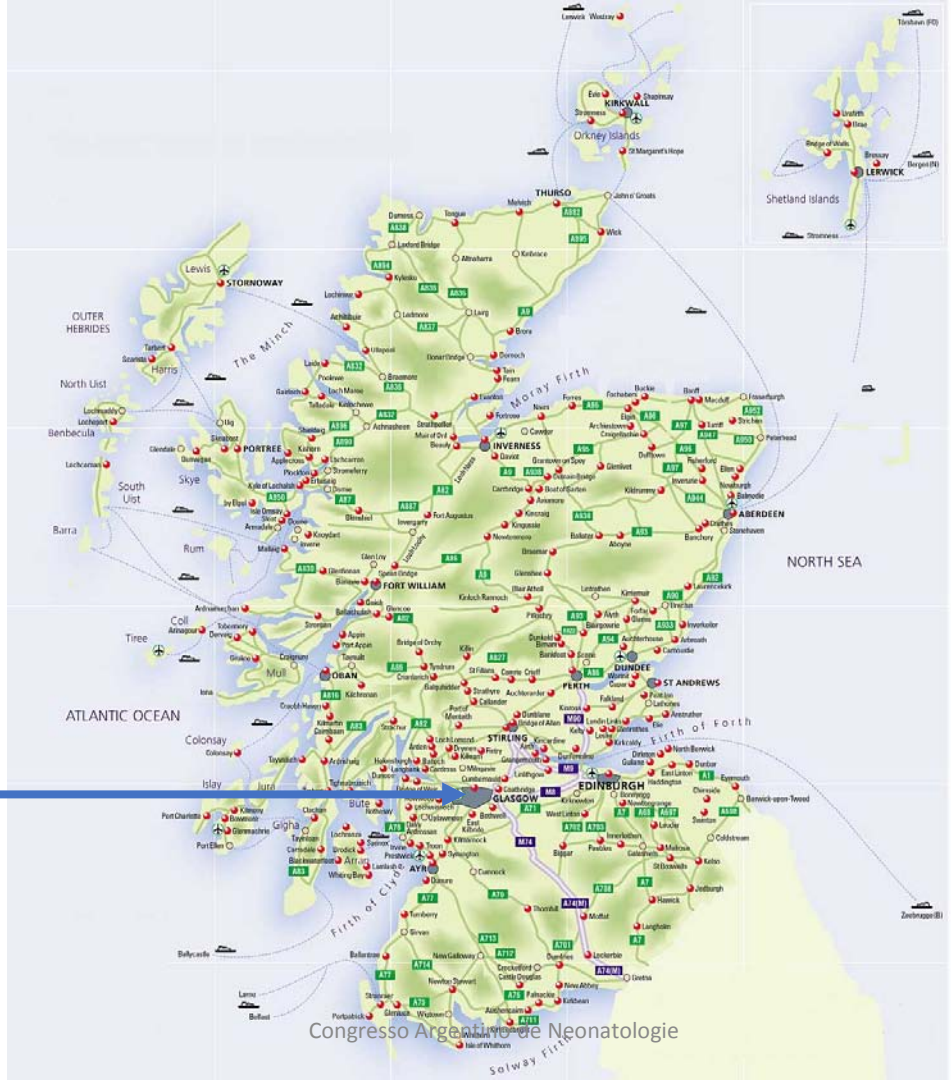

Glasgow
KIRKWALL
Orkney Islands
THURSO
LERWICK
Shetland Islands
Lewis
STORNOWAY
OUTER HEBRIDES
Harris
North Uist
Benbecula
The Minch
Moray Firth
INVERNESS
PORTREE
Skye
South Uist
Barra
Rum
Coll
Tiree
Mull
FORT WILLIAM
OBAN
ABERDEEN
NORTH SEA
DUNDEE
PERTH
ST ANDREWS
ATLANTIC OCEAN
Colonsay
Islay
Jura
STIRLING
Firth of Forth
EDINBURGH
GLASGOW
Bute
Arran
AYR
Firth of Clyde
Solway Firth

Cecilia Grierson (1859-1934)

First woman to receive a medical degree in Argentina

Founder of first nursing school in Argentina and National Obstetrics Association

PEOPLE MAKE GLASGOW

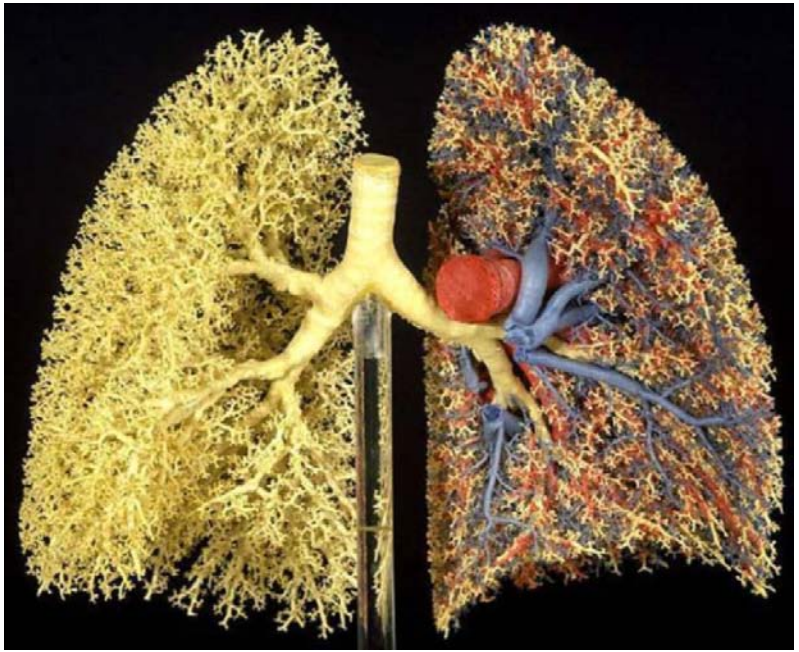
Challenges in Pulmonary Hypertension (PH)

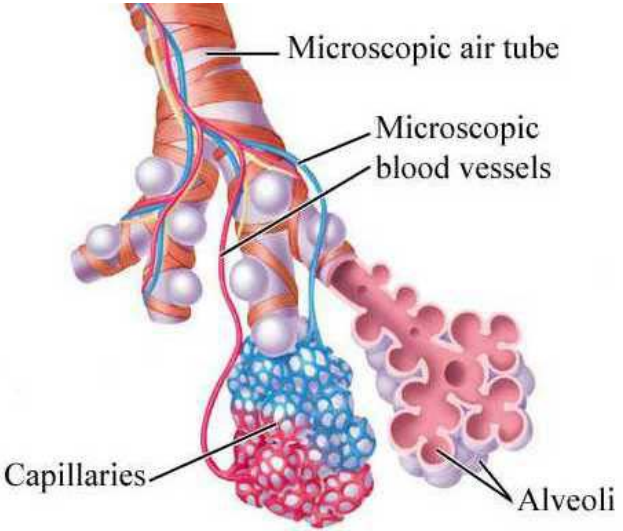
- Congenital heart disease or PH?
- Why is this baby so sick?
- Which therapies will work?

Overview

- Physiology of pulmonary circulation
- Pathophysiology of PH
- Clinical assessment and management
- Future therapies

PRESSURE = FLOW x RESISTANCE





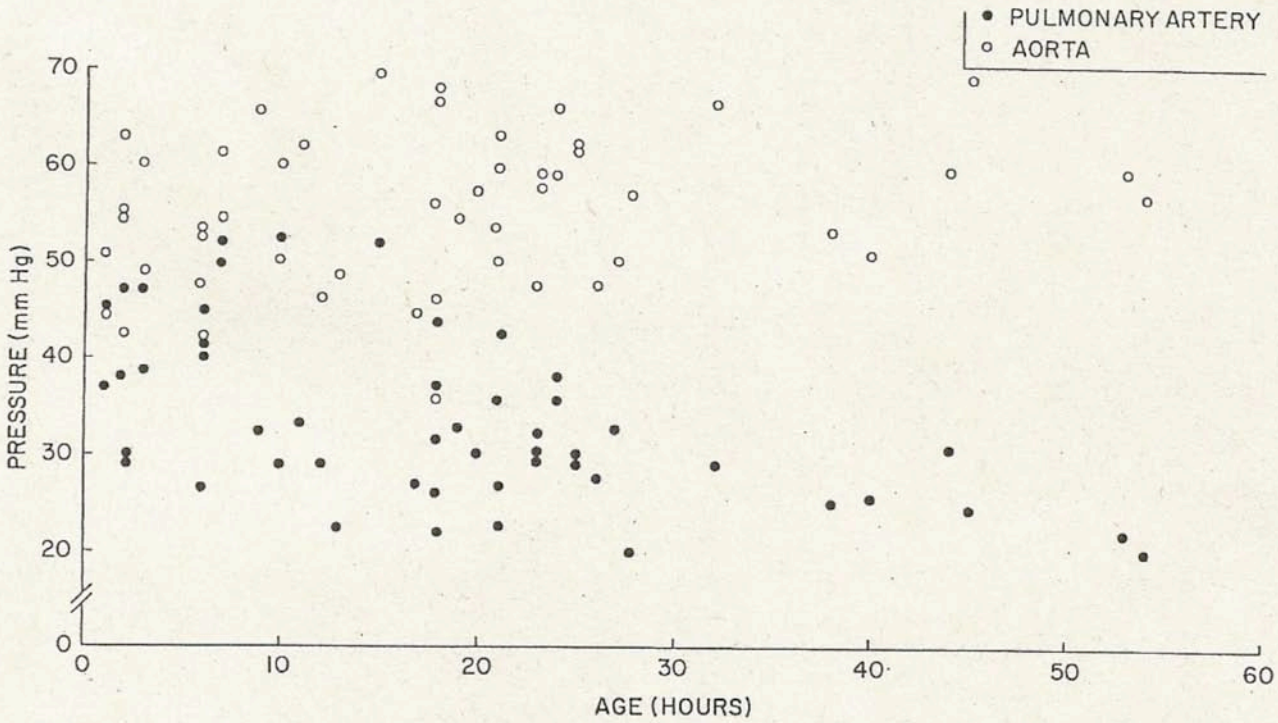
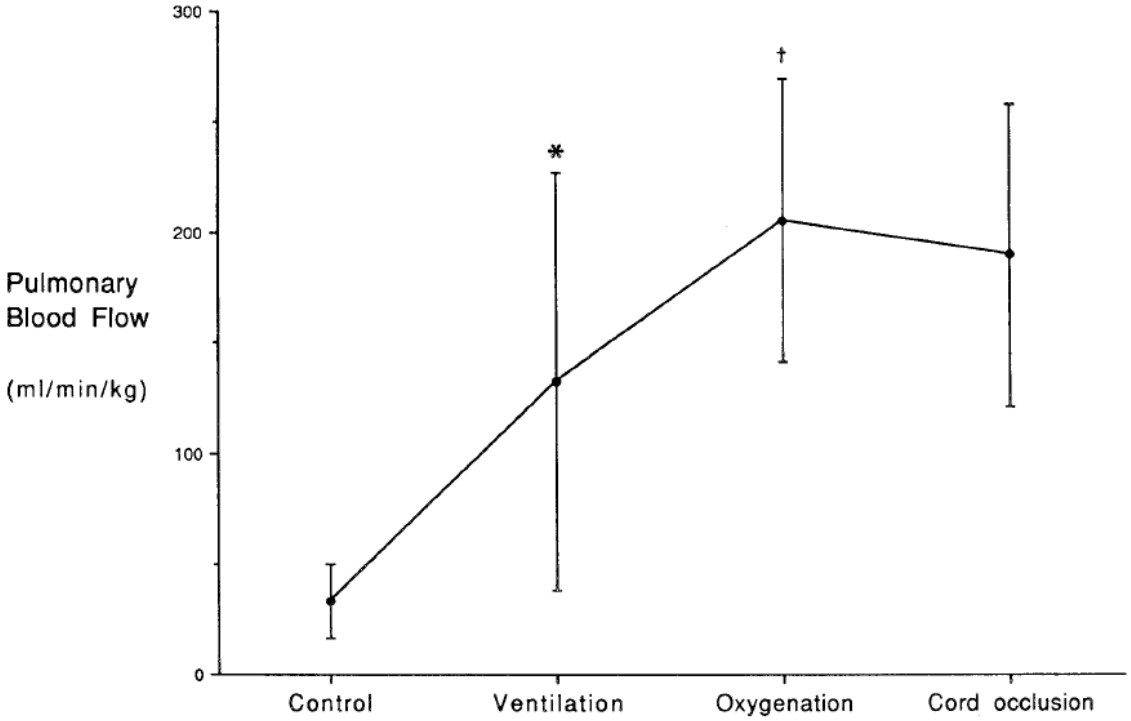


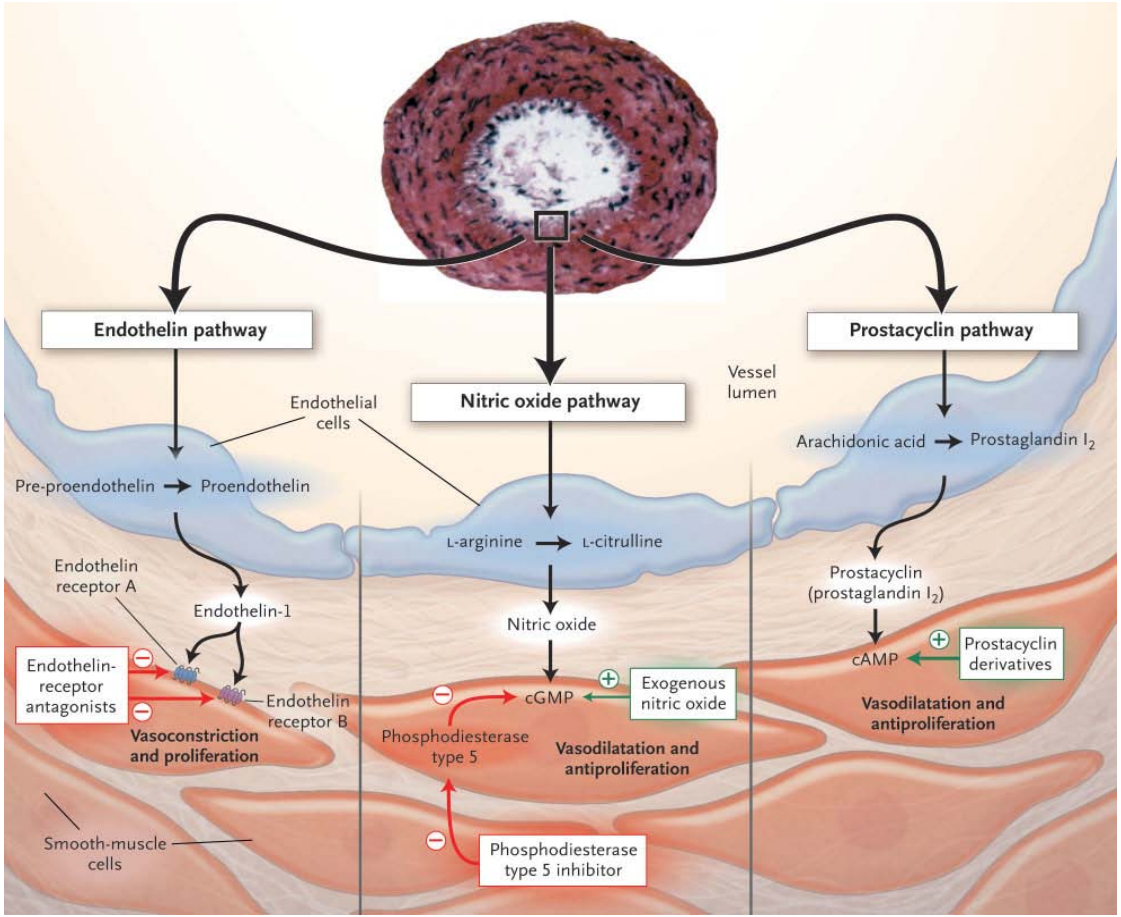
Fig. 1. Correlation of mean pulmonary arterial and systemic pressures with age in 51 normal term infants.

Changes in the Pulmonary Circulation during Birth-Related Events

DAVID F. TEITEL, HARRIET S. IWAMOTO, AND ABRAHAM M. RUDOLPH



Ped Res 1990



Marc Humbert, M.D., Ph.D., Olivier Sitbon, M.D., and Gérald Simonneau, M.D. N Engl J Med 2004;351:1425-36.

$PAP = PBF_{low} \times PV_{RESISTANCE}$

↑PAP = PBFlow x PVRESISTANCE

INCREASED PBF

Left to right shunts
Large AVM

INCREASED PVR

Hyperviscosity

↑PAP = PBF$_{low}$ x PV$_{RESISTANCE}$

INCREASED PBF

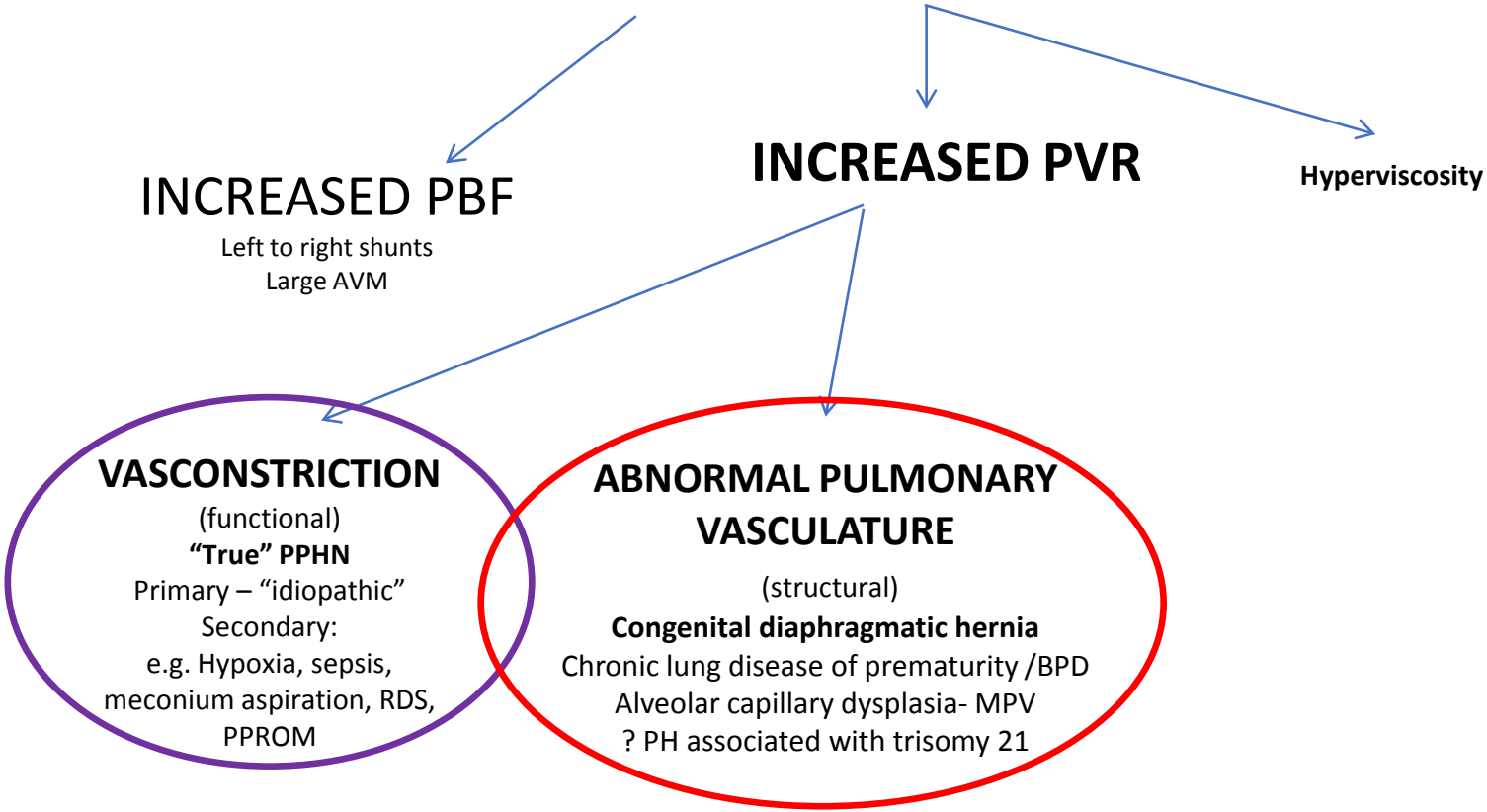
Left to right shunts
Large AVM

INCREASED PVR

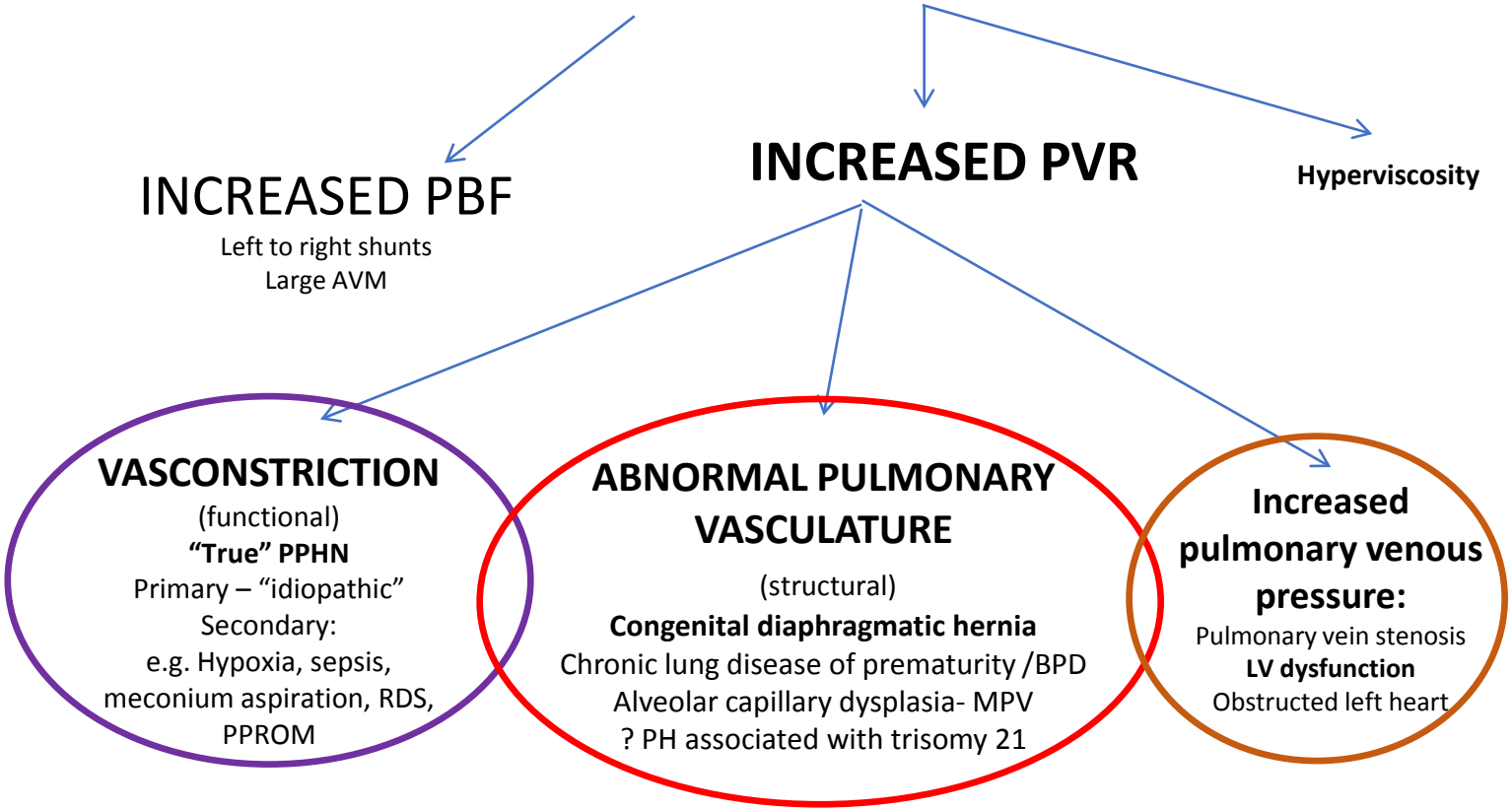
Hyperviscosity

VASCONSTRICTION
(functional)
"True" PPHN
Primary – "idiopathic"
Secondary:
e.g. Hypoxia, sepsis, meconium aspiration, RDS, PPROM

↑PAP = PBFlow x PVRESISTANCE

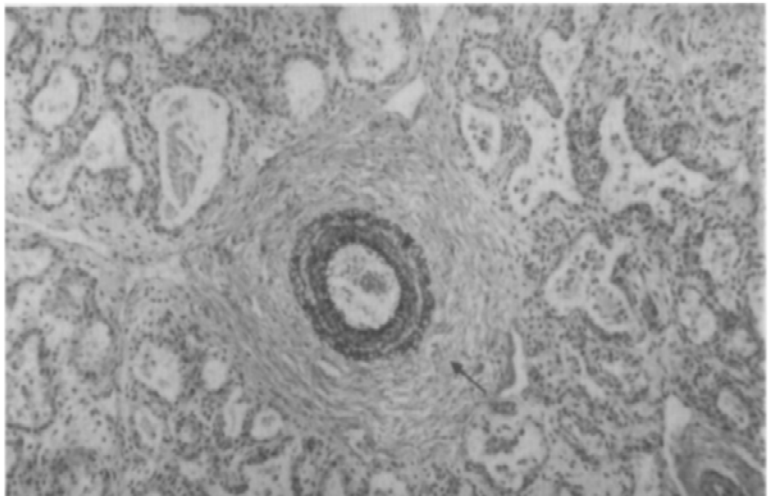


↑PAP = PBFlow x PVRESISTANCE

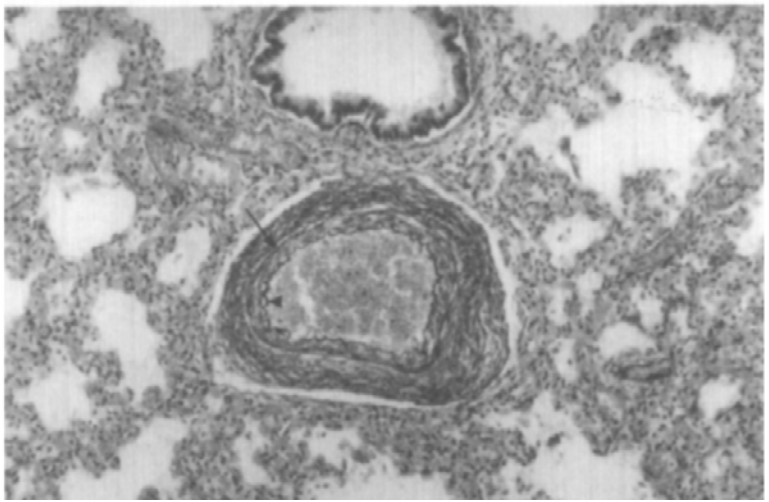


Abnormal pulmonary vascular structure in congenital diaphragmatic hernia (CDH)

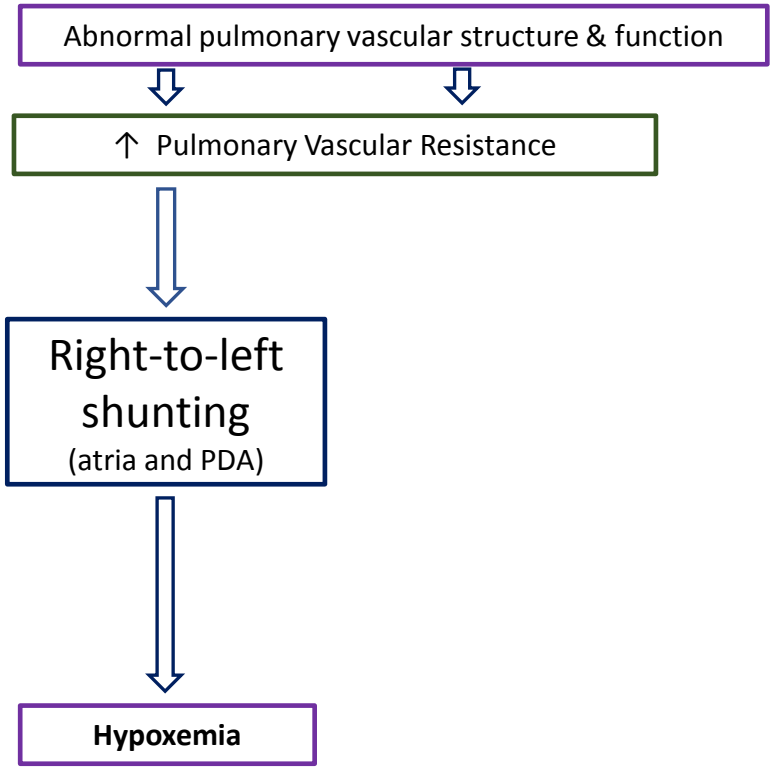
CDH

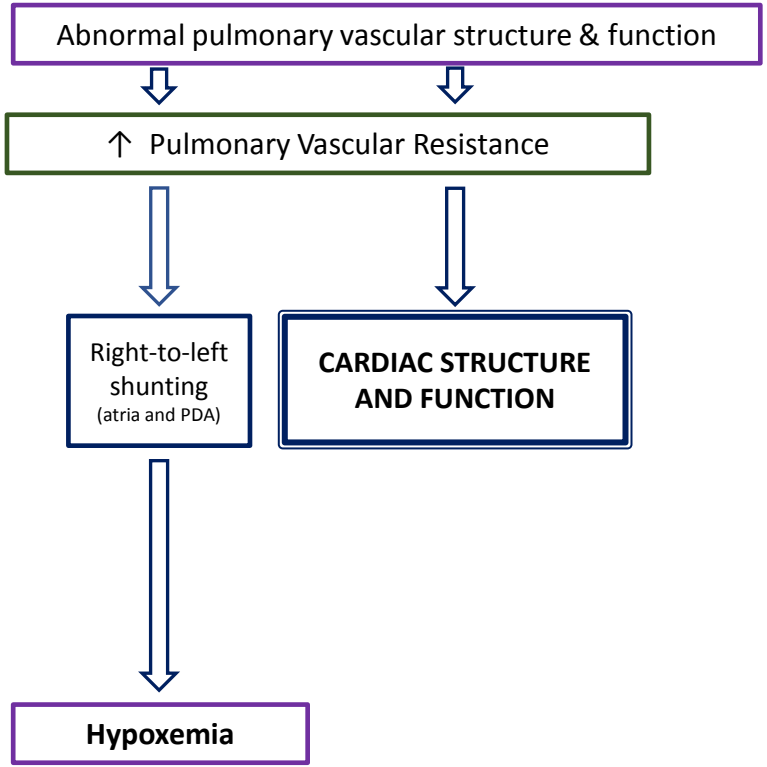


Controls

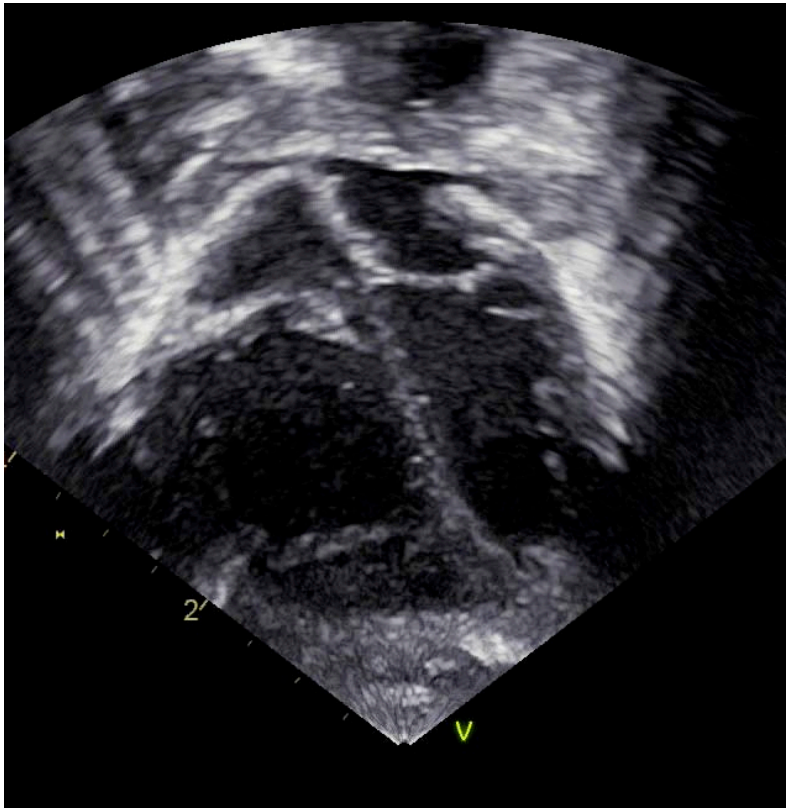


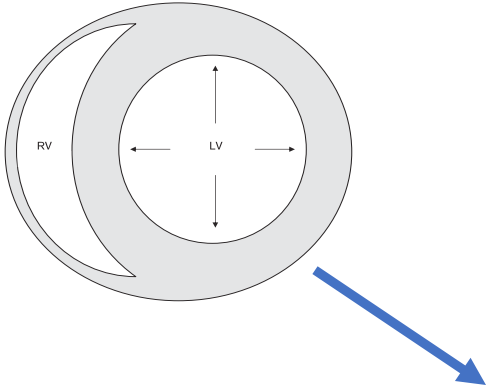
Yamataka and Puri, J Ped Surg 1997


Abnormal pulmonary vascular structure & function
↑ Pulmonary Vascular Resistance
Right-to-left shunting
(atria and PDA)
Hypoxemia

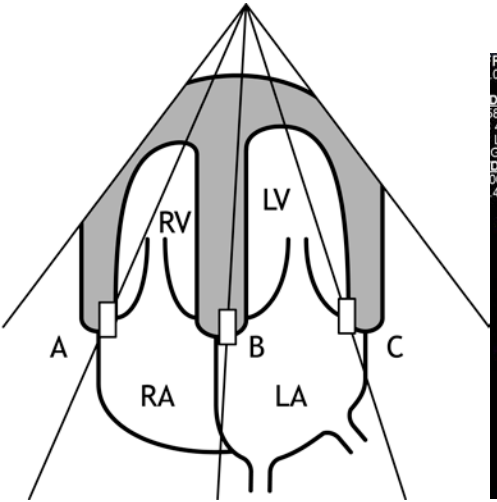

Abnormal pulmonary vascular structure & function
↑ Pulmonary Vascular Resistance
Right-to-left shunting
(atria and PDA)
CARDIAC STRUCTURE AND FUNCTION
Hypoxemia

RV dilatation and hypertrophy in PH

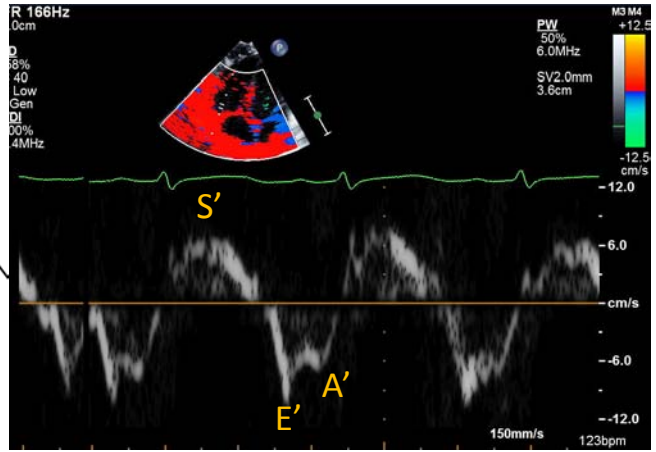




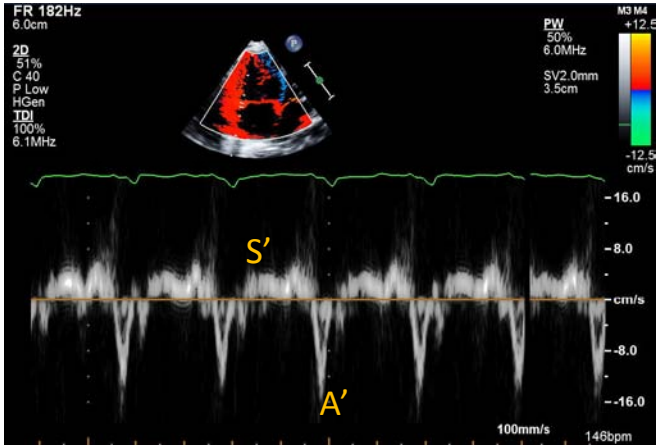
RV Diastolic dysfunction in PH: Tissue Doppler Imaging



Control infant – RV



RV in PH

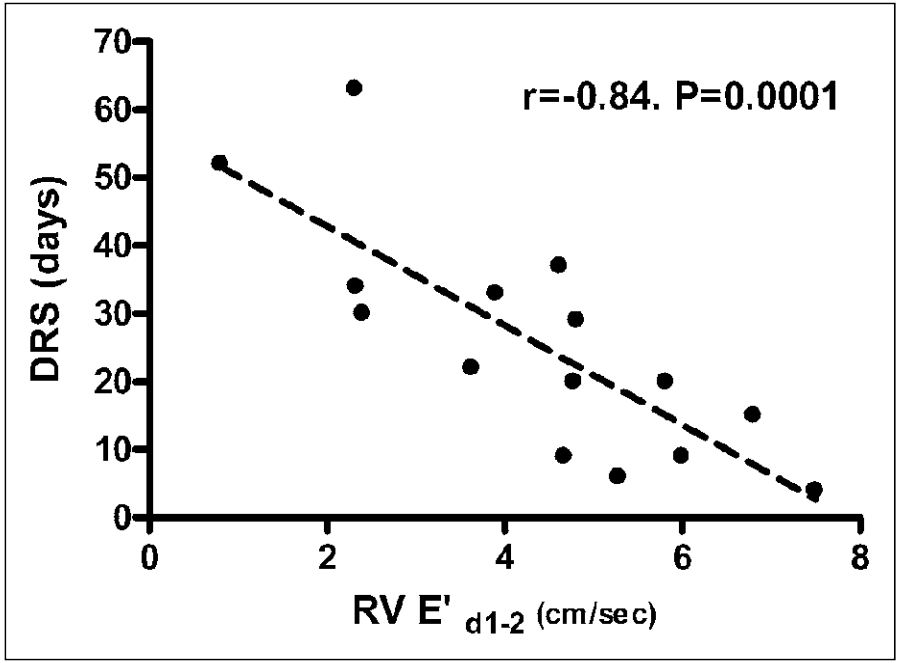


- Reduced systolic velocities
- **Loss of diastolic E' velocity**

Patel et al, Neonatology, 2009

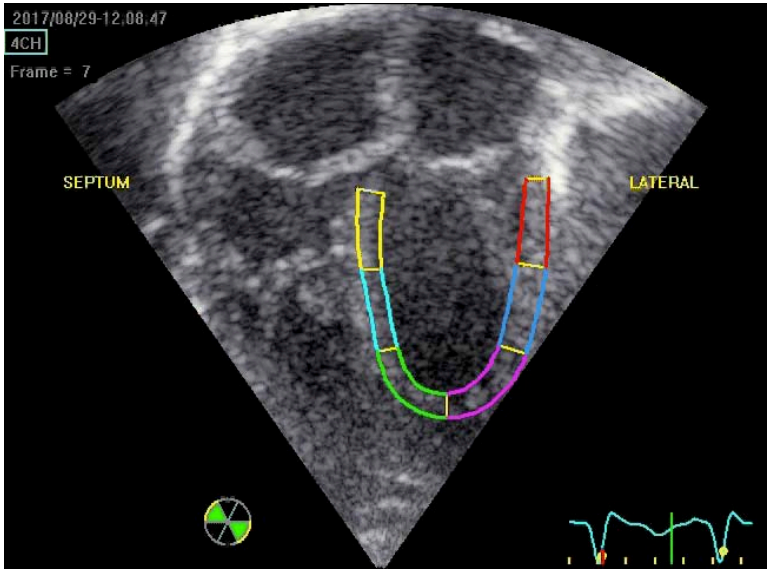
Right Ventricular Diastolic Function Measured by Tissue Doppler Imaging Predicts Early Outcome in Congenital Diaphragmatic Hernia

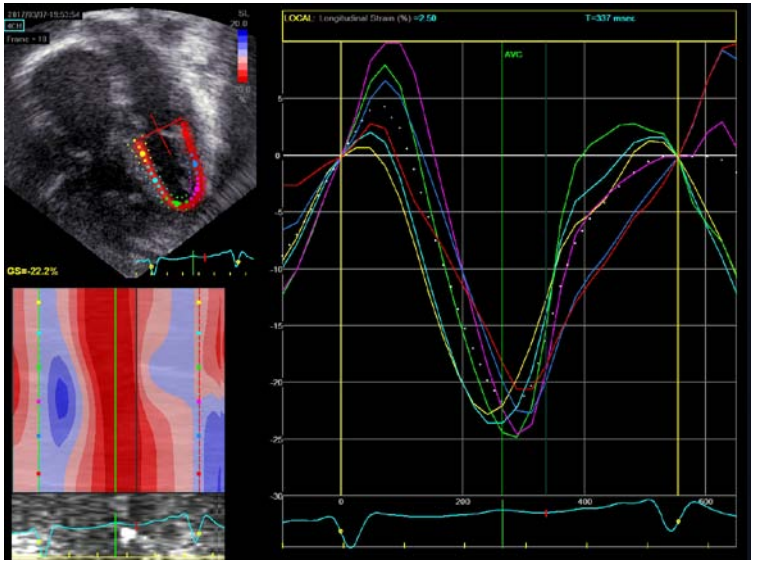
Florian Moenkemeyer, MD; Neil Patel, MD



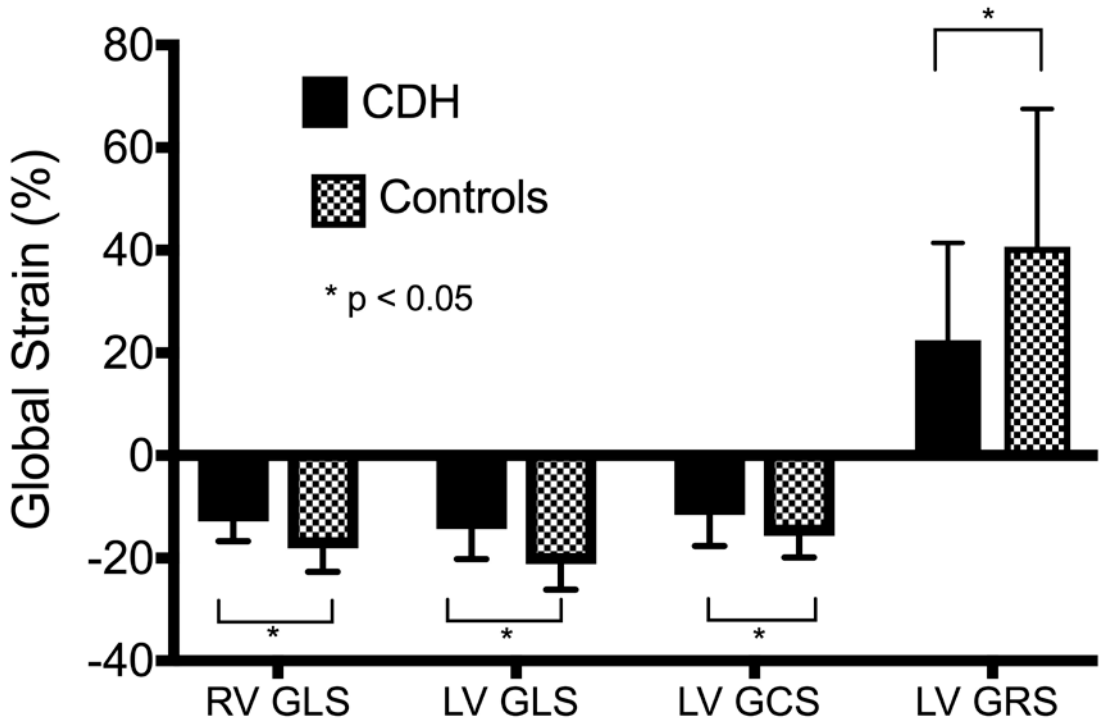
Ped Crit Care Med 2013

LV dysfunction in PH: speckle tracking echocardiography





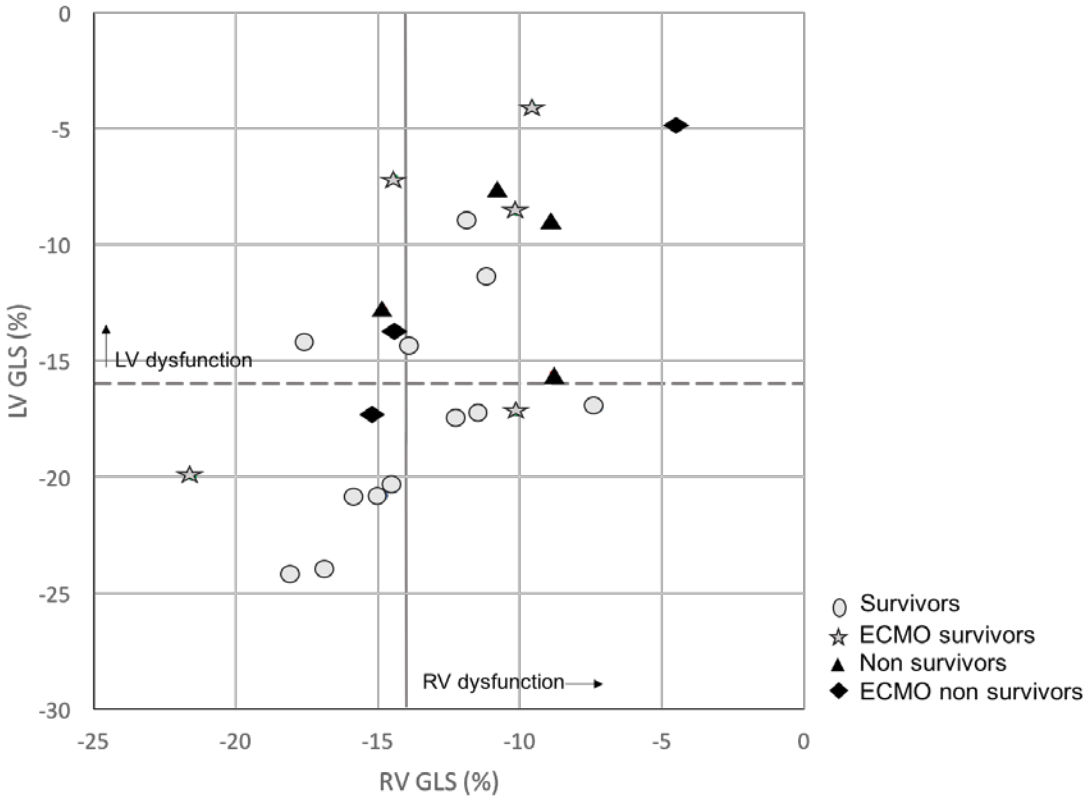
Ventricular strain in the RV and LV in CDH in first 48 hours of life



Patel et al 2018, J Peds 2018

Early Postnatal Ventricular Dysfunction Is Associated with Disease Severity in Patients with Congenital Diaphragmatic Hernia

Neil Patel, MD[1], Anna Claudia Massolo, MD[2], Anshuman Paria, MBBS[1], Emily J. Stenhouse, MBChB[3], Lindsey Hunter, MRCPCH[4], Emma Finlay, BSE[4], and Carl F. Davis, FRCS[5]



Patel et al, J Peds 2018

Why is there LV dysfunction in pulmonary hypertension?

Secondary to RV dysfunction:

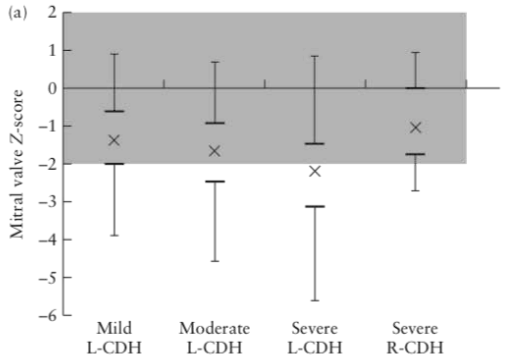
- **Ventricular interdependence:**
  - Shared muscle fibres
  - Shared septum
  - Shared pericardium

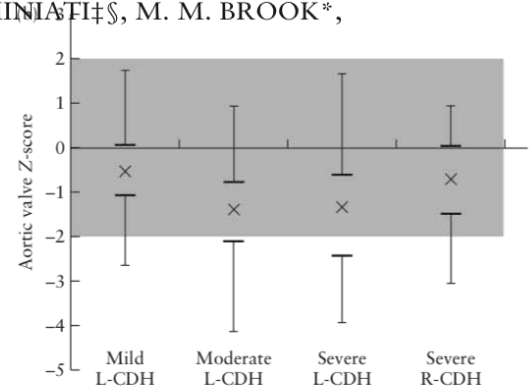
Primary LV dysfunction

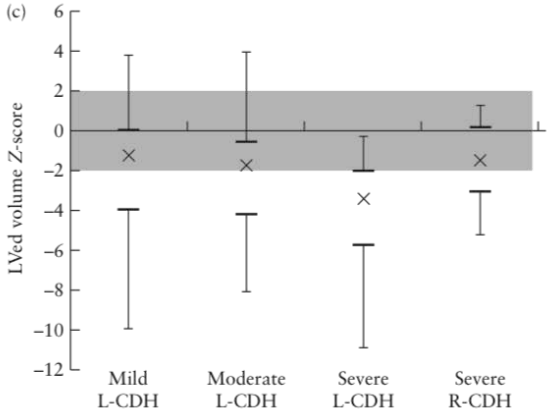
- **Transitioning LV at birth** (acute increase in afterload)
- **Hypoxia, acidosis**
- **Fetal LV hypoplasia (CDH)**

Severe left diaphragmatic hernia limits size of fetal left heart more than does right diaphragmatic hernia

F. A. BYRNE*, R. L. KELLER†, J. MEADOWS*, D. MINIATI‡§, M. M. BROOK*, N. H. SILVERMAN* and A. J. MOON-GRADY*§



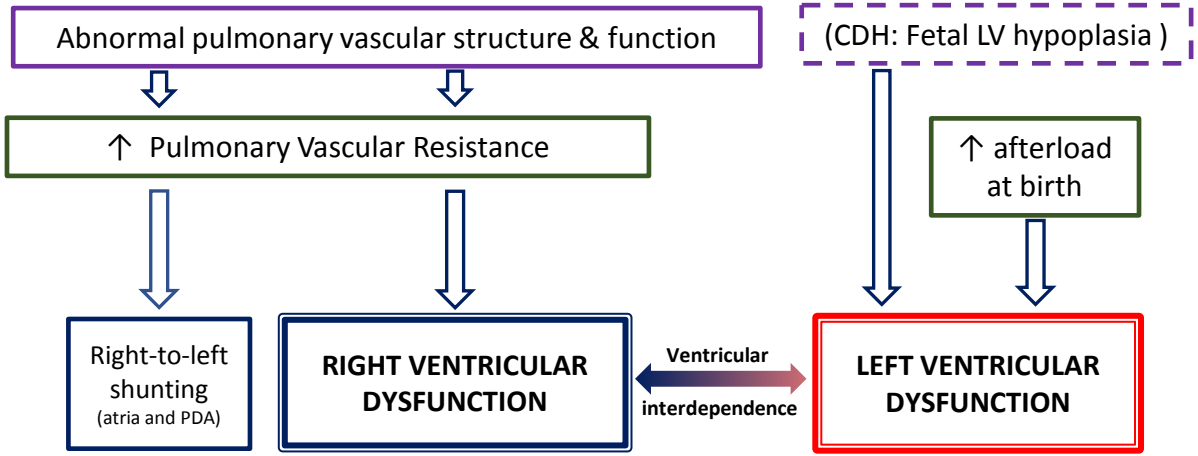


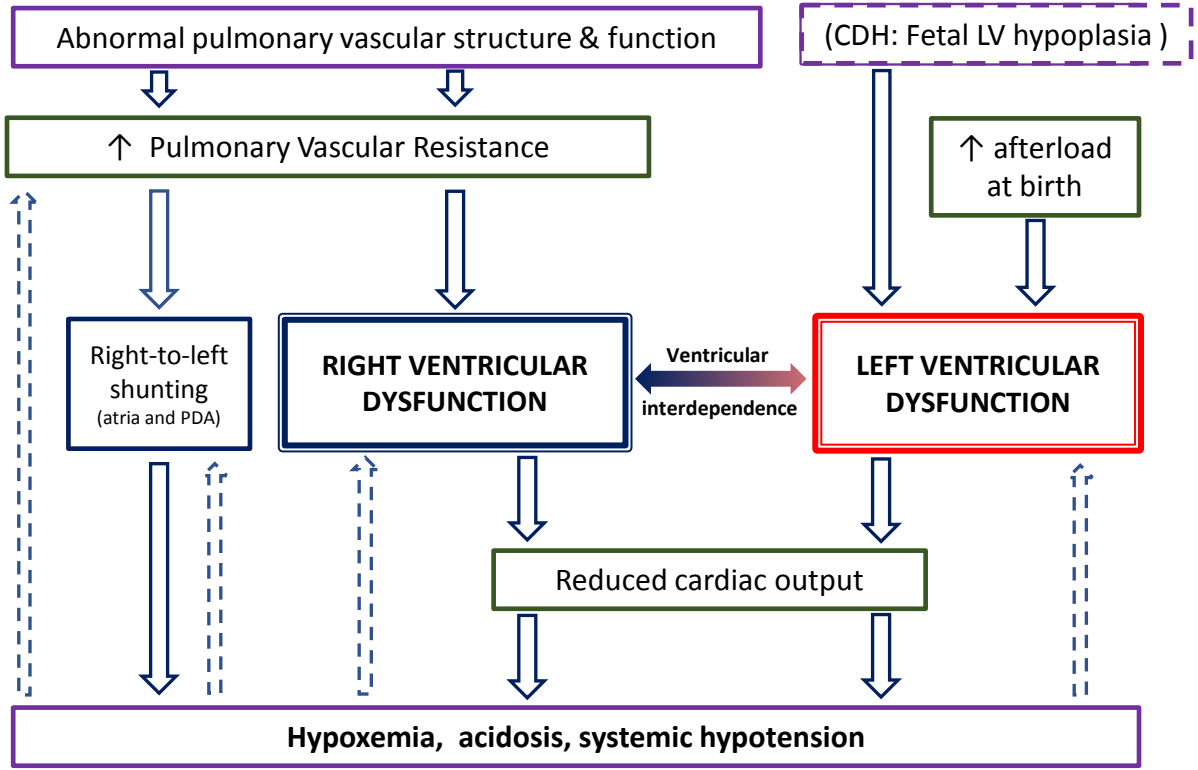


GA: 16-37 weeks
N = 171 L CDH
N = 17 R CDH

Severity based on lung volumes:
Severe: LHR<1, liver up
Moderate: LHR >1
Mild: liver down

Ultrasound Obstet Gynecol 2015; **46**: 688–694


Abnormal pulmonary vascular structure & function
(CDH: Fetal LV hypoplasia)
↑ Pulmonary Vascular Resistance
↑ afterload at birth
Right-to-left shunting (atria and PDA)
RIGHT VENTRICULAR DYSFUNCTION
Ventricular interdependence
LEFT VENTRICULAR DYSFUNCTION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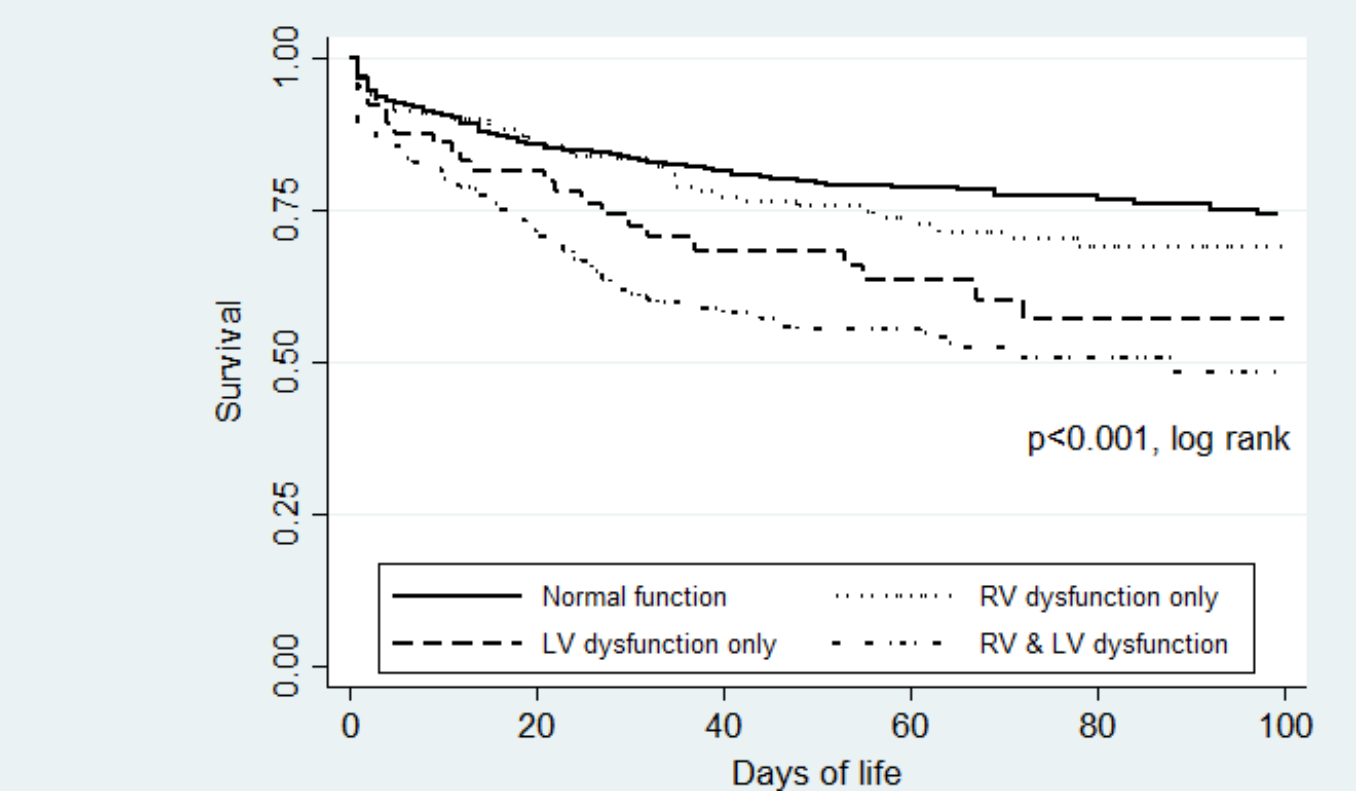
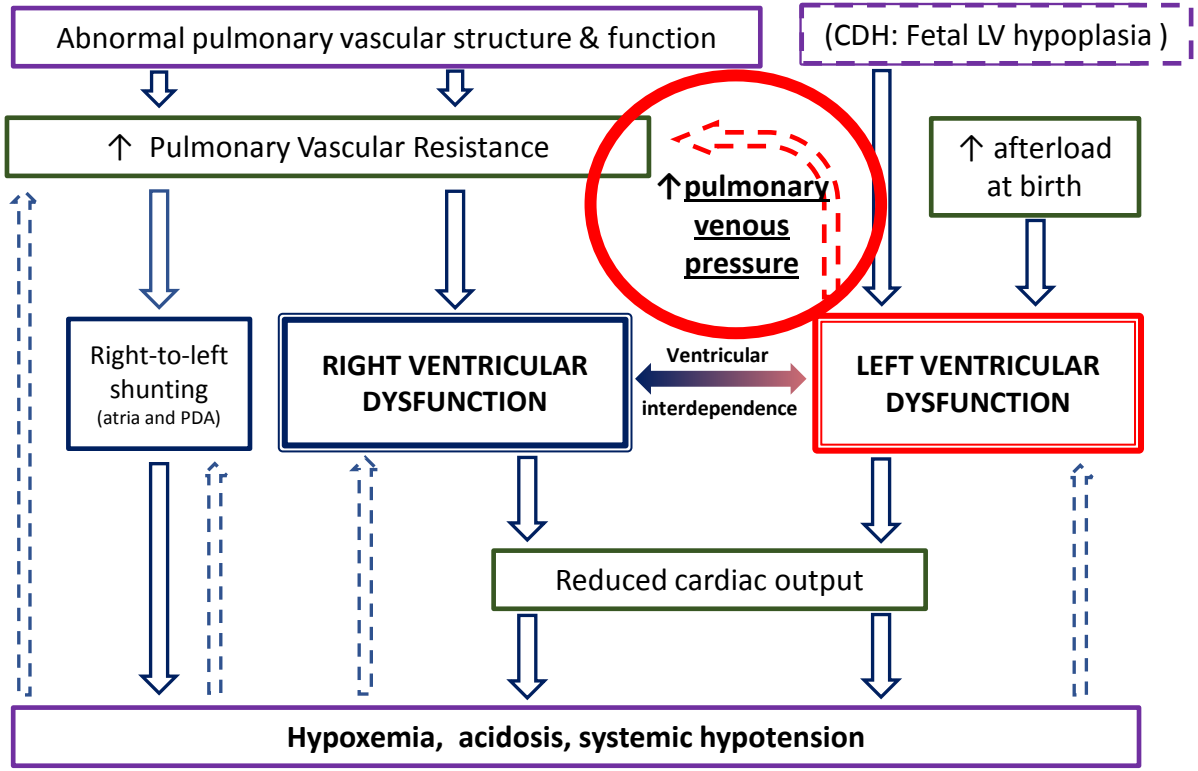
RIGHT VENTRICULAR DYSFUNCTION
Ventricular interdependence
LEFT VENTRICULAR DYSFUNCTION
Reduced cardiac output
Hypoxemia, acidosis, systemic hypotension

Ventricular function and outcome in CDH



Patel et at al, for the CDH Study Group, unpublished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Right-to-left shunting (atria and PDA)
RIGHT VENTRICULAR DYSFUNCTION
Ventricular interdependence
LEFT VENTRICULAR DYSFUNCTION
Reduced cardiac output
Hypoxemia, acidosis, systemic hypotension

A clinical definition of PH in neonates: “clinically significant pulmonary hypertension”

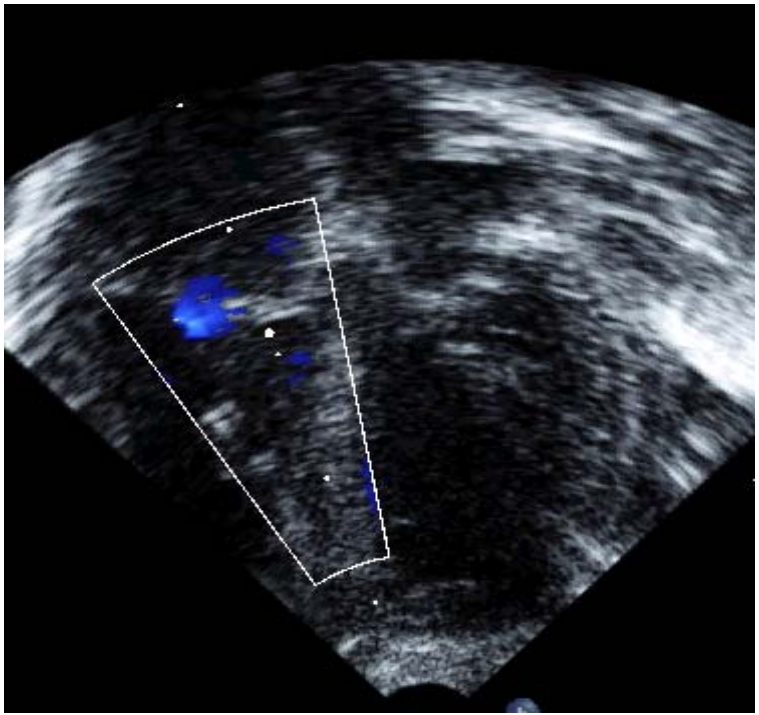
1. **↑ PAP / PVR**
2. **Right-to-left shunting**
3. **Cardiac dysfunction (RV and LV)**

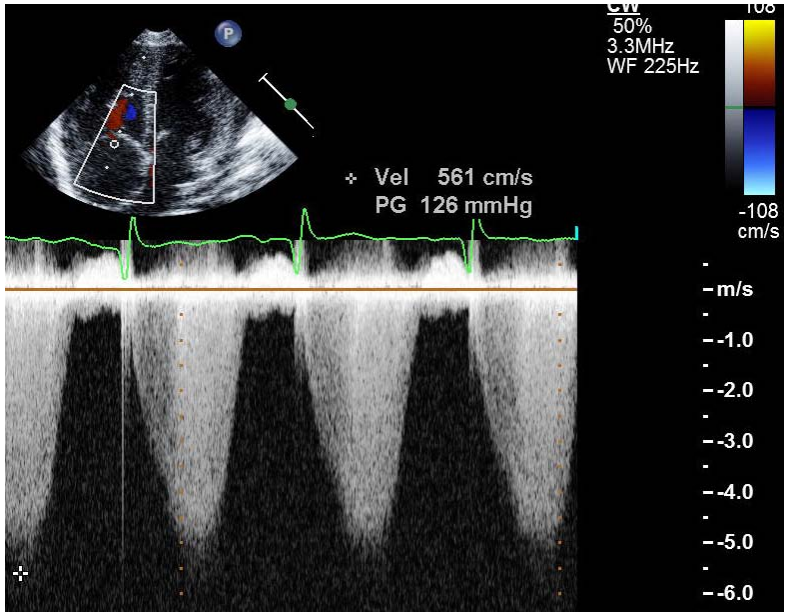
- *Hypoxemia*
- *Acidosis*
- *Systemic hypotension*

Assessment of clinical significance of PH

Oxygenation / oxygen delivery	PVR / PAP	CARDIAC FUNCTION
Arterial oxygen saturations, SaO_2 (post ductal)	Pre-post ductal saturations	Systemic Blood Pressure: pulse pressure
PaO_2	**Echocardiographic assessment:** • Tricuspid regurgitation velocity • PDA shunting pattern • Time to peak velocity in pulmonary artery • Septal shape	**Echocardiographic assessment:** • "Eyeballing" from 2d loops • Quantitative measures: ➢ Tissue Doppler imaging ➢ Speckle tracking echocardiography
Lactate		
Venous oxygen saturation (SVO_2)		

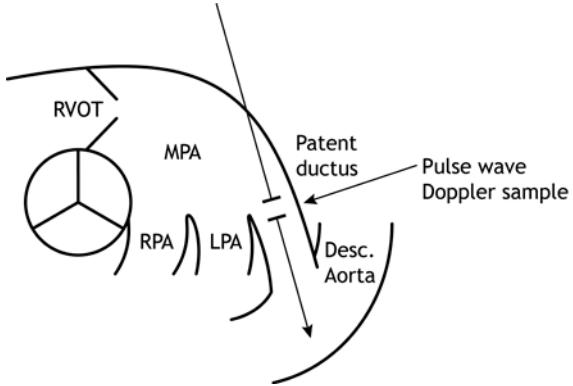
Estimation of RV systolic pressure (PAP) using Tricuspid regurgitation velocity

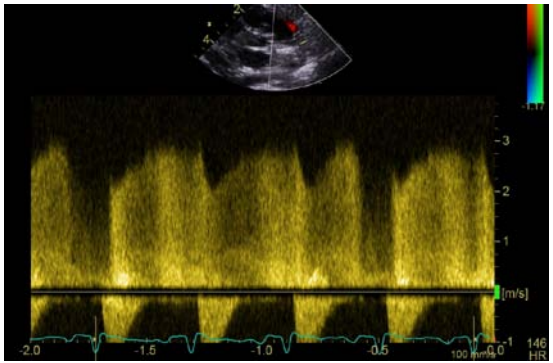




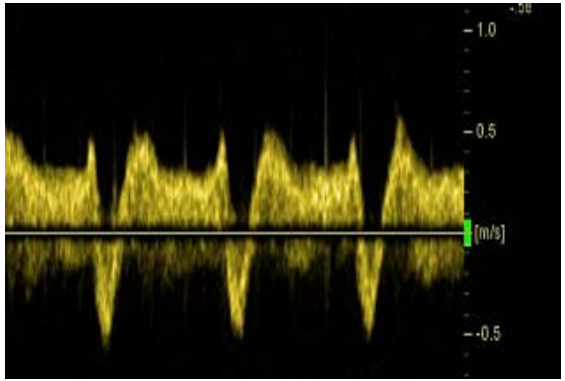
$$\Delta P = 4v^2$$

Use of PDA flow to assess pulmonary artery pressure

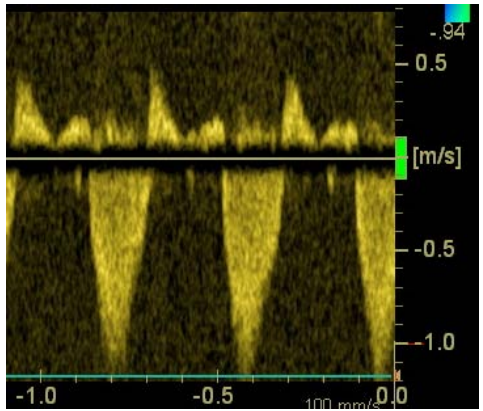




PAP < SBP



PAP = SBP



PAP > SBP

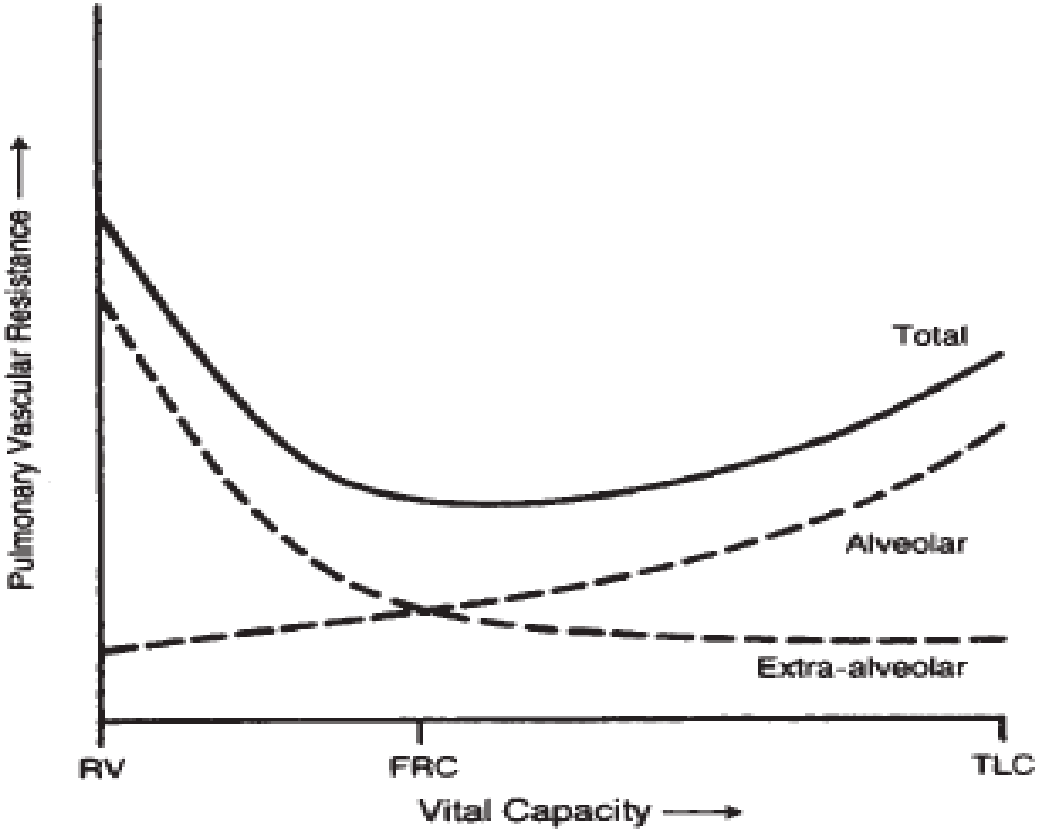
Targeted treatment of “clinically-significant PH”

1. **Treat underlying cause** e.g. hypoxia, sepsis

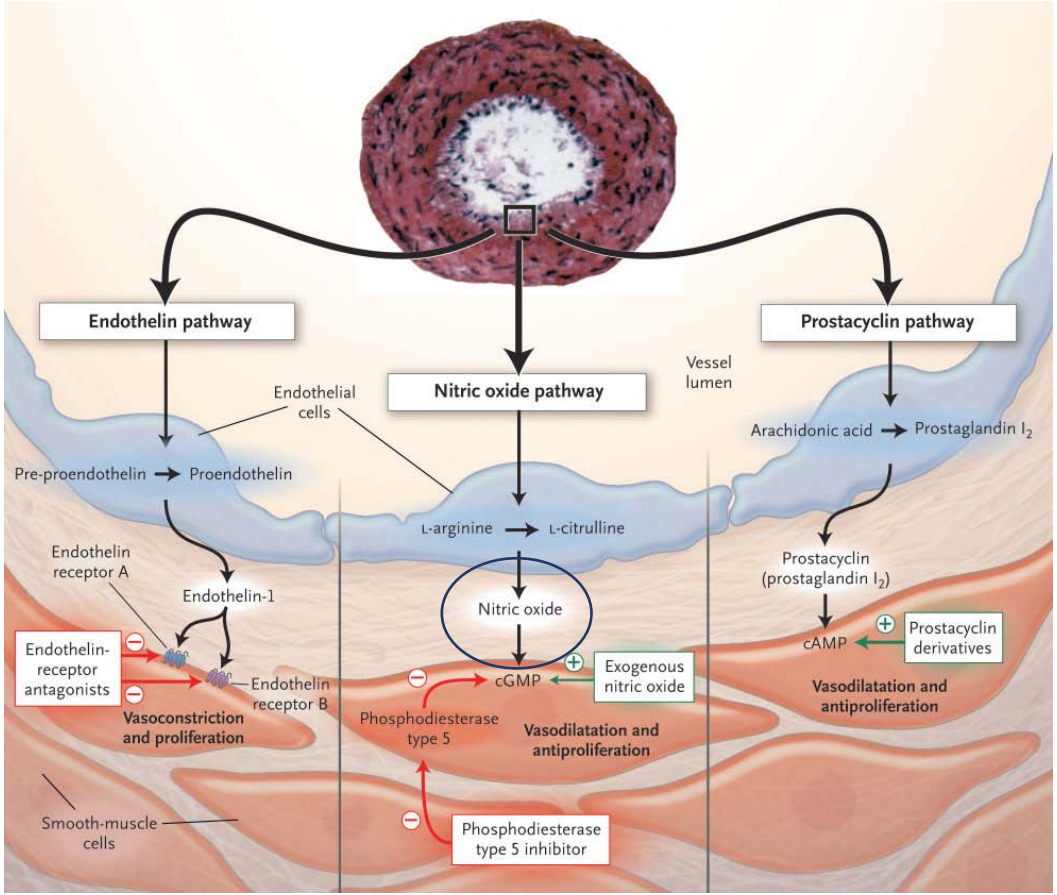
2. **REDUCE PVR** (if elevated)
   I. Optimize sedation, acid base,
   II. Optimize ventilation
   III. Pulmonary vasodilator therapy

3. **Support cardiac function**
   1. Improve systolic and diastolic RV and LV function
   2. Maintain ductus using PGE_1
   3. ECMO

Lung volume and PVR



Targeted Pulmonary vasodilator therapies



Inhaled Nitric Oxide, RCT evidence:

- **Term "PPHN":** Improves oxygenation and **reduces death/ECMO**
- I**n preterm infants**: **no evidence of benefit**, except in **PPROM** (prolonged preterm rupture of membranes)
- **CDH-PH:** Improves oxygenation. **No reduction in death or ECMO**

Inhaled Nitric Oxide Use in Neonates With Congenital Diaphragmatic Hernia

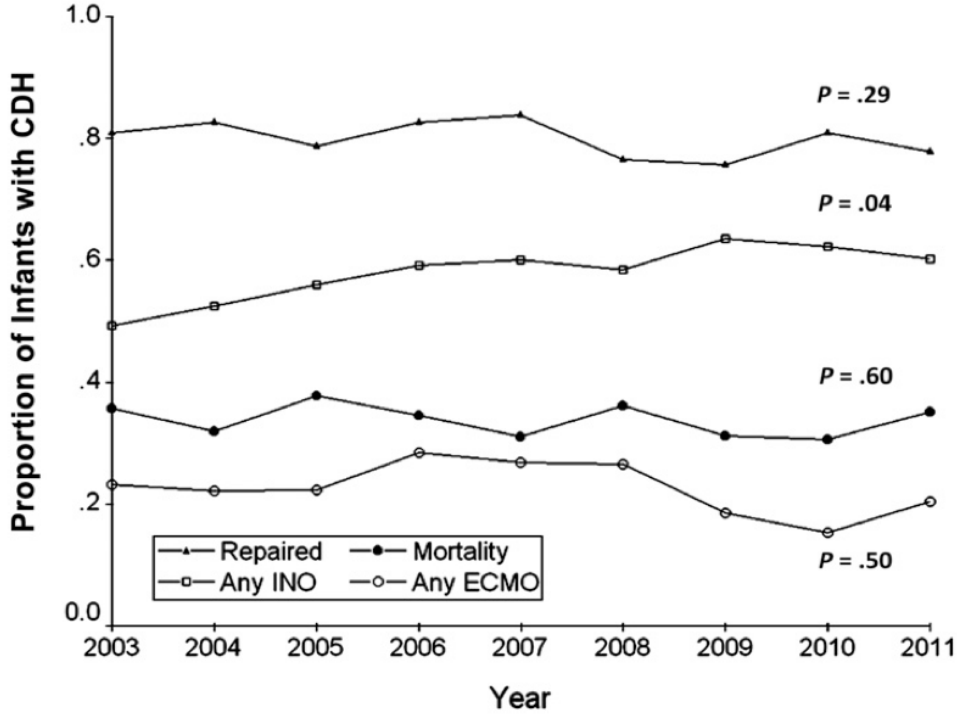


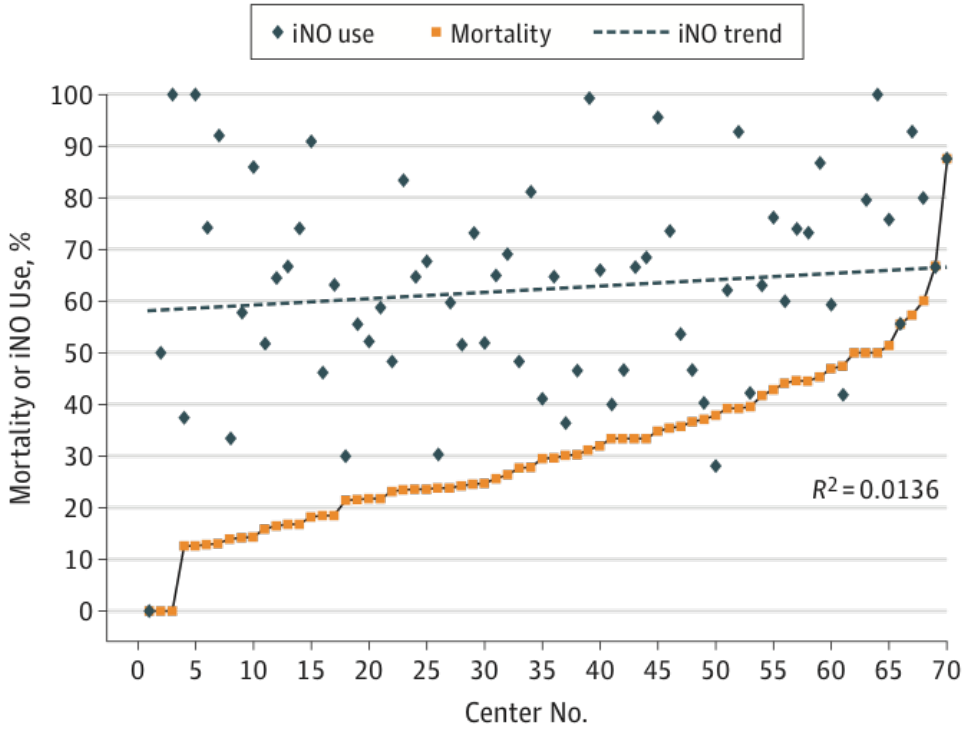
FIGURE 2

Trends in nitric oxide use, ECMO use, rate of repair, and mortality for 1713 infants with CDH at 33 PHIS hospitals, 2003 to 2011.

- 57% received iNO
- Median DAILY charge for iNO was $5753
- Estimated total cohort iNO charges $81 million

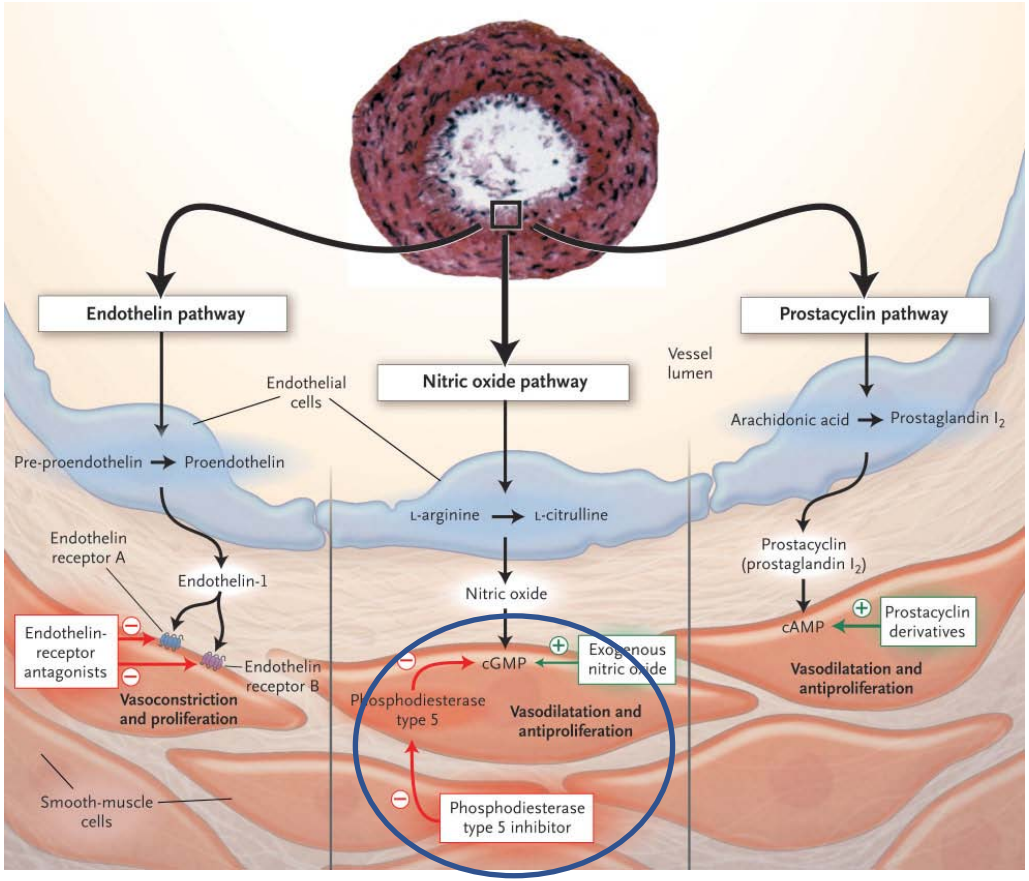
CAMPBELL et al *Pediatrics* 2014;134:e420–e426

Figure 3. Association Between Inhaled Nitric Oxide (iNO) Use, Center, and Mortality $P = .01$ for Trend



Overall, there was a positive association between the trend of iNO use and mortality by center.

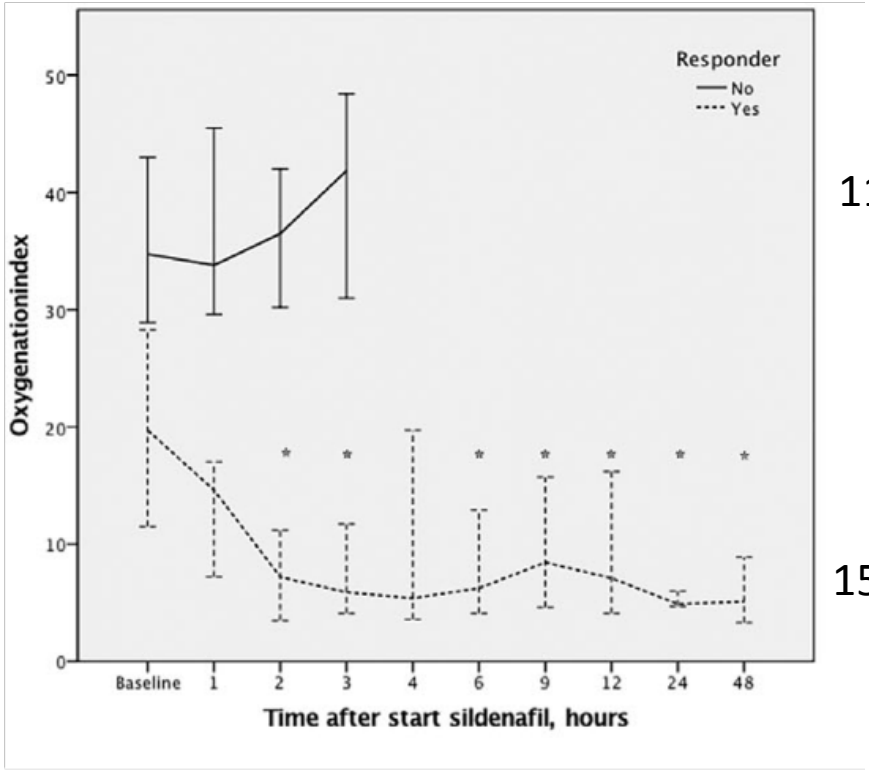
Putnam et al, JAMA Pediatr 2016



Marc Humbert, M.D., Ph.D., Olivier Sitbon, M.D., and Gérald Simonneau, M.D. N Engl J Med 2004;351:1425-36.

Continuous intravenous sildenafil as an early treatment in neonates with congenital diaphragmatic hernia

Florian Kipfmueller MD[1] | Lukas Schroeder MD[1] | Christoph Berg MD[2] | Katrin Heindel MD[1] | Peter Bartmann MD, PhD[1] | Andreas Mueller MD[1]

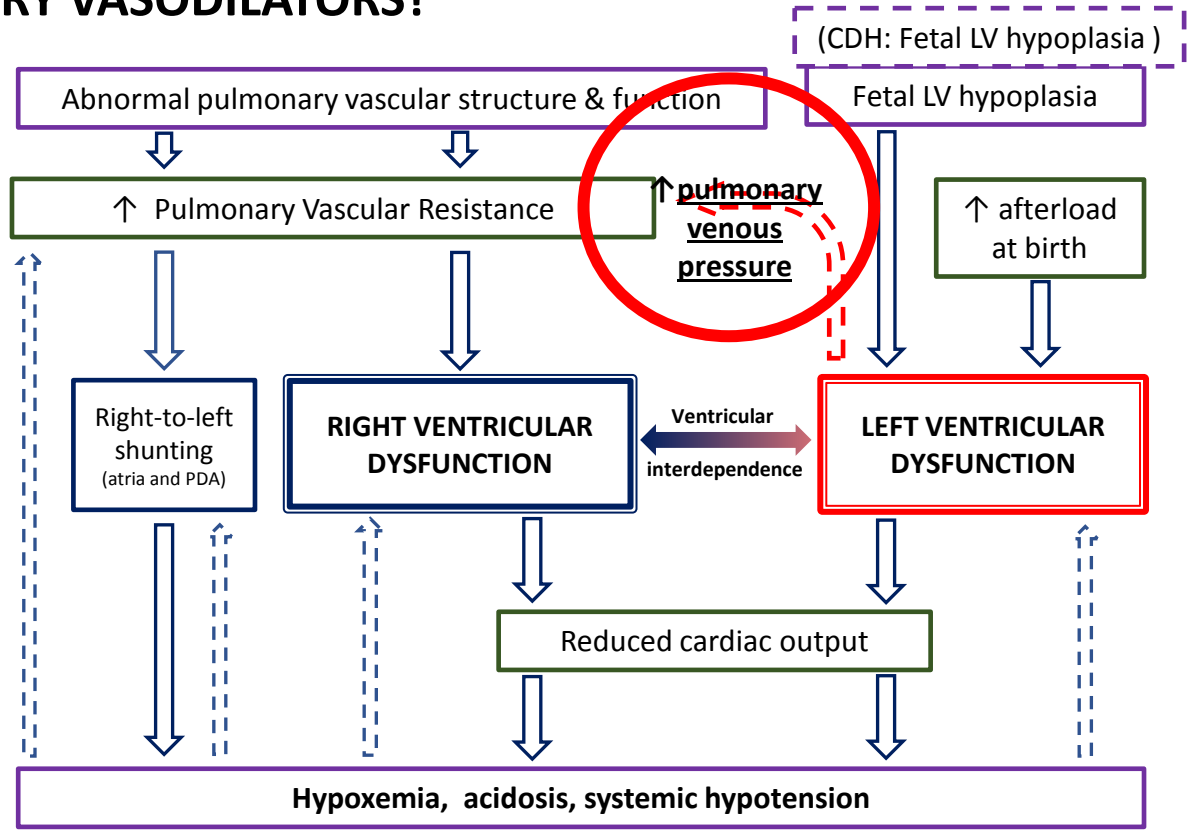


11 responders

15 non-responders

Pediatric Pulmonology 2018

DOES LV DYSFUNCTION ACCOUNT FOR NON-RESPONSE TO PULMONARY VASODILATORS?



CoDiNOS trial (Europe)

Population:

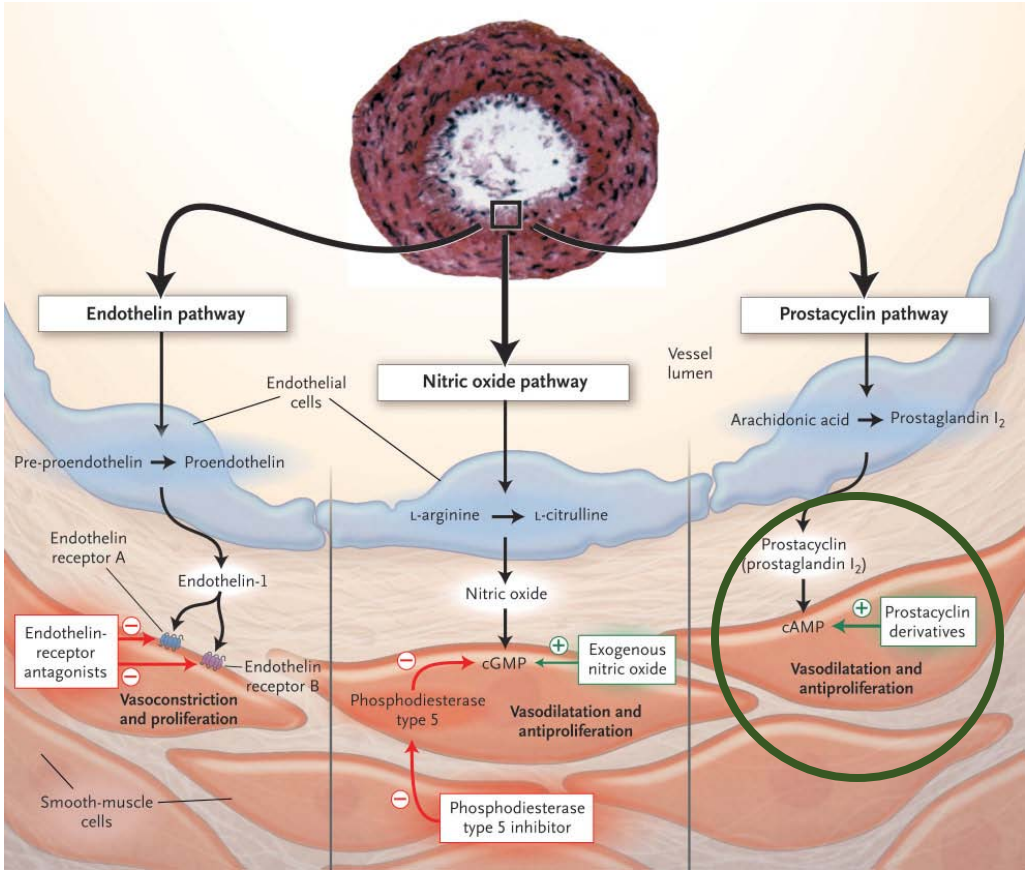
Infants with CDH & PH day 0-7 of life

Intervention:

Randomised to iNO or IV sildenafil

Primary Outcomes:

- Incidence of PH on day 14 of life

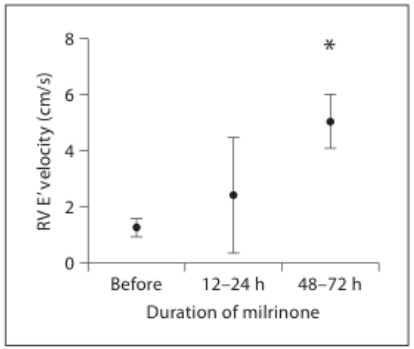


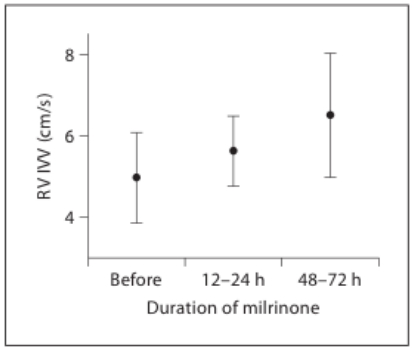
Milrinone
(PDE3 inhibitor)

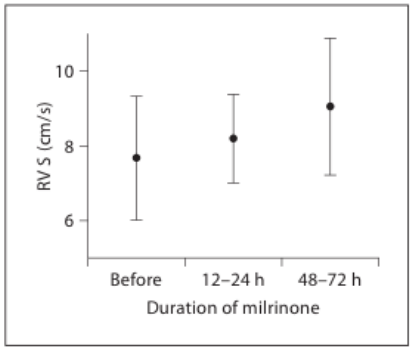
Marc Humbert, M.D., Ph.D., Olivier Sitbon, M.D., and Gérald Simonneau, M.D. N Engl J Med 2004;351:1425-36.

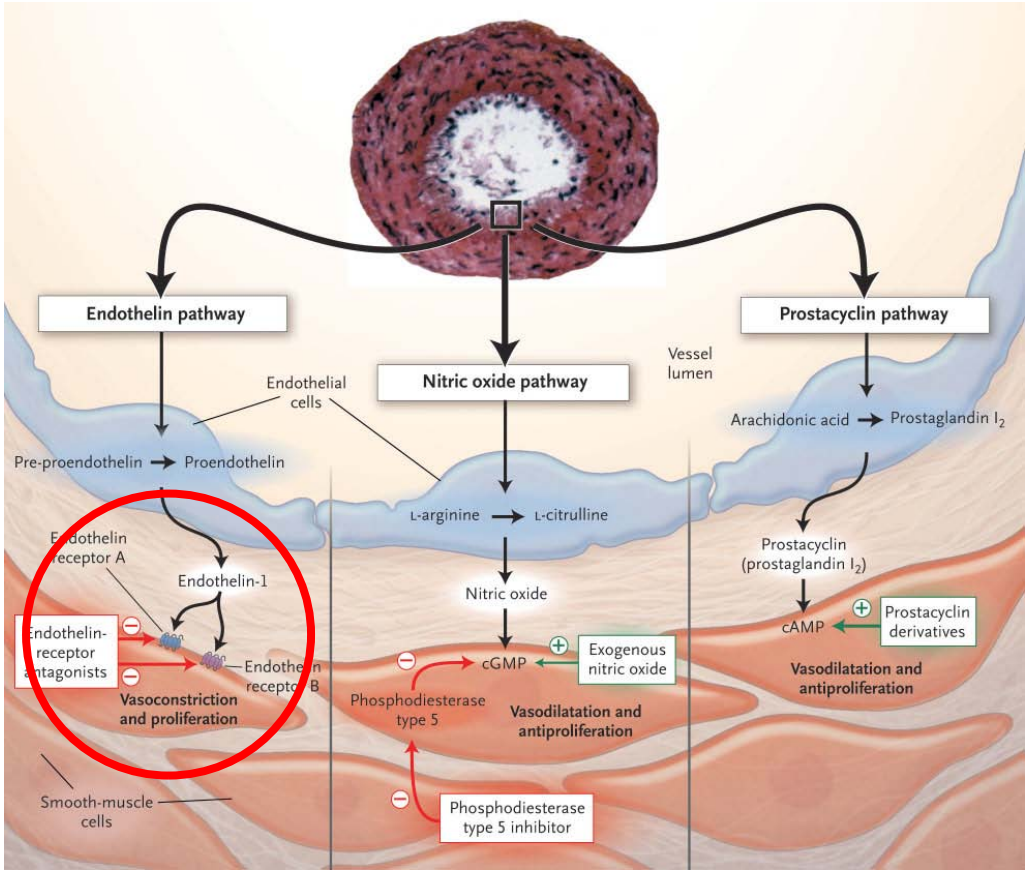
Use of Milrinone to Treat Cardiac Dysfunction in Infants with Pulmonary Hypertension Secondary to Congenital Diaphragmatic Hernia:

		Duration of milrinone therapy		
		pre	12–24 h post	48–72 h post
PDA flow velocity, m/s	left to right	0.8 (1.1)	0.8 (0.4)	0.5 (0.13)
	right to left	1.9 (0.6)	1.3 (0.1)	1.1 (0.3)
FiO_2		0.55 (0.19)	0.47 (0.25)	0.47 (0.43)
Mean airway pressure, cm H_2O		11.8 (4.1)	10.3 (5.8)	8.6 (1.7)
OI		10.6 (5.6)	7.9 (6.2) *	5.1 (2.6)*, **
Mean BP, mm Hg		52.7 (4.3)	53.7 (11.5)	51 (7.3)
Systolic BP, mm Hg		72.6 (6.3)	75 (20.7)	67 (9.9)
Diastolic BP, mm Hg		42.8 (4.2)	43 (6.9)	43 (6.3)



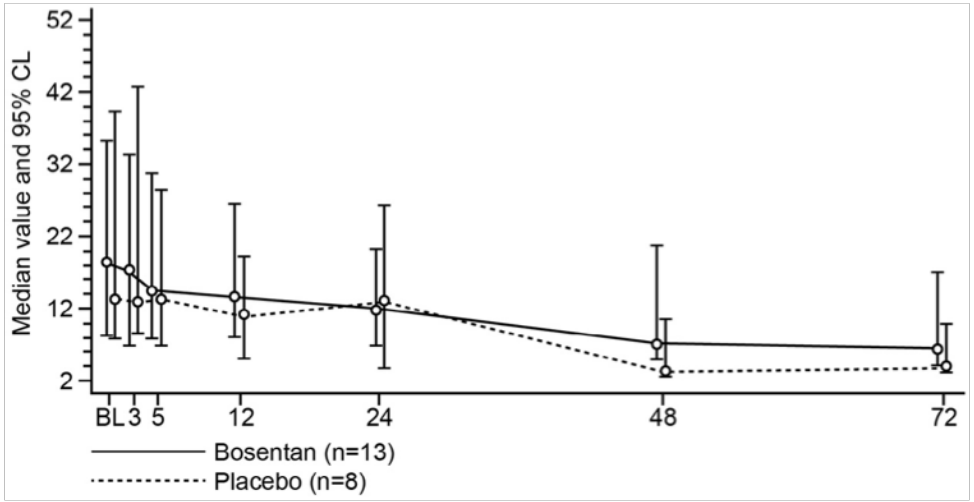






Marc Humbert, M.D., Ph.D., Olivier Sitbon, M.D., and Gérald Simonneau, M.D. N Engl J Med 2004;351:1425-36.

Bosentan as Adjunctive Therapy for Persistent Pulmonary Hypertension of the Newborn: Results of the Randomized Multicenter Placebo-Controlled Exploratory Trial



n=13

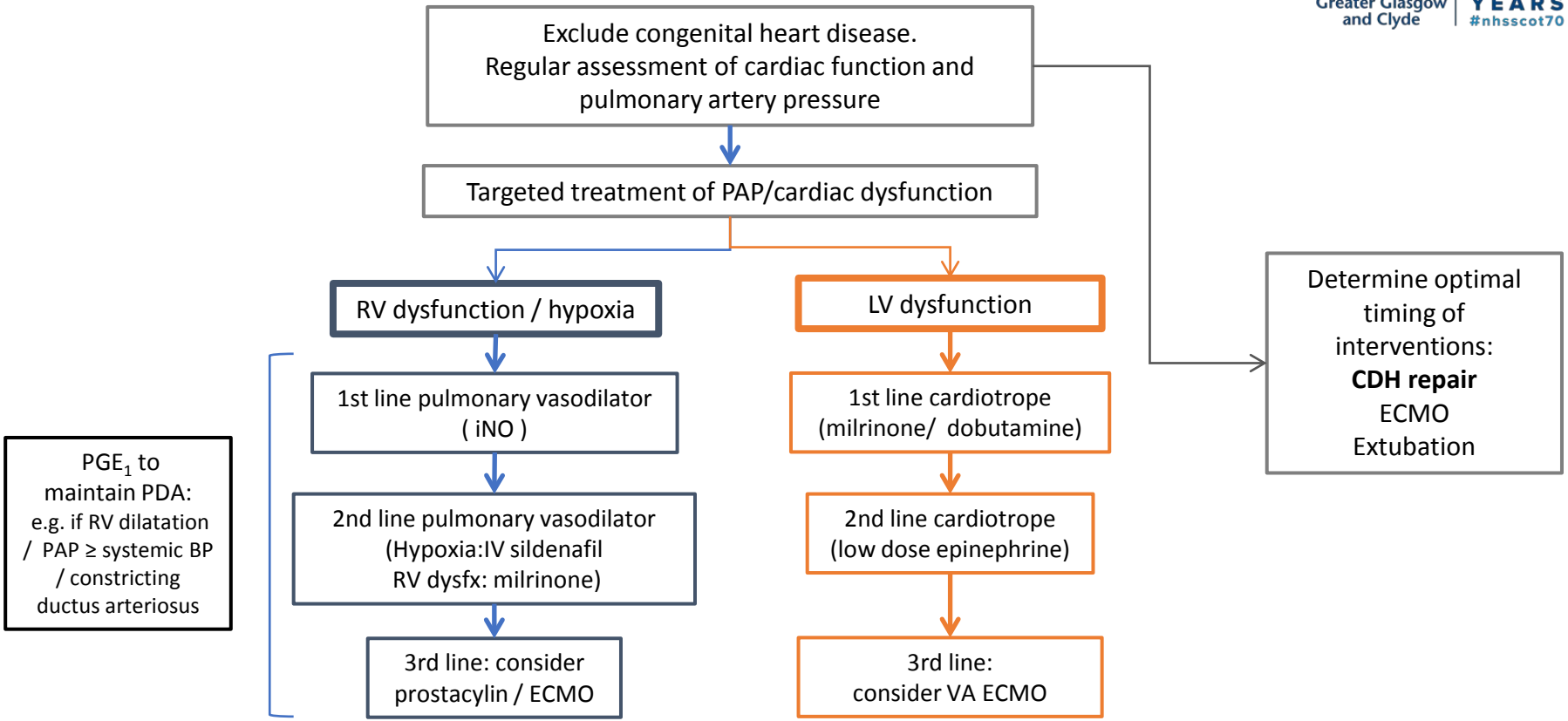
Figure 4. OI (median, 95% CI) during the first 72 hours of trial treatment. No difference was observed between the bosentan and placebo groups. *Not all patients had complete data available for all time points. *BL*, baseline.

Steinhorn et al, (Future-4 Study), J Peds 2016

Prostaglandin E1

- Maintains PDA as “blow-off valve” for pressure-loaded RV
- May act as pulmonary vasodilator
- Use early to maintain PDA if:
    1. *RV dilated / dysfunctional and..*
    2. *PAP = or > systemic BP and..*
    3. *PDA closing or closed*

Targeted therapy of PAP and cardiac dysfunction



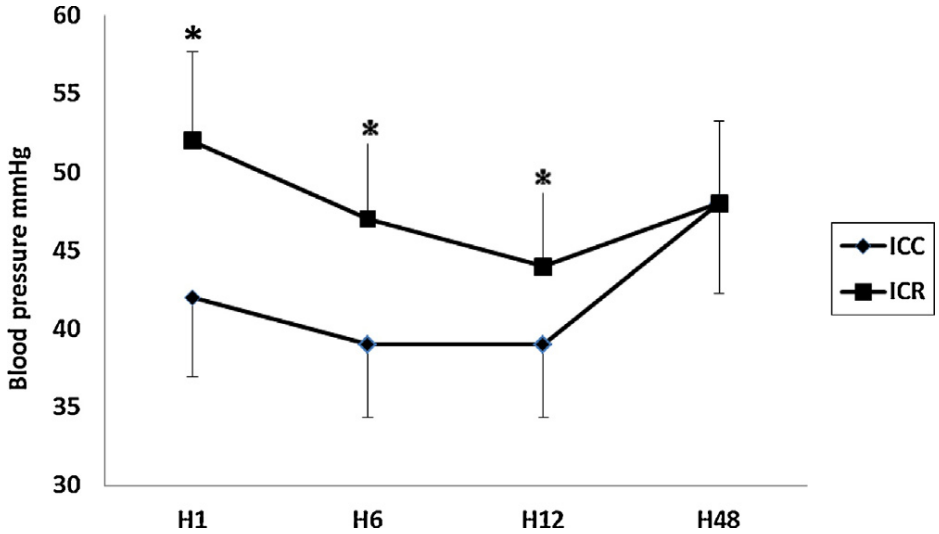
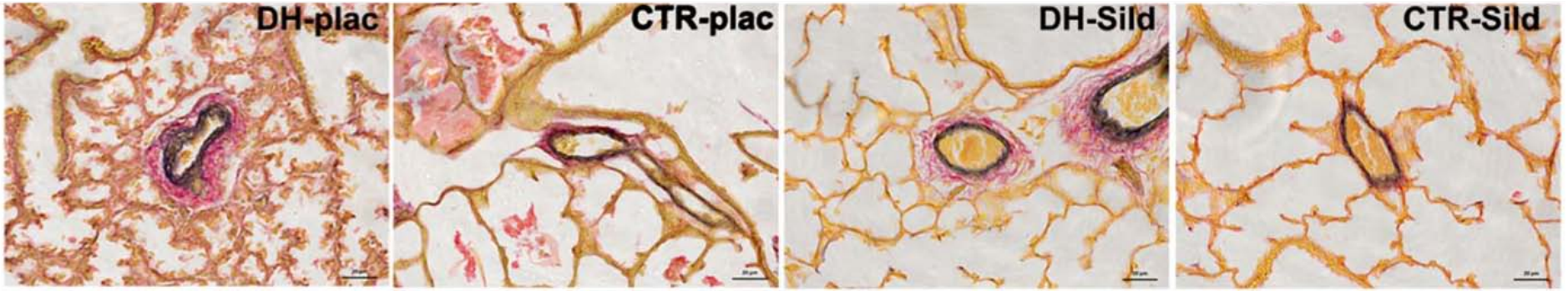


Fig. 2. Mean ± SD change in blood pressure (mmHg) after birth in immediate cord clamping (ICC) and intact cord resuscitation (ICR) groups. * $p < 0.05$ for comparison between groups.

Transplacental sildenafil rescues lung abnormalities in the rabbit model of diaphragmatic hernia



Russo FM, *et al*. *Thorax* 2016;**71**:517–525.

The International Congenital Diaphragmatic Hernia Symposium

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