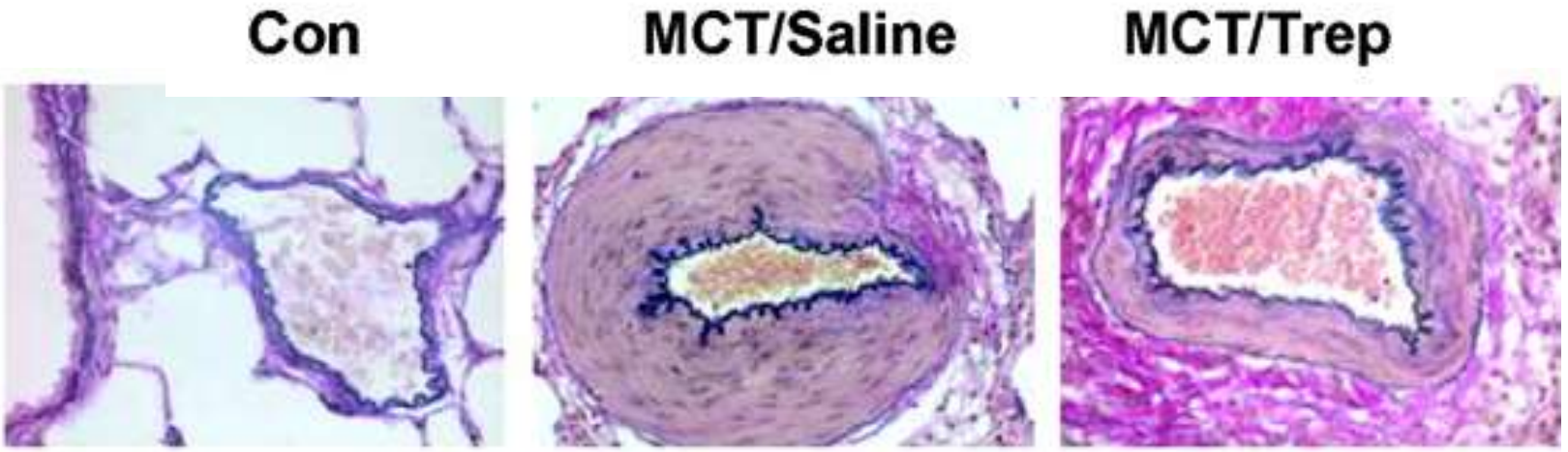
Pulmonary hypertension -> pulmonary vascular disease

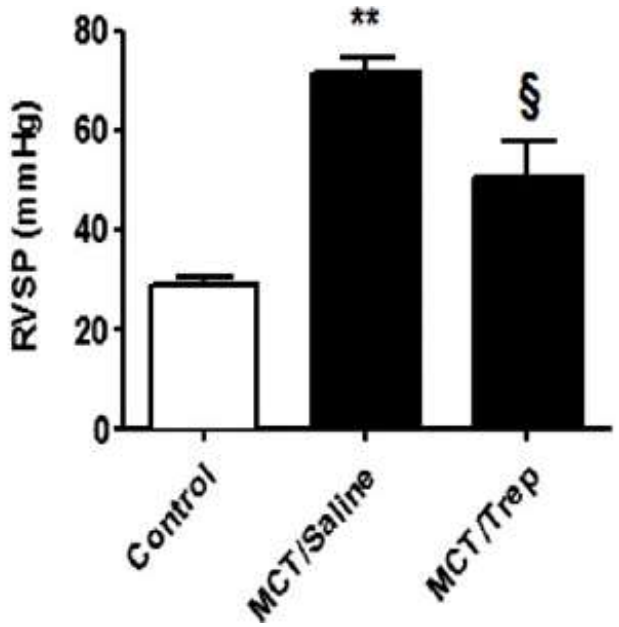
Chronic fetal hypoxia and pulmonary vascular disease



Is vascular remodeling reversible?

Treprostinil inhibits progression of pulmonary hypertension in MCT-exposed rats.





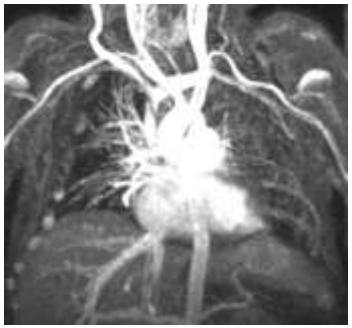
Yang J et al. *Circulation Research*. 2010;107:252-262

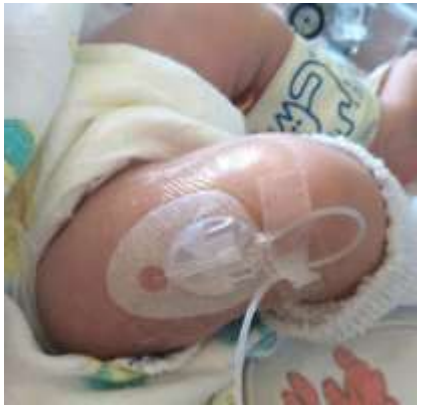
THE JOURNAL OF PEDIATRICS • www.jpeds.com CLINICAL AND LABORATORY OBSERVATIONS

Short-Term Treprostinil Use in Infants with Congenital Diaphragmatic Hernia following Repair

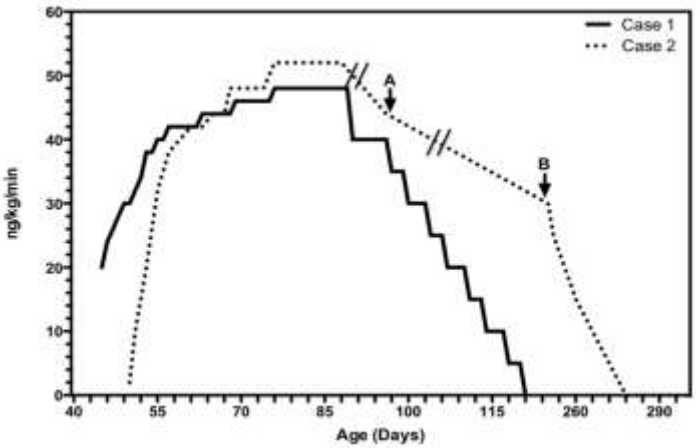
Emma Olson, PNP[1], Leslie A. Lusk, MD[2], Jeffrey R. Fineman, MD[1], Laura Robertson, MD[3], and Roberta L. Keller, MD[2]

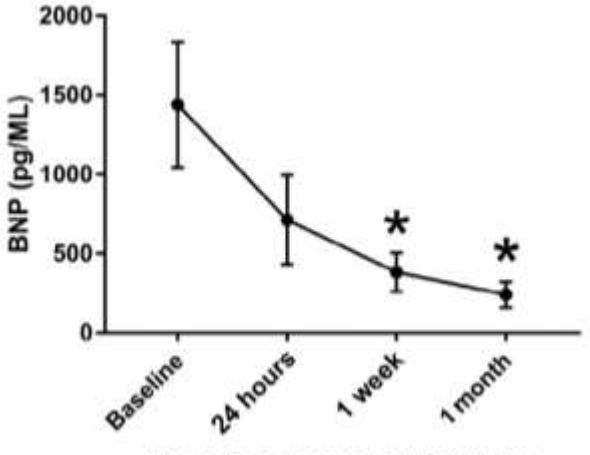
case #1 / *case #2*	pre	2 weeks	8 weeks	30 weeks
Support	SIMV 25/6 nCPAP 7	HFNC 4L nCPAP 6	HFNC 2L NC 0.5L	NC 0.5L NC 0.5L
FiO2 (%)	0.5 0.4	0.4 0.25	0.3 1	1 1
RVP	supraS supraS	supraS ½ S	< ½ S < ½ S	< ½ S < ½ S
BNP (pg/mL)	4080 143	161 80	25 5	5 7
iNO	20ppm 20ppm	-	-	-
Remodulin® (ng/kg/m)	- -	42 42	35 44	0 30
Other	-	-	Bosentan® -	- Bosentan®





Remodulin® titration curve





ARTICLE IN PRESS
THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Treprostinil Improves Persistent Pulmonary Hypertension Associated with Congenital Diaphragmatic Hernia

Kendall M. Lawrence, MD[1], Holly L. Hedrick, MD[1,2], Heather M. Monk, PharmD[3], Lisa Herkert, MSN, CRNP[1], Lindsay N. Waqar, MPH[1], Brian D. Hanna, MDCM, PhD[2,4], William H. Peranteau, MD[1,2], Natalie E. Rintoul, MD[2,4], and Rachel K. Hopper, MD[2,4]

Acute pulmonary hypertension in preterm infants

Journal of Perinatology 2005; 25:495–499

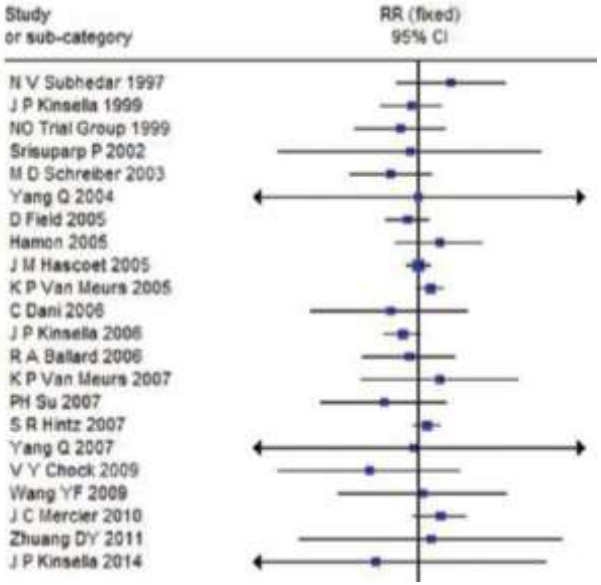
www.nature.com/jp

Pulmonary Hypertension and Right Ventricular Dysfunction in Growth-Restricted, Extremely Low Birth Weight Neonates

Olivier Danhaive, MD
Renée Margossian, MD
Tal Geva, MD
Stella Kourembanas, MD

-7 infants
-GA 29 w (25-32) - BW 650 g (450-790)
-Intrauterine growth restriction - olighydramnios
-Acute pulmonary hypertension crisis after period of respiratory stability
-RV Pressure 70 mmHg (40-95) with RV dysfunction
-Corresponds to PDA closure
-R/ dopamine/milrinone (iNO not approved)

Effect of iNO on death
n= 666 subjects/673 controls <28 weeks



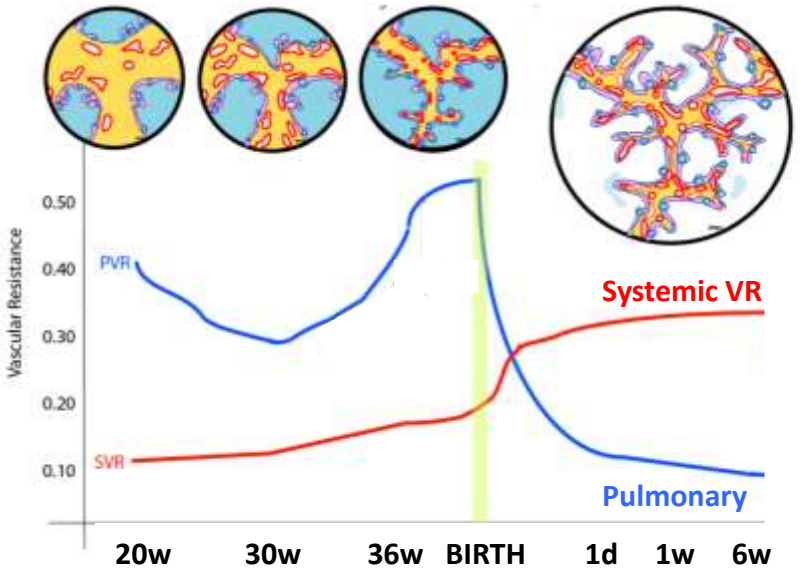
Yang Y. J Res Med Sci 2016, **21**:41

Persistent pulmonary hypertension of the newborn in extremely preterm infants: a Japanese cohort study

Hidehiko Nakanishi, Hideyo Suenaga, Atsushi Uchiyama, Satoshi Kusuda, on behalf of the Neonatal Research Network, Japan

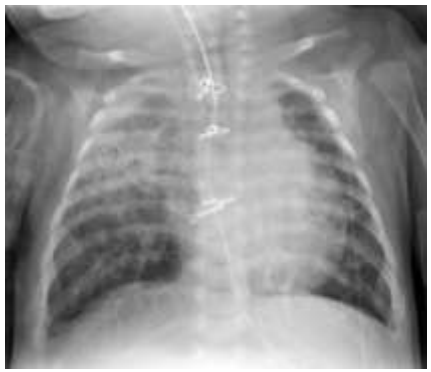
Arch Dis Child Fetal Neonatal Ed 2018;**0**:F1–F8.

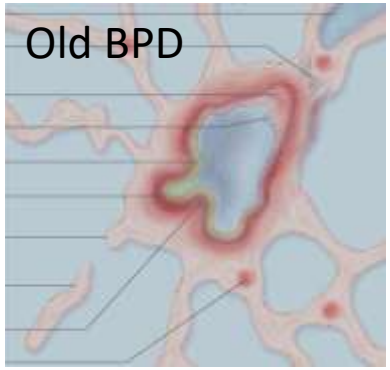
- 12,954 infants <28 weeks 2003-2012
- Incidence PPHN 8.2%
- Chorioamnionitis - PROM

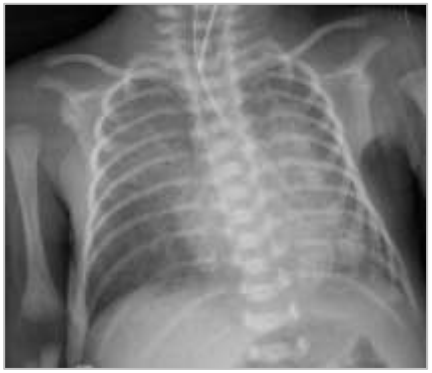


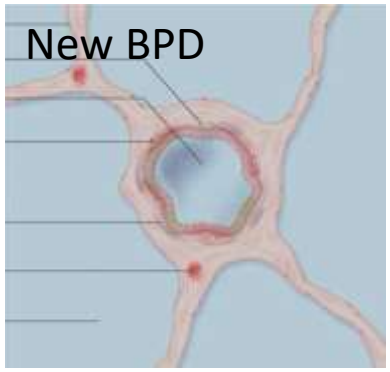
From: S. Lakshminrusimha

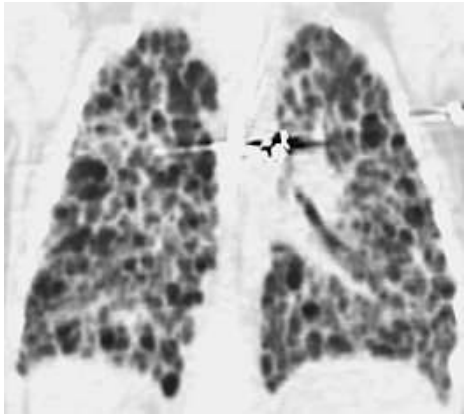
Chronic pulmonary hypertension in preterm infants with BPD

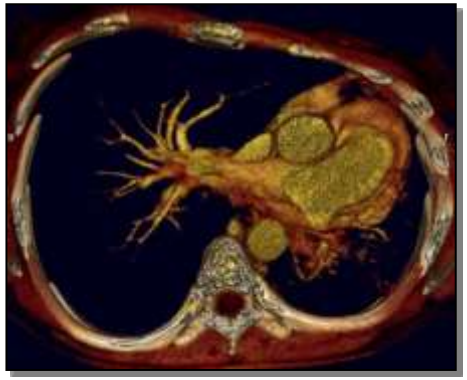




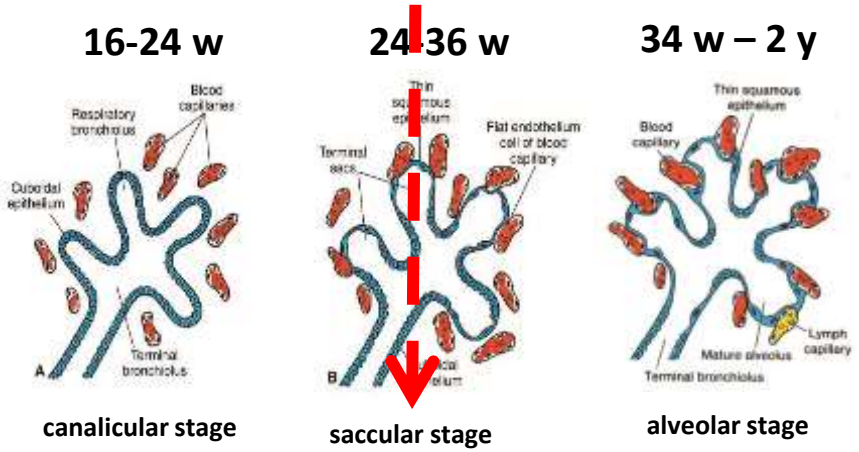








16-24 w **24-36 w** **34 w – 2 y**



canalicular stage **saccular stage** **alveolar stage**

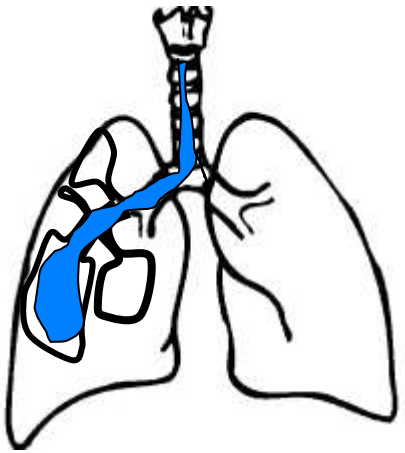
Developmental

Postnatal lung injury

Early RDS: prevent lung injury:

- Low tidal volumes (4 - 6 ml/kg)
- Short inspiratory times
- Increase PEEP without over-distension (as reflected by high
- Lower O_2Sat target (8 92%) + permissive hypercapnea

Low Tidal Volume
Short Insp Times



Established BPD: prevent pulmonary vascular disease

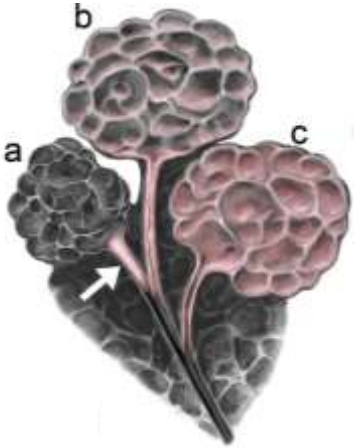
Prevent heterogeneity:

- Larger tidal volumes (10 - 12 ml/kg)
- Longer inspiratory times (> 0.6 sec)

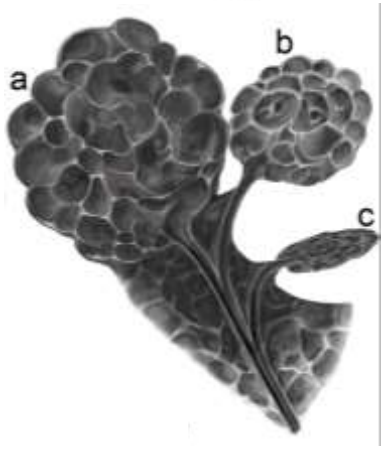
Prevent hypoxia and hypercarbia:

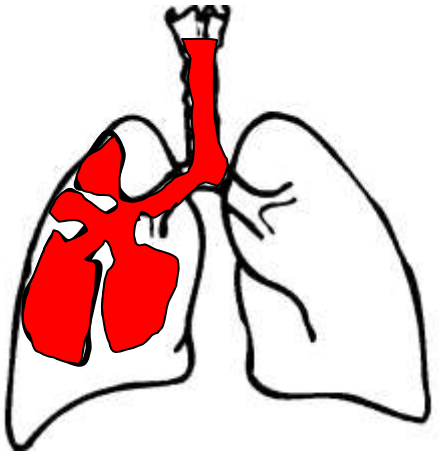
Slower rates (better emptying) - high PEEP

Treat aspiration and airway malacia



Higher Tidal Volume
Longer Insp Time

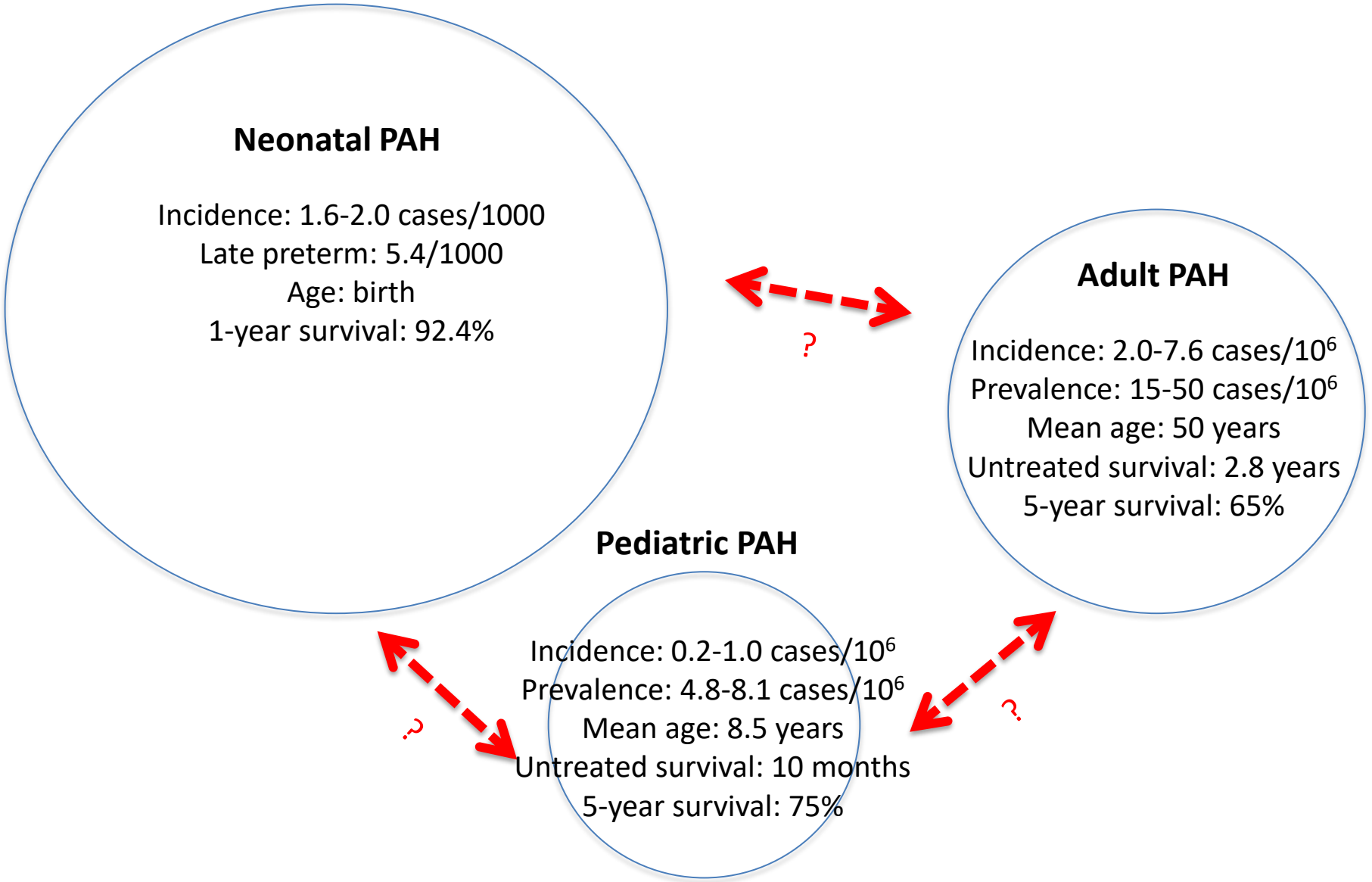




Recognize and treat pulmonary hypertension

- Serial echocardiography (cardiac catheterization)
- Inhaled nitric oxide
- Transition to sildenafil
- If unable to wean from iNO, consider treprostinil or bosentan

A lifespan perspective of pulmonary hypertension



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Levy M. Eur Respir J 2016; 48: 1118–1126

Thenappan T. BMJ 2018:360:j5492
Farber HW. CHEST 2015; 148(4):1043-1054

What about PPHN non-responders?

Extracorporeal Life Support Registry 2000-2010

Table 1. Demographics and clinical variables

Variable	Irreversible Pulmonary Dysplasia (n=32)	Persistent Pulmonary Hypertension of the Newborn (n=1,504)	
Gestational age, wks	38.8 ± 0.2 (35–41)	38.7 ± 0.2 (30–44)	.82
Apgar at 5 mins	8.0 ± 0.4 (0–10)	7.6 ± 0.1 (0–10)	.32
Pre-ECMO blood gas			
pH	7.23 ± 0.04 (6.88–7.62)	7.23 ± 0.01 (6.27–7.77)	.99
pCO_2, torr	48.5 ± 4.3 (17–137)	51.5 ± 0.6 (9–180)	.50
pO_2, torr	38.4 ± 3.6 (9–95)	42.0 ± 0.7 (5–326)	.34
HCO_3^-, mEq/L	20.6 ± 1.1 (9–36)	22.4 ± 0.2 (4–68)	.10
SaO_2, %	62.7 ± 5.1 (5–100)	68.1 ± 0.6 (3–100)	.35
Venoarterial ECMO access, %	68	63	.71
Age placed on ECMO, days	5.3 ± 1.1 (1–23)	3.0 ± 0.1 (1–29)	*.04*
Duration of ECMO, days	11.1 ± 1.2 (1–25)	6.8 ± 0.1 (1–37)	<.001
Survival to discharge, %	3	81	<.001

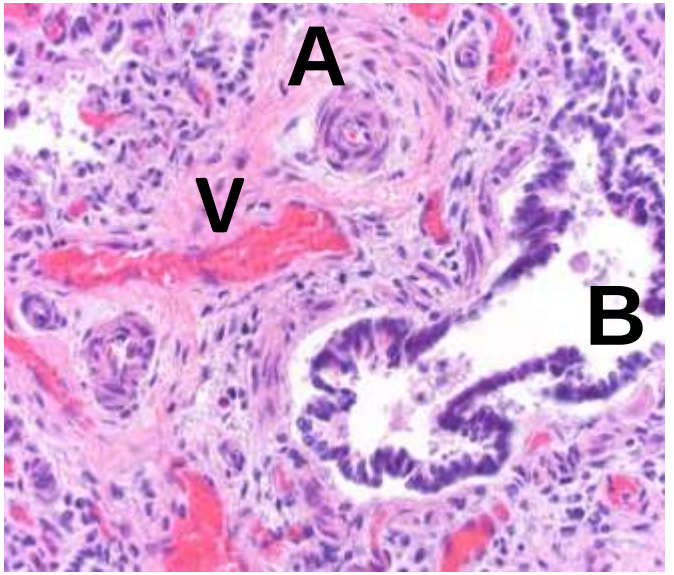
ECMO, extracorporeal membrane oxygenation.
Average values expressed at mean ± SE of the mean with range in parentheses.

Lazar DA Pediatr Crit Care Med 2012:13:188

Alveolar Capillary Dysplasia with Misaligned Pulmonary Veins

First described in 1948

- Lethal refractory hypoxemia
- Entire lung or a single lobe, with severe retardation of alveolar development
- Associated malformations
- Occasionally familial
- Likely **genetic disease of lung development**



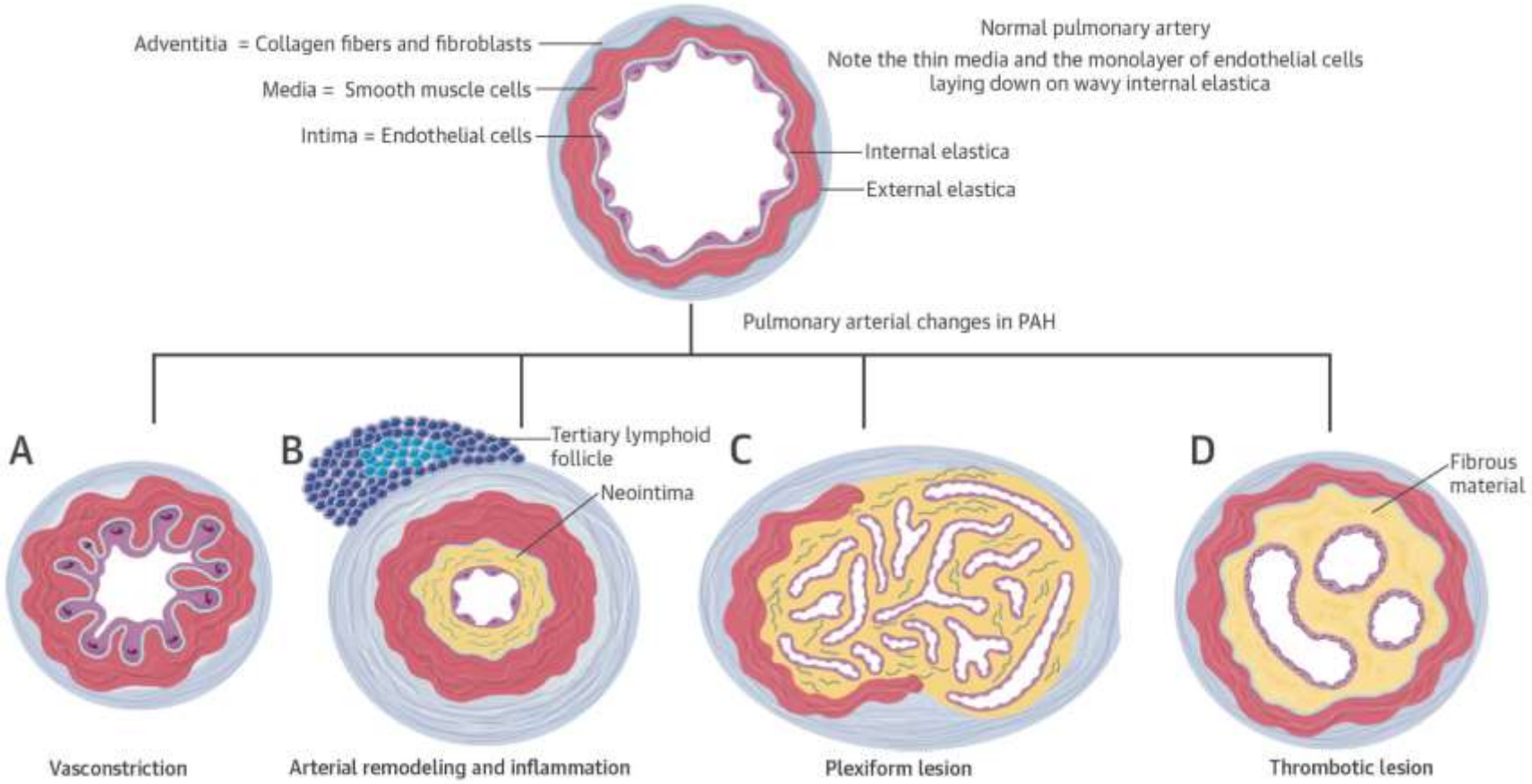
MacMahon, *Congenital alveolar dysplasia of the lungs,* Am J pathol 1948;24:919

ARTICLE

Genomic and Genic Deletions of the FOX Gene Cluster on 16q24.1 and Inactivating Mutations of *FOXF1* Cause Alveolar Capillary Dysplasia and Other Malformations

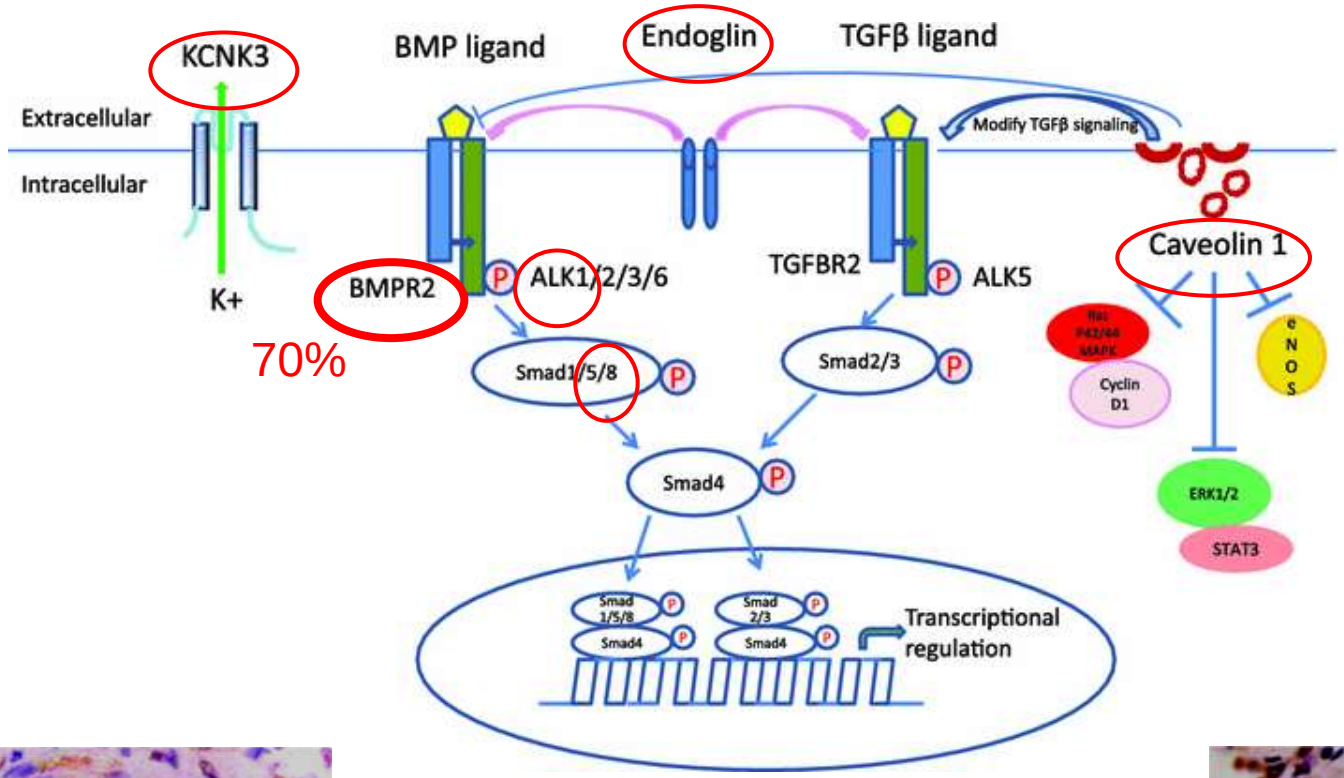
The American Journal of Human Genetics *84*, 780–791, June 12, 2009

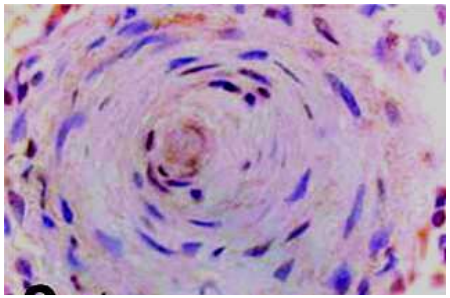
What can we learn from adult pulmonary hypertension?



Imbalance in injury repair mechanisms

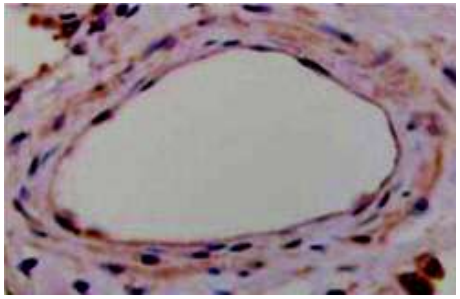
Adult idiopathic pulmonary hypertension is caused by genetic defects in the TGF-β signaling pathway



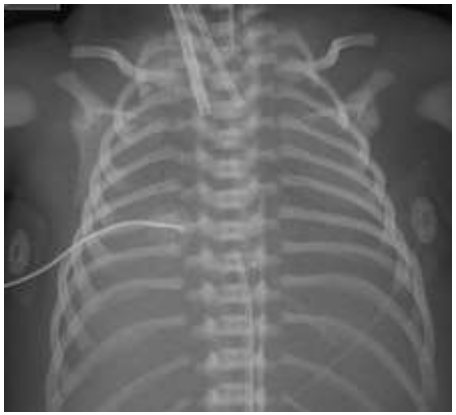


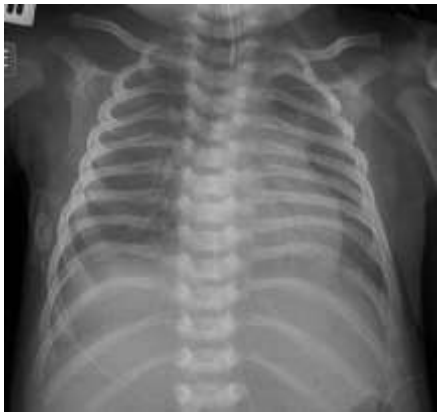
Proliferation
Migration
Angiogenesis

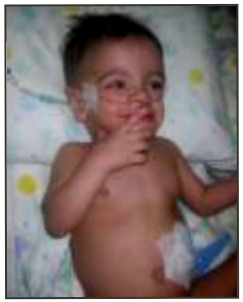
Apoptosis
Cell cycle control
Resolution of inflammation
Alveolar maturation



- Late preterm female 36w
- PPHN at birth
- SIMV, HFOV, iNO, ECMO
- Home on O2 and sildenafil at 2 months
- Re-hospitalized at 5 months for PAH
- Died at 6 months of refractory hypoxemia



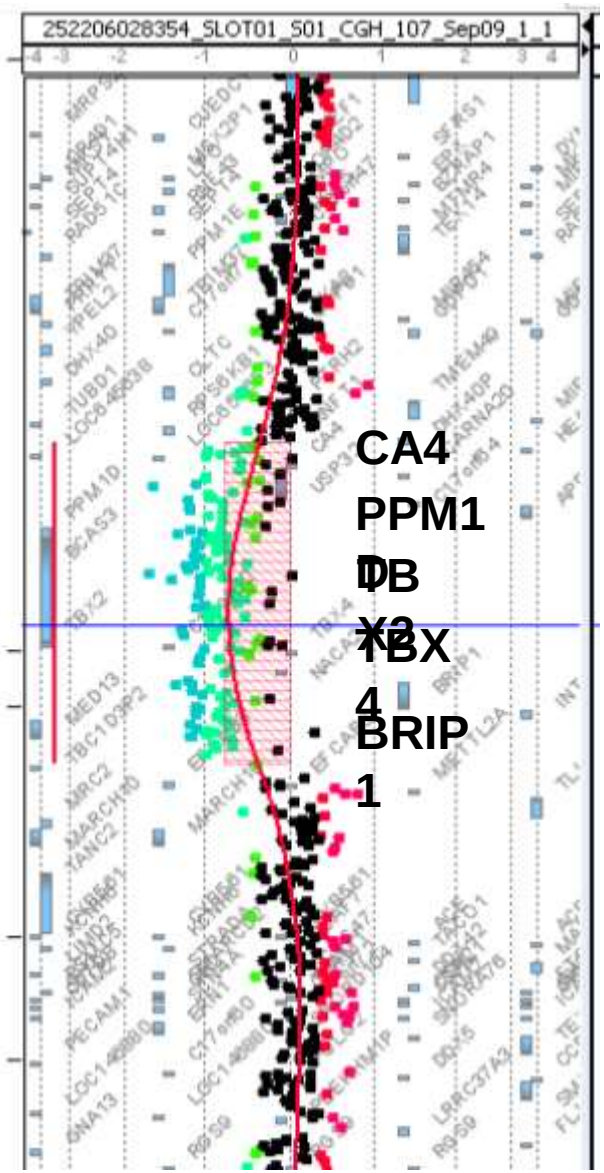




TBX4 is a candidate gene for infantile pulmonary hypertension

17q23.1 deletion

(chr17 [55515485-63165569] x1)



19 children with pulmonary arterial hypertension and TBX4 variants

Clinical course:

- Mean age at diagnosis: 11 months (1 m – 12 y)

- 10/19 presented as severe PPHN in neonatal period (ECMO in 4, iNO in 9) – All discharged – mean age 37 days, 6 on oxygen, 2 on sildenafil

- Mean age at follow up: 10y (2m – 29y)

  11 on 2-3 medications

  5 on single medication

  2 on no medication

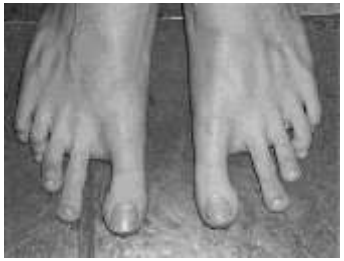
- 3 subjects died (5m, 8m, 29y); 2 were transplanted (8y, 18y)

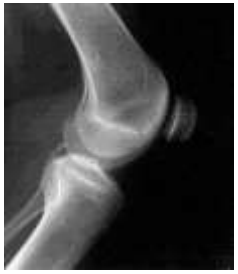
Associated anomalies:

- 8/19 small patella syndrome, foot and other skeletal anomalies

- 9/19 developmental delay

- 6/19 PDA and 9/19 ASD





Genetics:

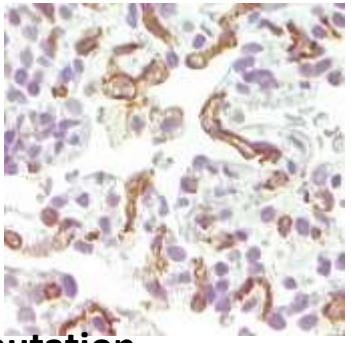
6 genomic deletions

10 gene-dysrupting mutations

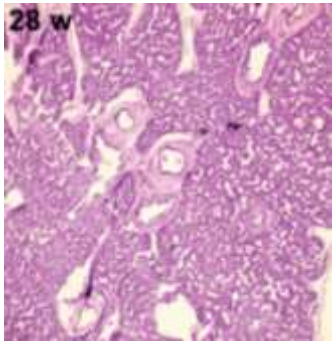
3 missense mutations likely affecting gene function

5 familial cases – variable penetrance

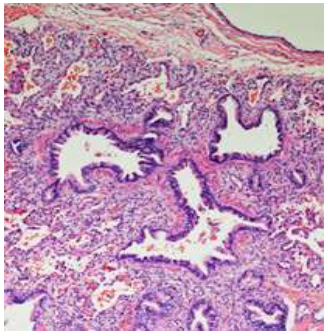
control



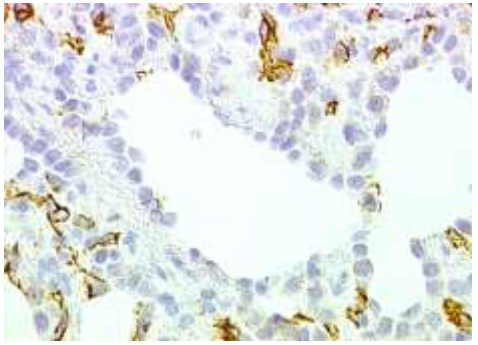
24 week newborn



TBX4 mutation

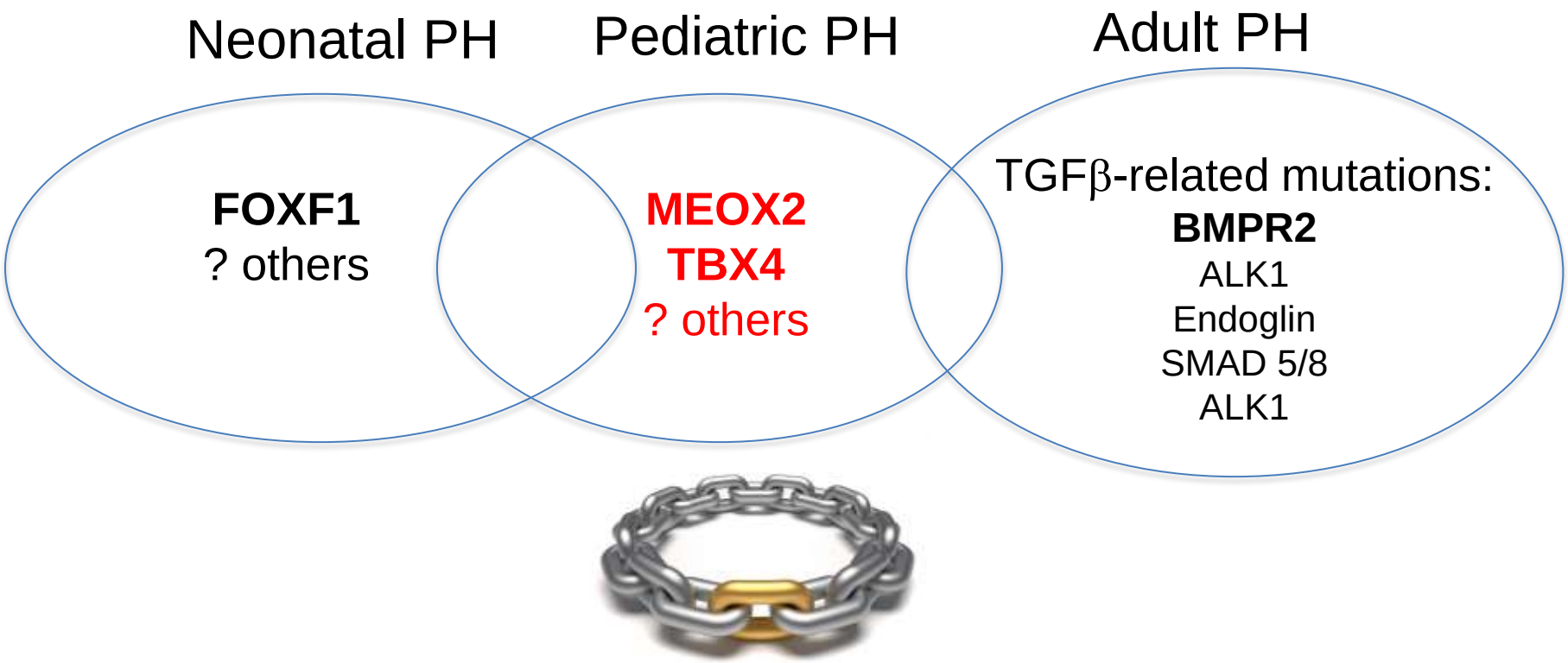


TBX4 mutation



Unpublished data

Pediatric pulmonary hypertension: primarily a developmental lung vascular disorder



ORIGINAL ARTICLE

Exome Sequencing in Children With Pulmonary Arterial Hypertension Demonstrates Differences Compared With Adults

Zhu N. Et al. Circ Genom Precis Med. 2018;11:e001887.

Rare, predicted deleterious variants in TBX4 are enriched in pediatric patients and de novo variants in novel genes may explain ≈19% of pediatric-onset IPAH cases.

Pulmonary vascular disease in newborn and children