NHS Greater Glasgow and Clyde | 70 YEARS #nhsscot70

Pulmonary Hypertension and Cardiac Dysfunction in Congenital Diaphragmatic Hernia: Knowns and unknowns

Neil Patel MD

Neonatologist

Royal Hospital for Children

Glasgow, UK

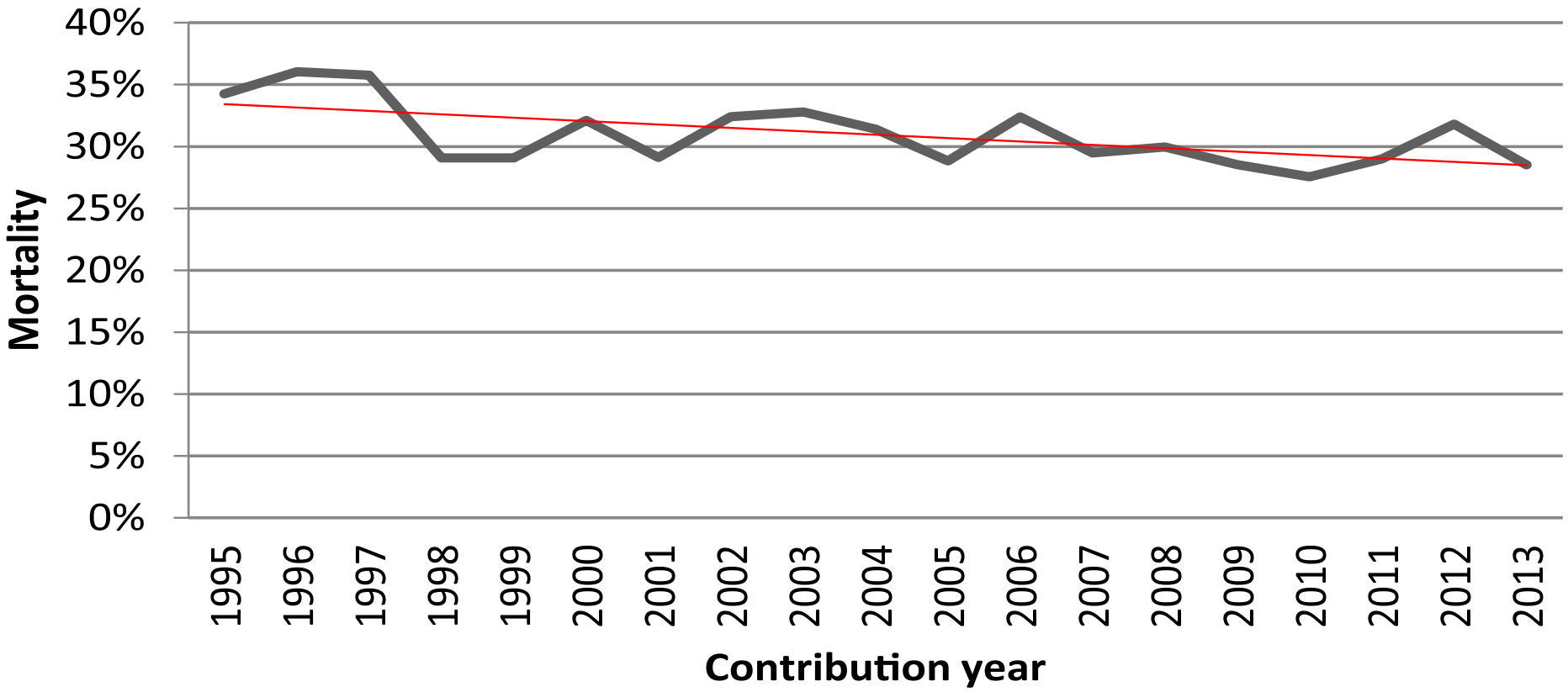


Fig. 1. Congenital Diaphragmatic Hernia Study Group overall mortality by year.

M.T. Harting, K.P. Lally / Seminars in Fetal & Neonatal Medicine 19 (2014) 370–375

Pulmonary hypoplasia

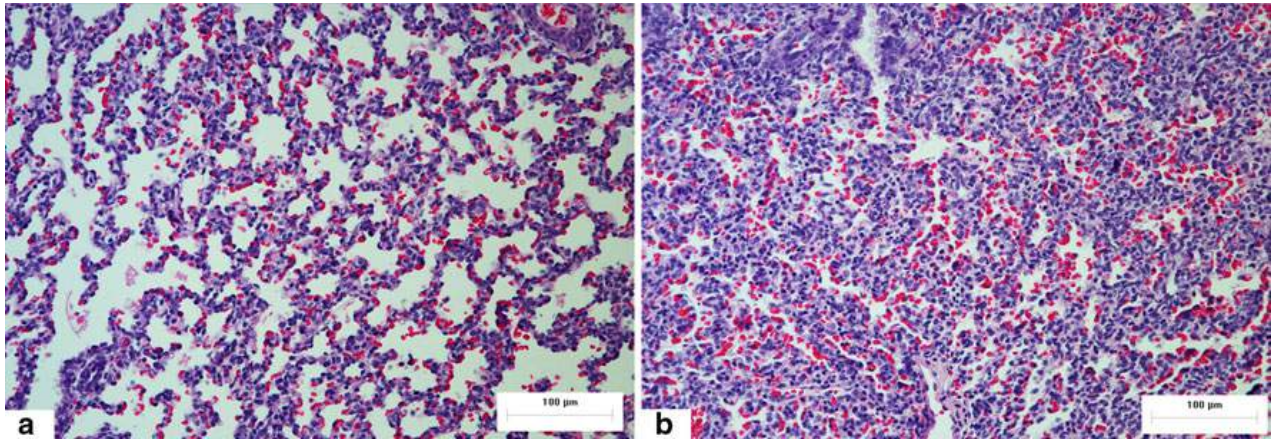
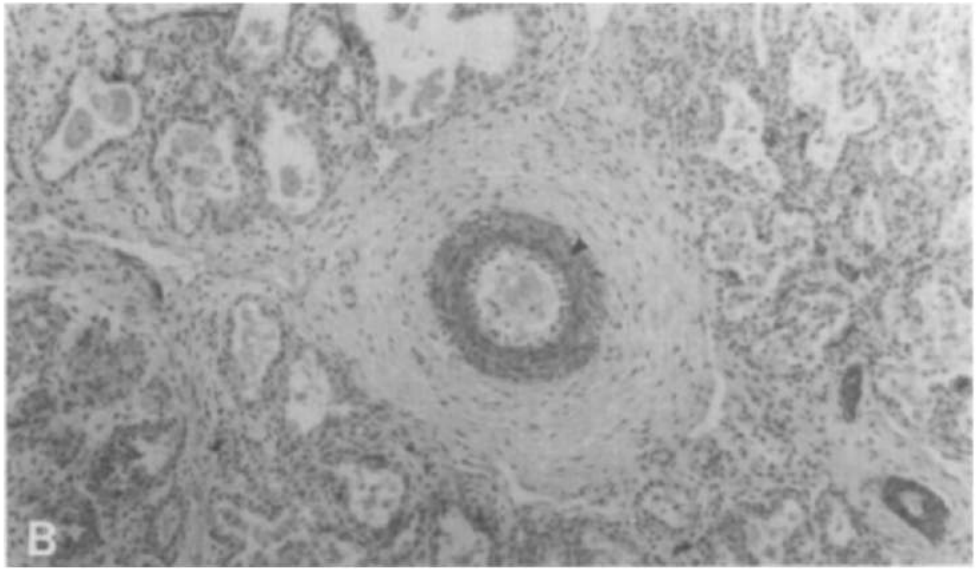


Fig. 2 **a** Lung of control group. **b** Lung with CDH. The histology showed decrease in airspace with pulmonary hypoplasia in CDH group

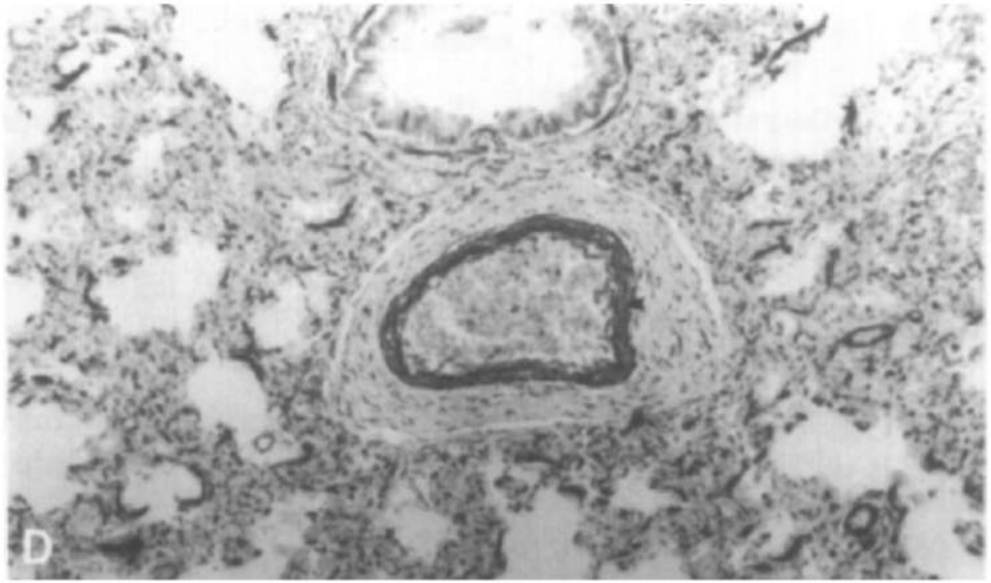
Schmidt et al 2012

Abnormal pulmonary vasculature in CDH

CDH



Control



Yamataka and Puri, J Ped Surg 32 (3), 1997, 387-390

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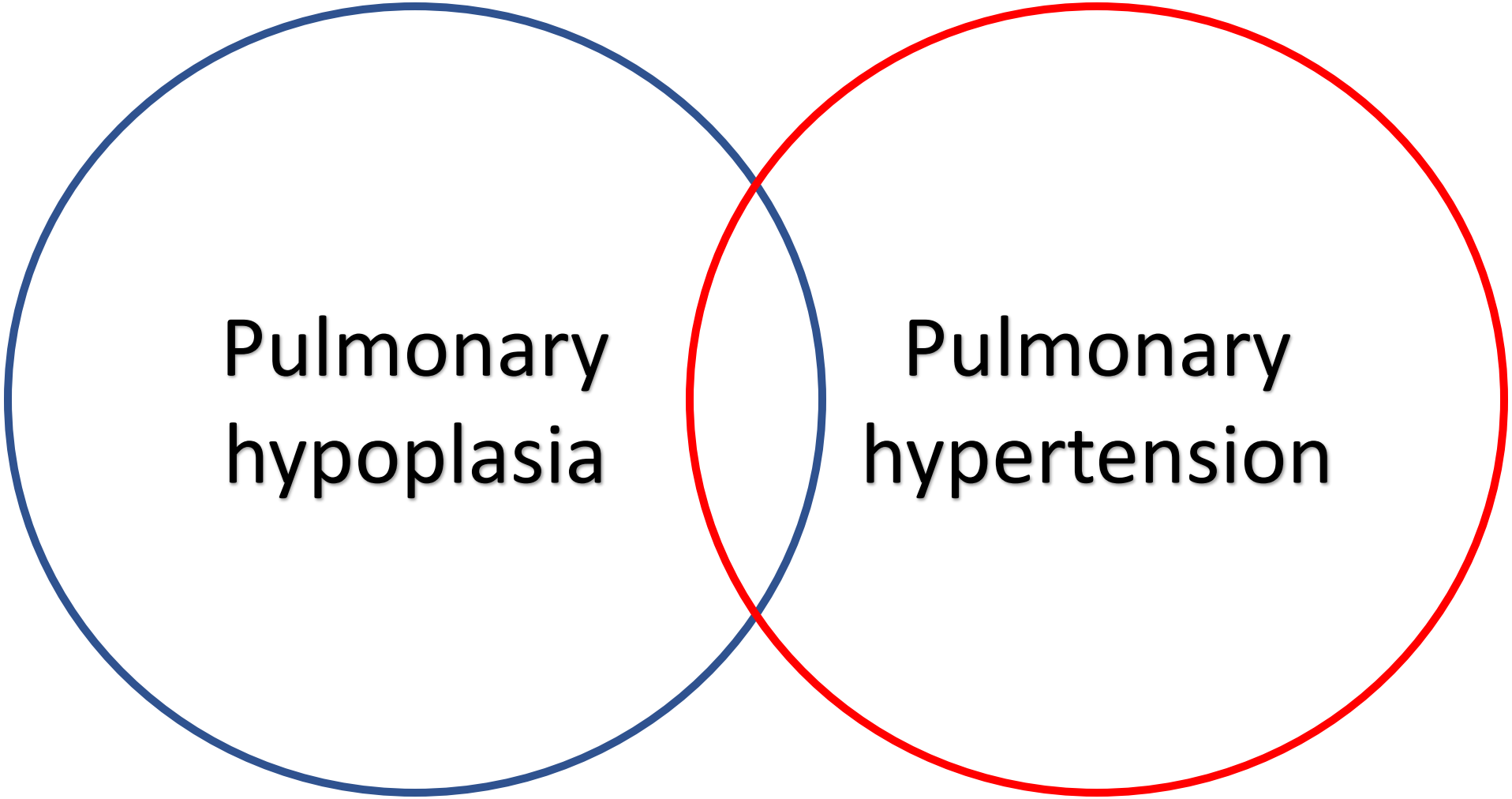
Table II. Outcomes in infants alive with and without PH at 1, 2, 3, 4, and 6 weeks

	Death			Death or prolonged intubation (≥28 d)			Death or prolonged respiratory support (≥56 d) or home oxygen*		
	% Outcome (N)	*P* value	AUROC (95% CI)	% Outcome (N)	*P* value	AUROC (95% CI)	% Outcome (N)	*P* value	AUROC (95% CI)
Week 1 (n = 136)†									
With PH (n = 128)‡	18% (23/128)	*P* = .35	0.73	25% (32/128)	*P* = .20	0.72	41% (52/128)	*P* = .023	0.7
Without PH (n = 8)	0% (0/8)		(0.64, 0.82)	0% (0/8)		(0.65, 0.81)	0% (0/8)		(0.62, 0.79)
Week 2 (n = 133)									
With PH (n = 86)	23% (20/86)	*P* < .001	0.87	34% (29/86)	*P* < .001	0.83	55% (47/86)	*P* < .001	0.8
No PH (n = 47)	0% (0/47)		(0.81, 0.94)	0% (0/47)		(0.75, 0.91)	6% (3/47)		(0.72, 0.88)
Week 3 (n = 128)									
With PH (n = 55)	27% (15/55)	*P* < .001	0.83	40% (22/55)	*P* < .001	0.77	65% (36/55)	*P* < .001	0.74
No PH (n = 73)	0% (0/73)		(0.70, 0.95)	3% (2/73)		(0.64, 0.89)	12% (9/73)		(0.64, 0.83)
Week 4 (n = 126)									
With PH (n = 46)	28% (13/46)	*P* < .001	0.76	43% (20/46)	*P* < .001	0.72	65% (30/46)	*P* < .001	0.73
No PH (n = 80)	0% (0/80)		(0.59, 0.93)	3% (2/80)		(0.58, 0.86)	16% (13/80)		(0.64, 0.83)
Week 6 (n = 123)									
With PH (n = 34)	26% (9/34)	*P* < .001	0.91	-	-	-	62% (21/34)	*P* < .001	0.63
No PH (n = 89)	1% (1/89)		(0.80, 1.00)				21% (19/89)		(0.42, 0.82)

*Per definition of bronchopulmonary dysplasia in infants >32 wk gestational age.[15] Nine infants were discharged on O_2 prior to 56 d (median 37 d, range 20-55).
†Four infants died prior to 1 wk echocardiogram.
‡PH is defined as estimated pulmonary arterial pressures ≥2/3 systemic pressures.

Lusk et al, J Peds, 2014


Pulmonary hypoplasia
Pulmonary hypertension

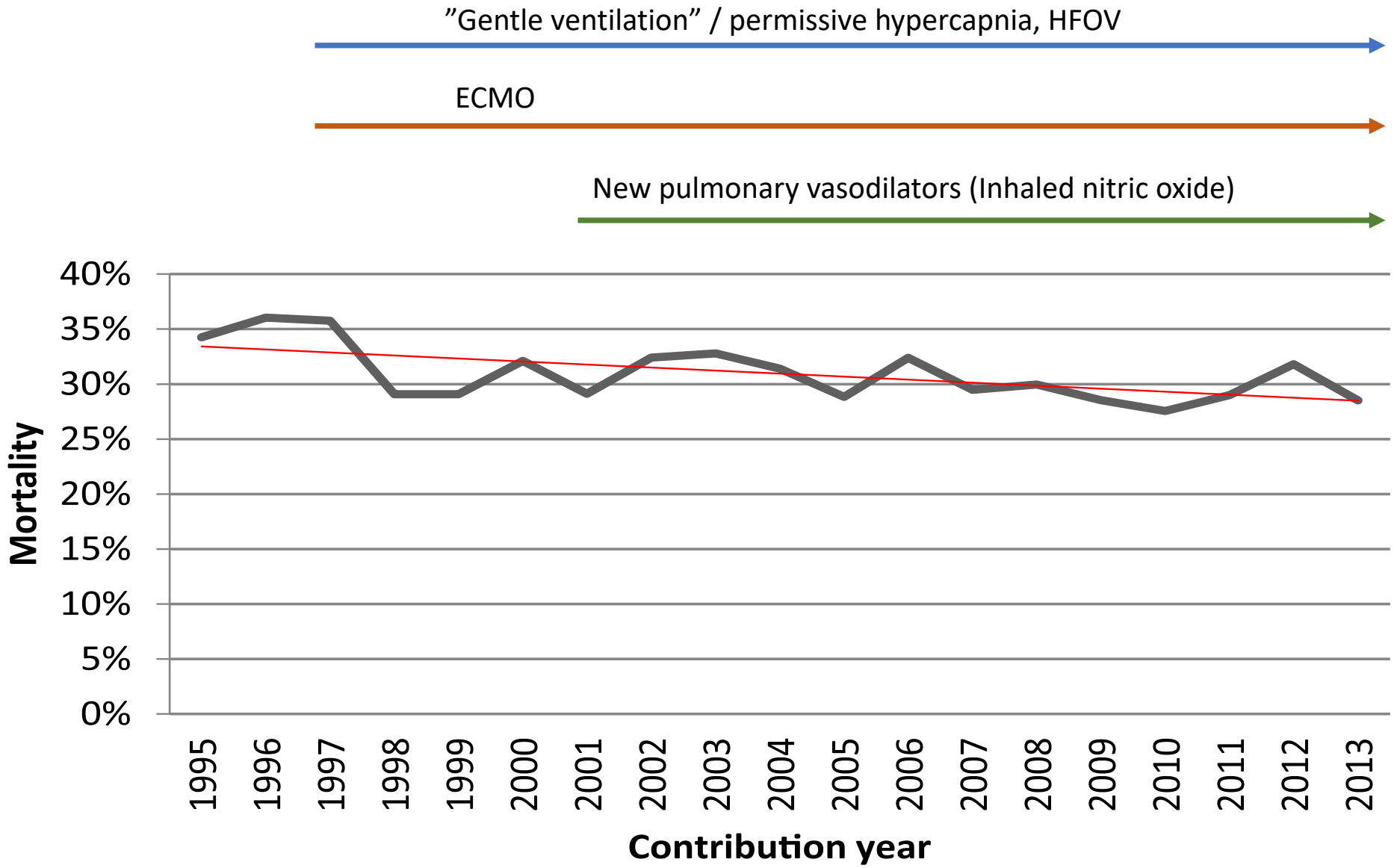
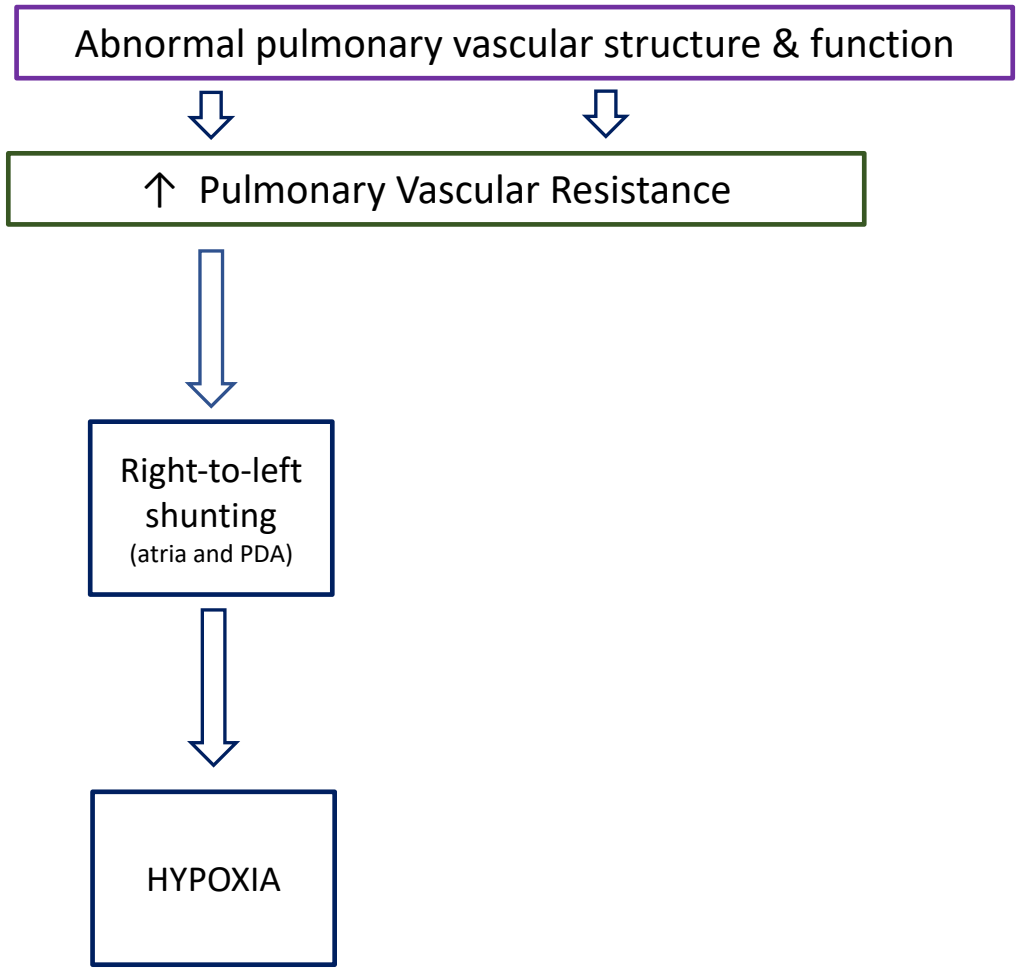
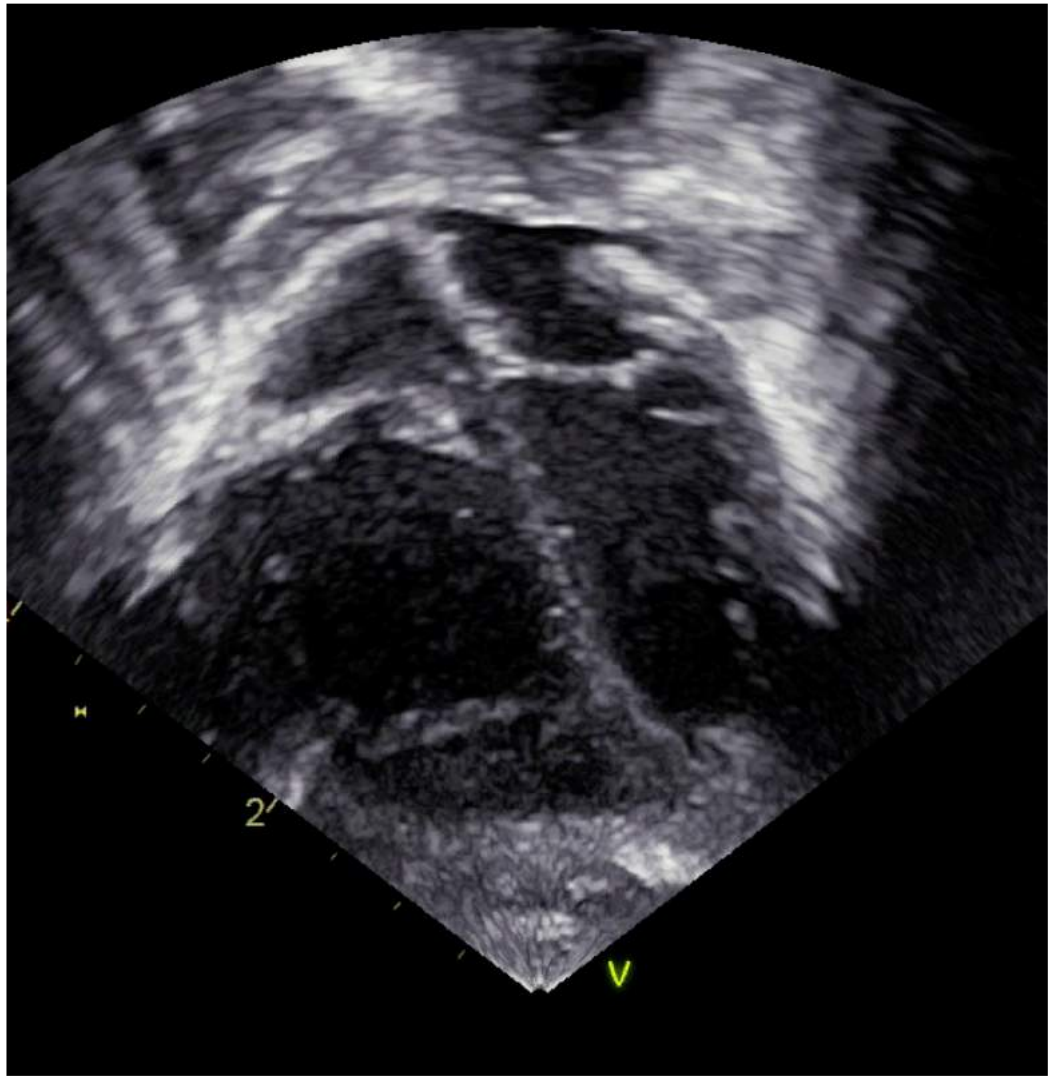


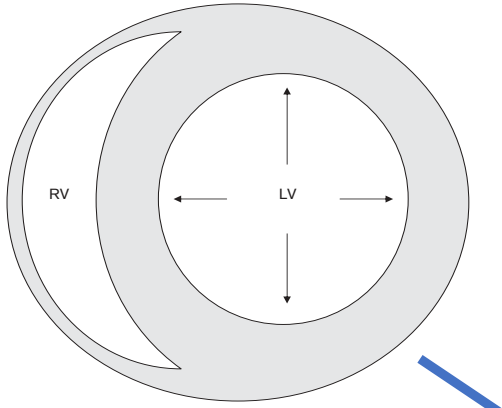
Fig. 1. Congenital Diaphragmatic Hernia Study Group overall mortality by year.

M.T. Harting, K.P. Lally / Seminars in Fetal & Neonatal Medicine 19 (2014) 370–375

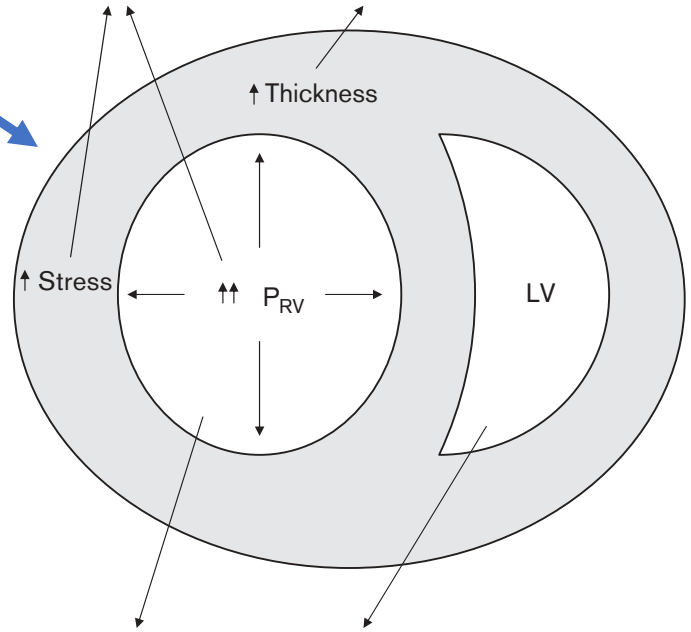

Abnormal pulmonary vascular structure & function
↑ Pulmonary Vascular Resistance
Right-to-left shunting
(atria and PDA)
HYPOXIA

RV dilatation and hypertrophy in pulmonary hypertension





(A) ↓ Coronary perfusion pressure + ↑ O_2Demand = ↓ *Supply/Demand*



(B) ↑↑ RV Distention &↓ LV Filling = ↓ *Cardiac Output*

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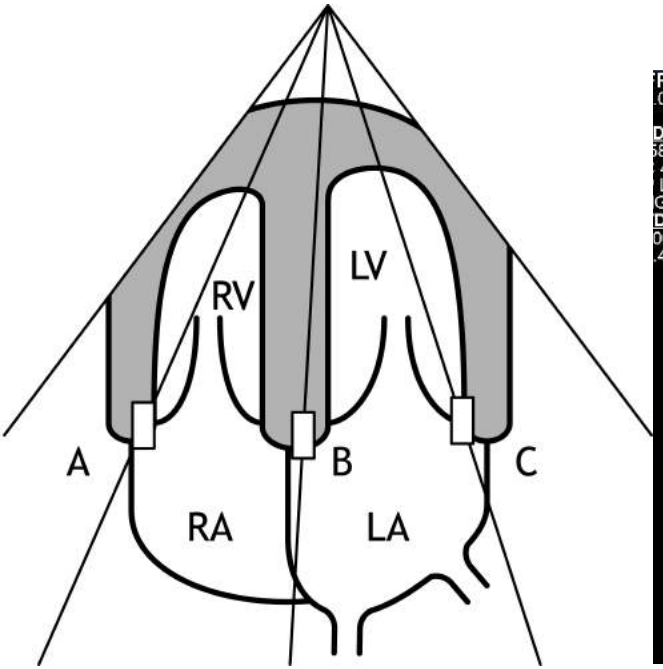
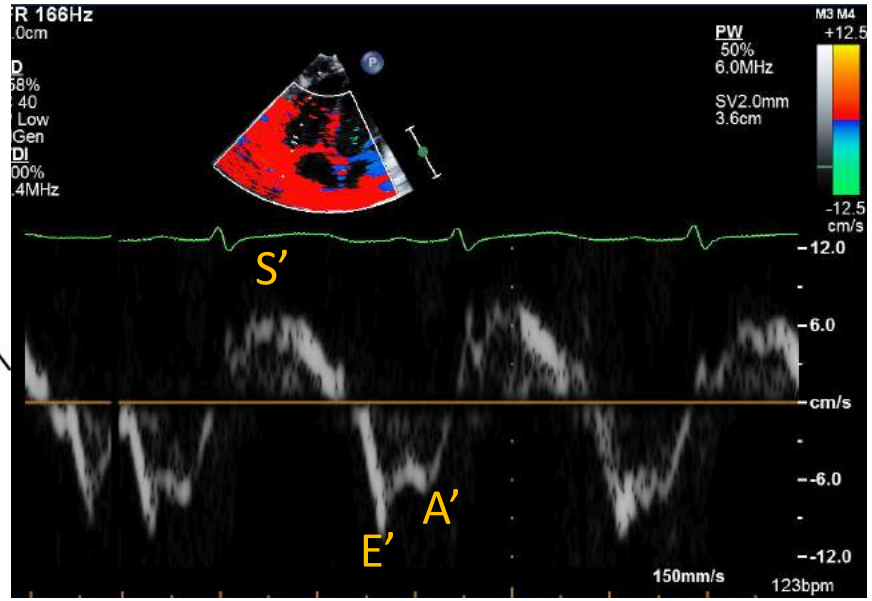
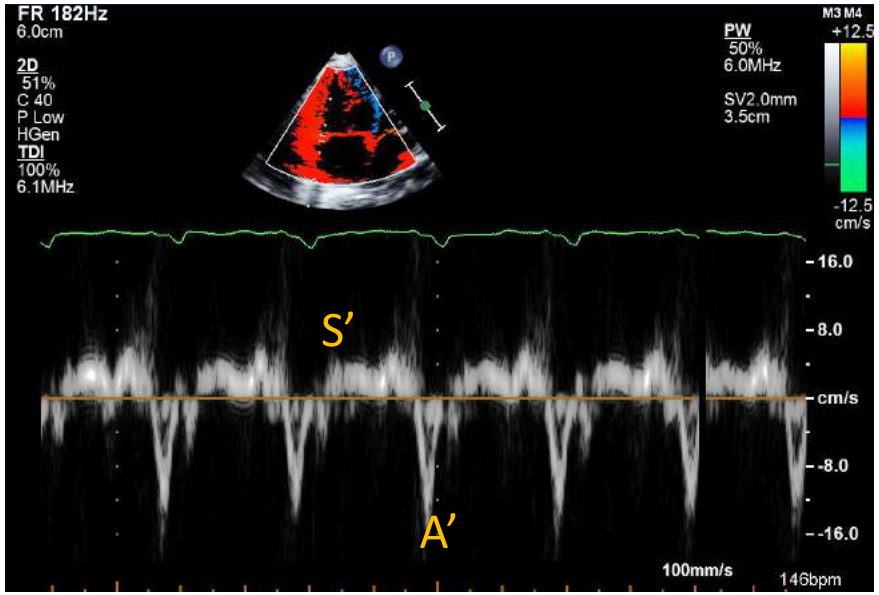
RV Diastolic dysfunction in PH: Tissue Doppler Imaging



Control infant – RV

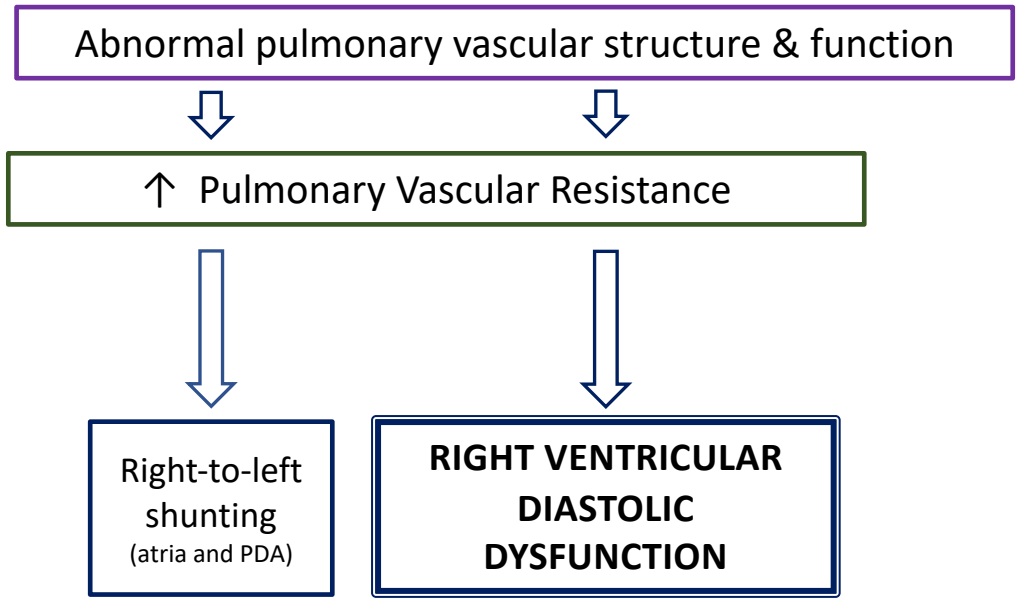


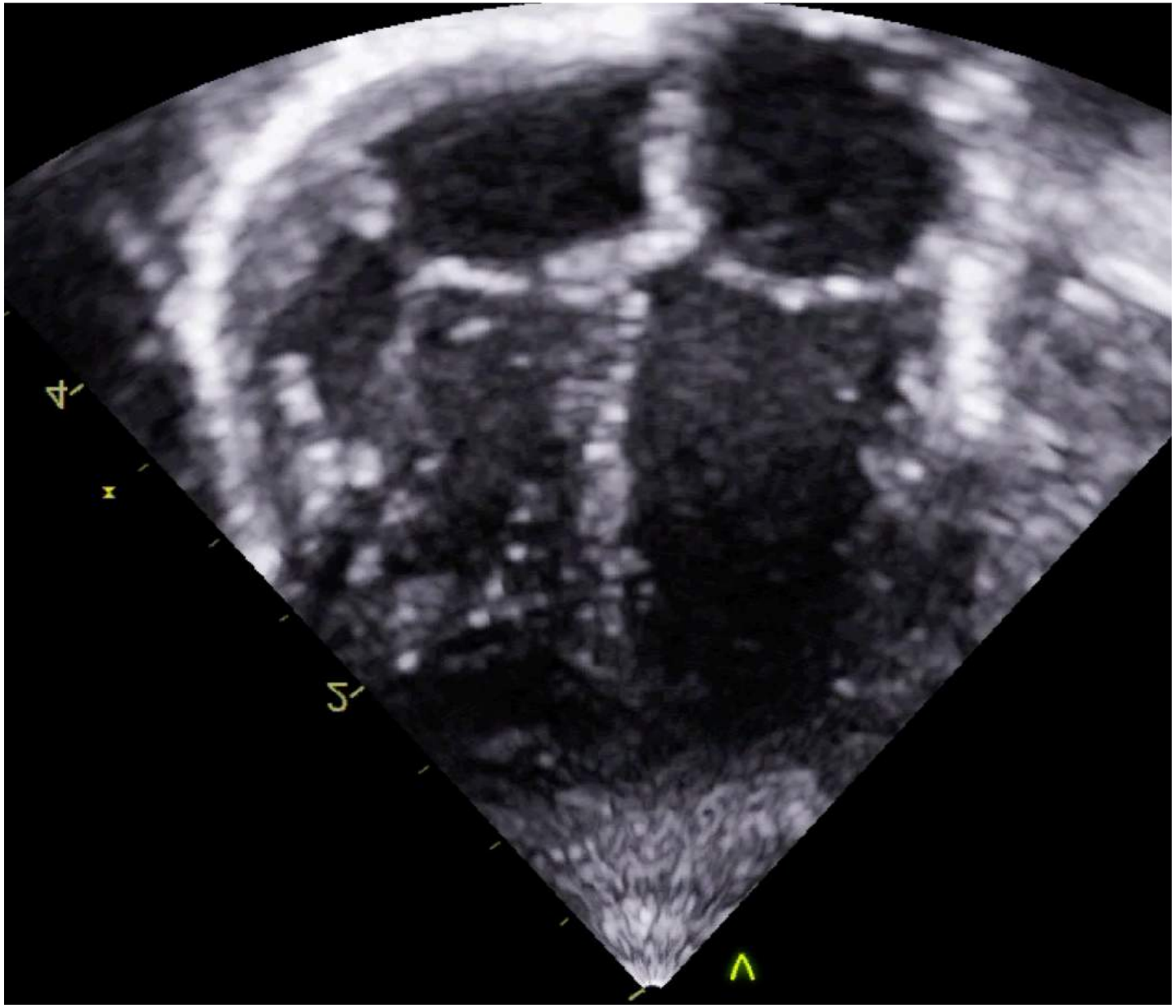
RV in PH



- Reduced systolic velocities
- **<u>Loss of diastolic E' velocity</u>**

Patel et al, Neonatology, 2009


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



Assessing cardiac function: speckle tracking echocardiography

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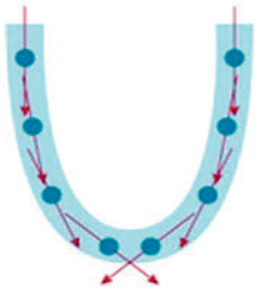
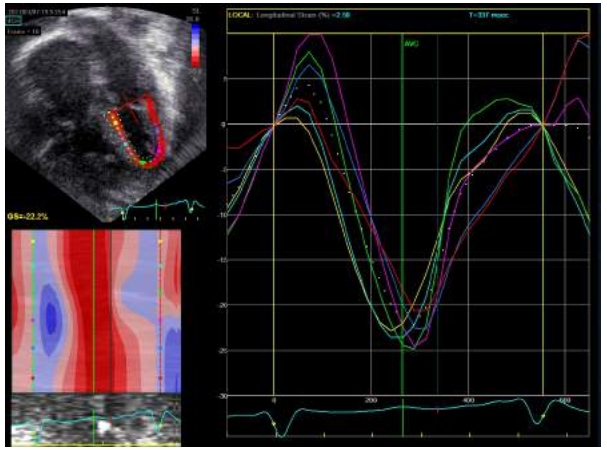
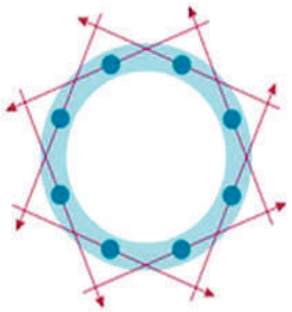
Global longitudional strain (GLS)



longitudinal

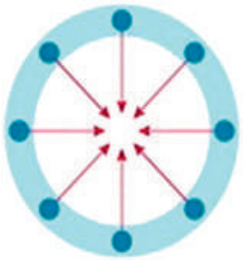


Global circumferential strain (GCS)

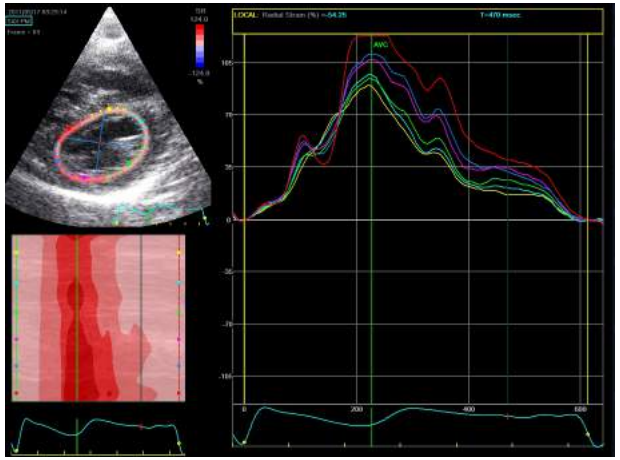


circumferential

Global radial strain (GRS)



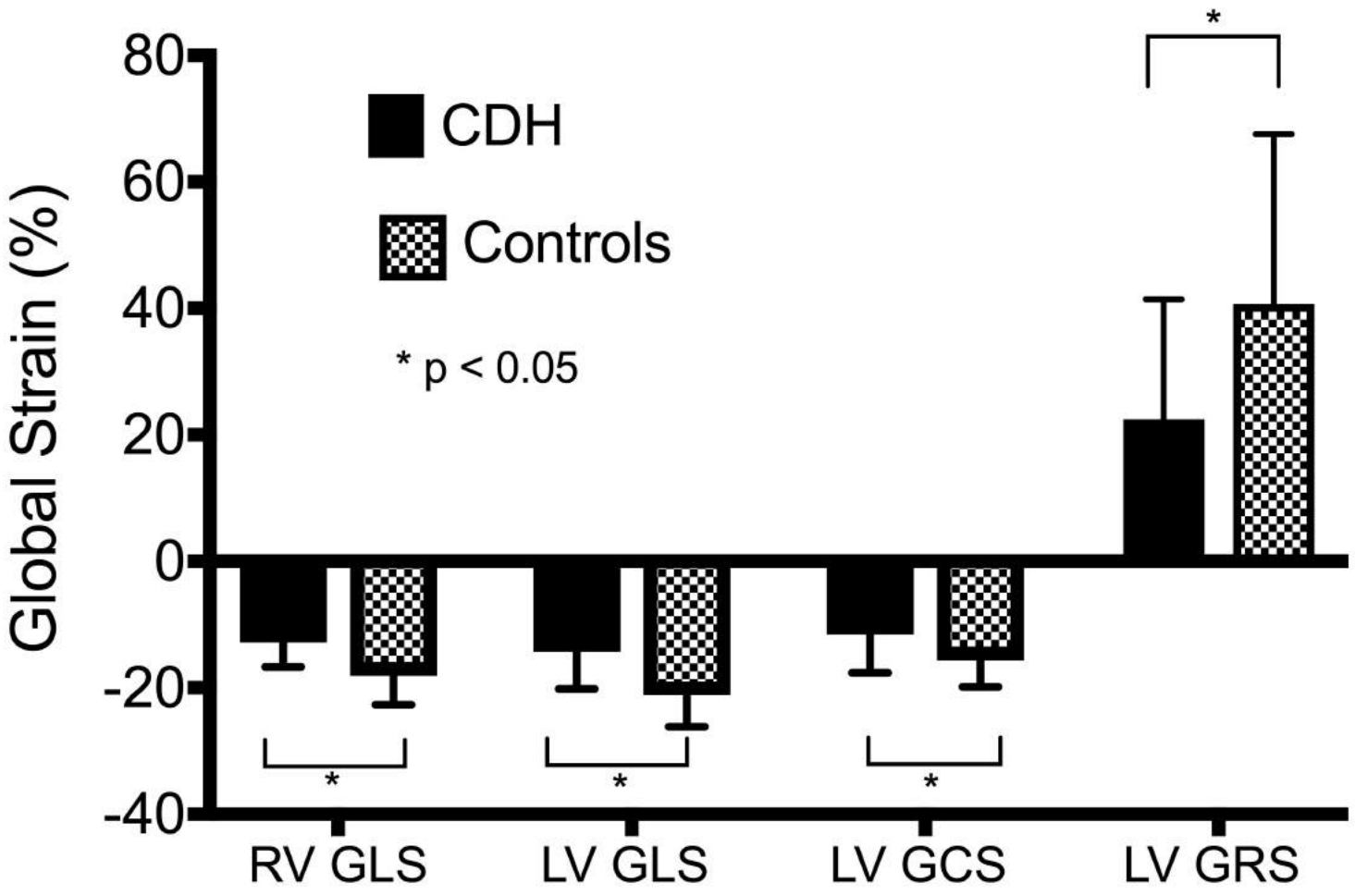
radial



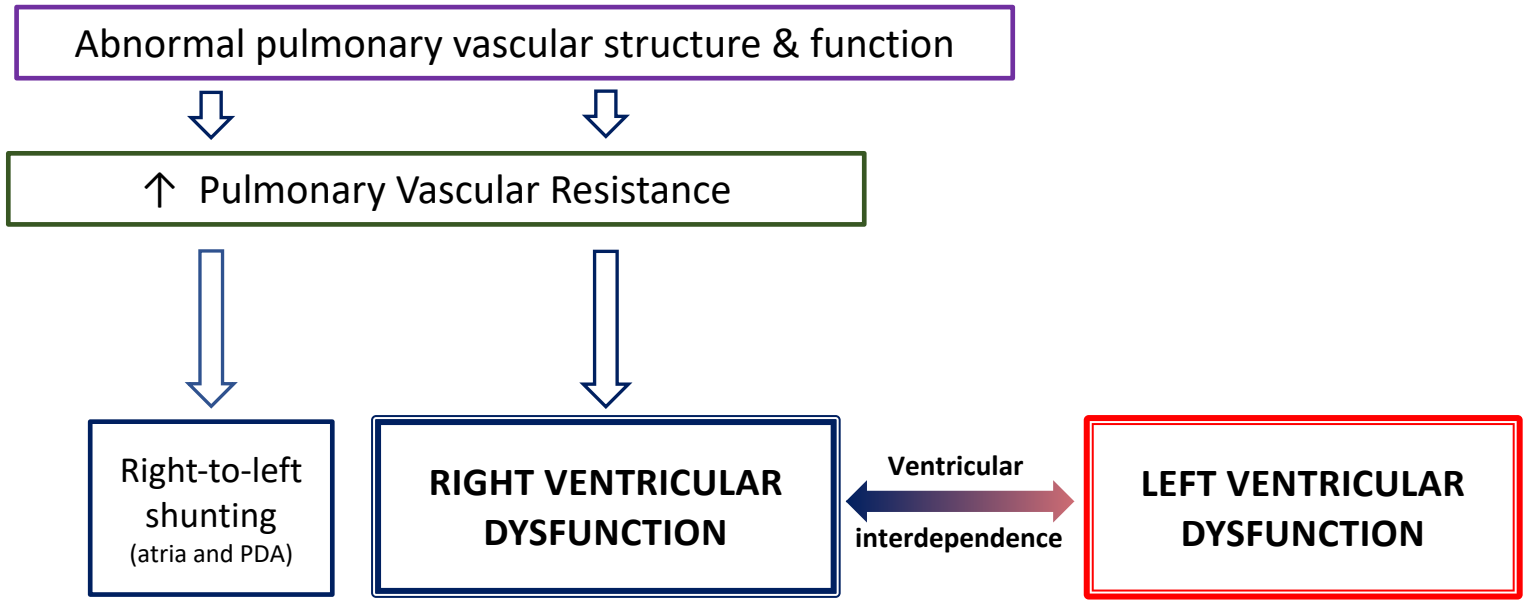
Neonatus 2019

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]

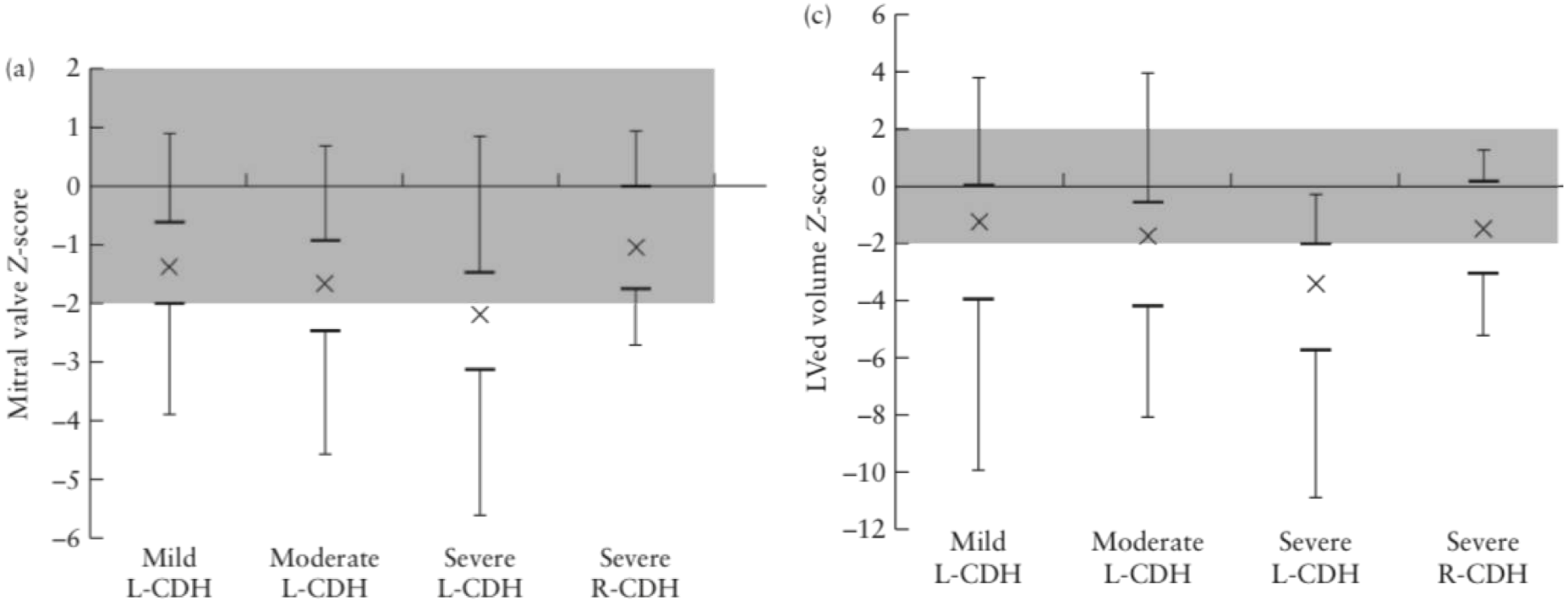


J Peds 2018

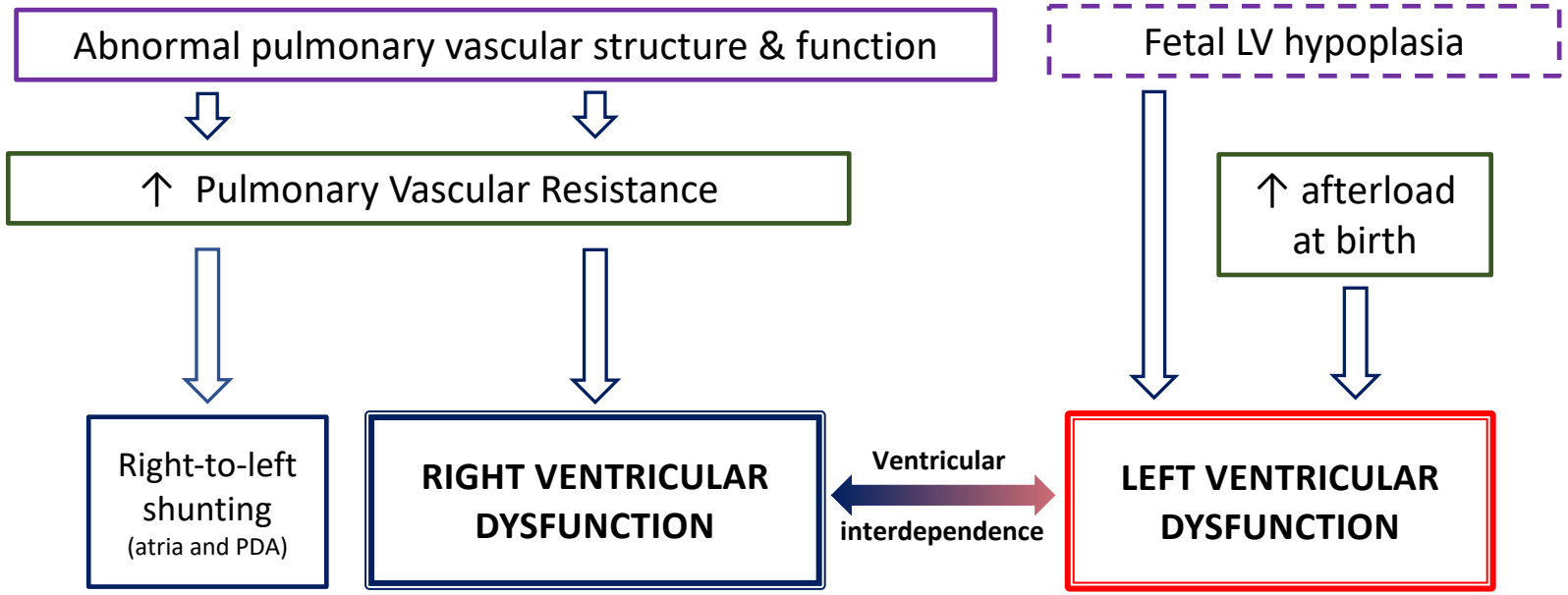

Abnormal pulmonary vascular structure & function
↑ Pulmonary Vascular Resistance
Right-to-left shunting
(atria and PDA)
RIGHT VENTRICULAR DYSFUNCTION
Ventricular
interdependence
LEFT VENTRICULAR DYSFUNCTION

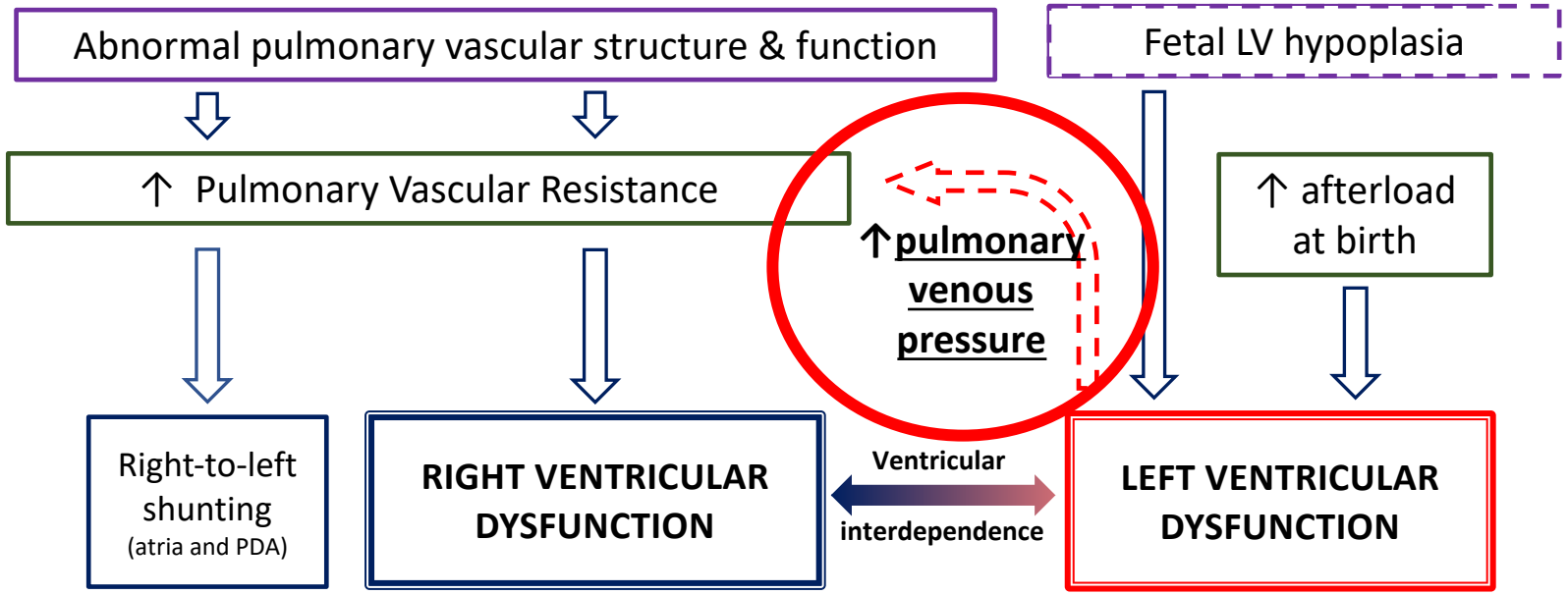
Severe left diaphragmatic hernia limits size of fetal left heart more than does right diaphragmatic hernia

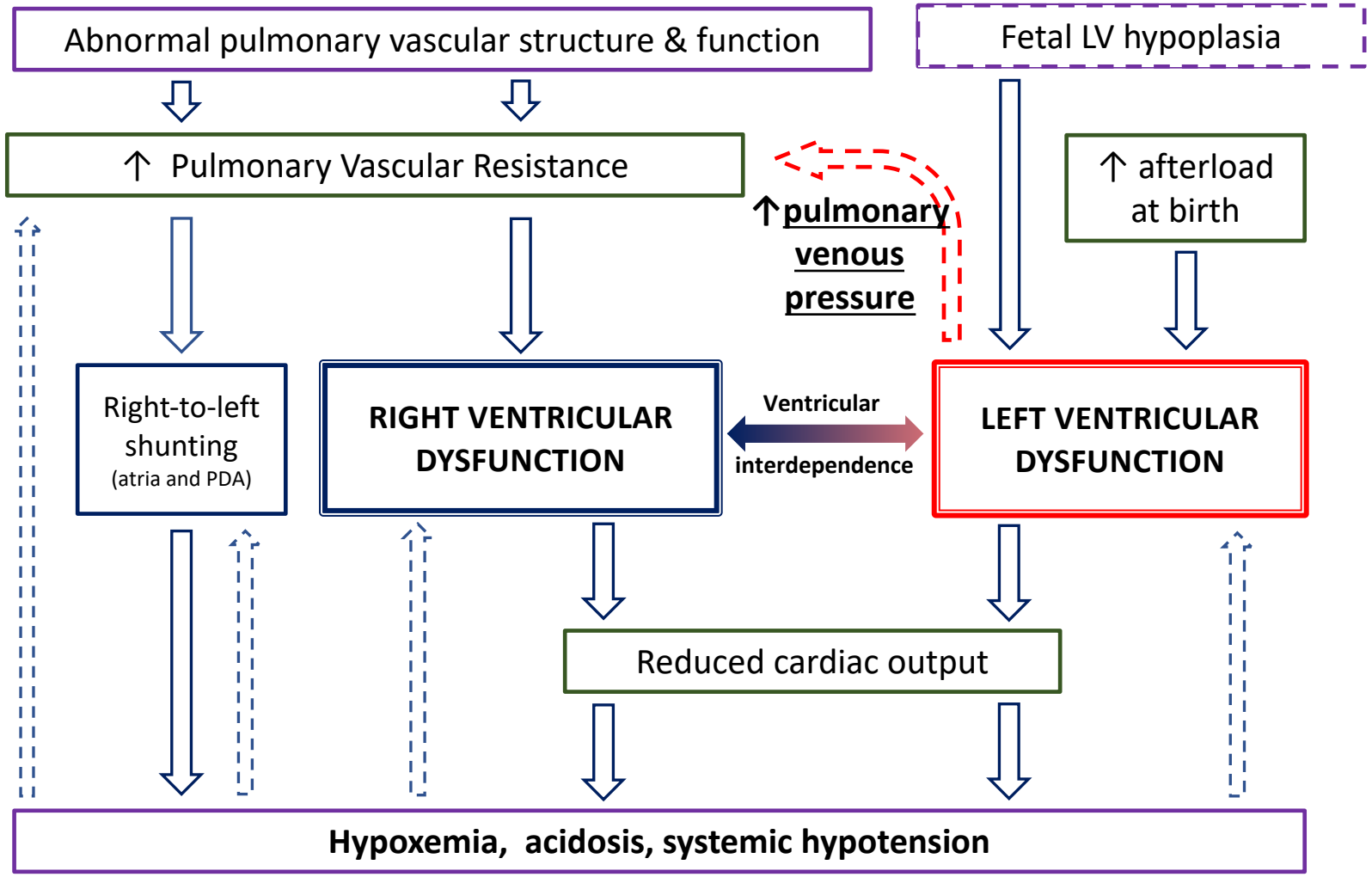
F. A. BYRNE*, R. L. KELLER†, J. MEADOWS*, D. MINIATI‡§, M. M. BROOK*, N. H. SILVERMAN* and A. J. MOON-GRADY*§



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


Abnormal pulmonary vascular structure & function
Fetal LV hypoplasia
↑ Pulmonary Vascular Resistance
↑ afterload at birth
Right-to-left shunting (atria and PDA)
RIGHT VENTRICULAR DYSFUNCTION
Ventricular interdependence
LEFT VENTRICULAR DYSFUNCTION


Abnormal pulmonary vascular structure & function
Fetal LV hypoplasia
↑ Pulmonary Vascular Resistance
↑pulmonary venous pressure
↑ afterload at birth
Right-to-left shunting
(atria and PDA)
RIGHT VENTRICULAR DYSFUNCTION
Ventricular
interdependence
LEFT VENTRICULAR DYSFUNCTION



Patel, Massolo, and Kipfmueller. Sem Perinatol 2019

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

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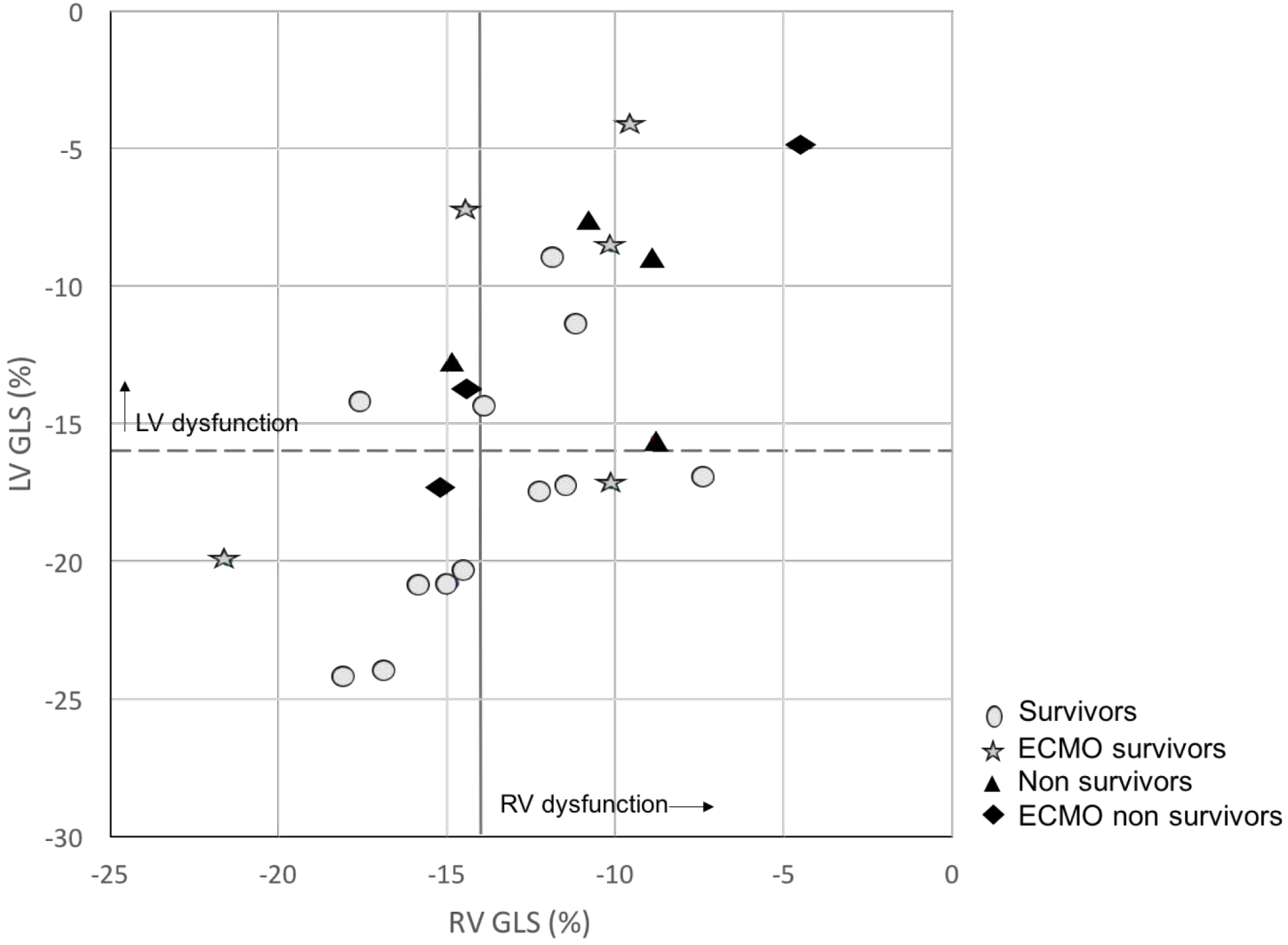
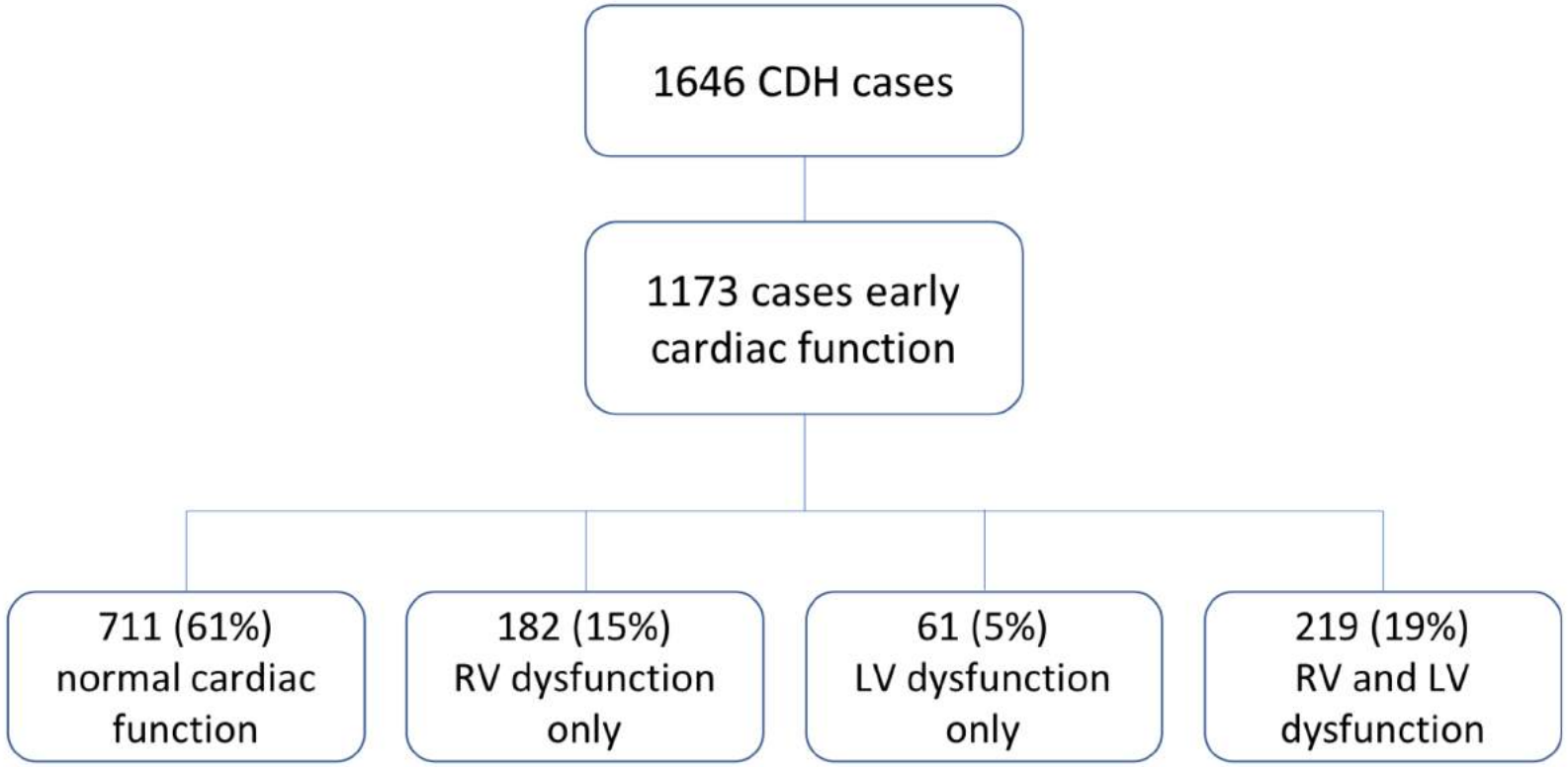


Neonatus 2019

J Peds 2018

Ventricular Dysfunction is a Critical Determinant of Mortality in Congenital Diaphragmatic Hernia

Neil Patel , Pamela A Lally , Florian Kipfmueller , Anna Claudia Massolo , Matias Luco , Krisa P Van Meurs , Kevin P Lally , Matthew T Harting , and , for the Congenital Diaphragmatic Hernia Study Group



AJRCCM 2019 in press

Ventricular Dysfunction is a Critical Determinant of Mortality in Congenital Diaphragmatic Hernia

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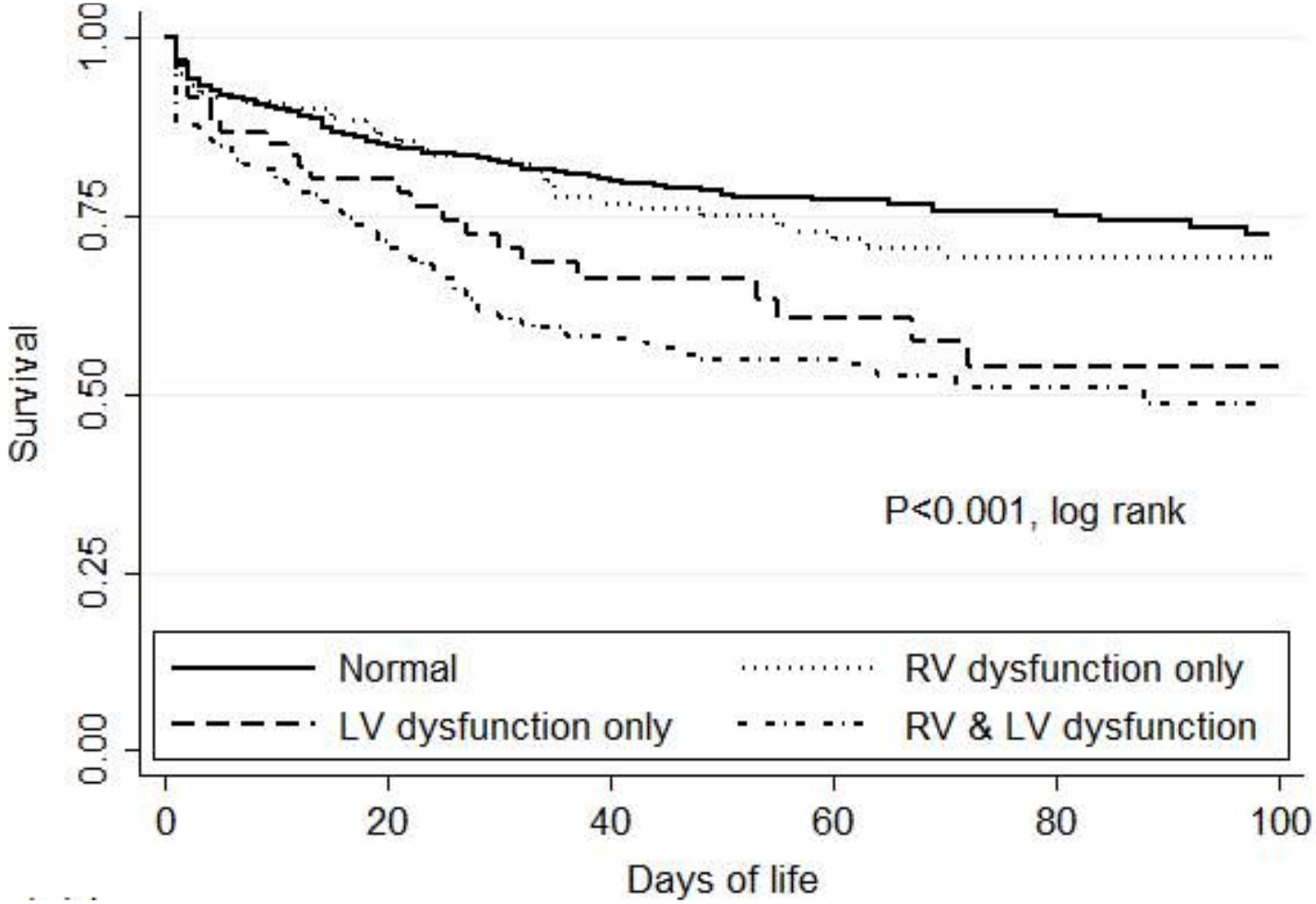
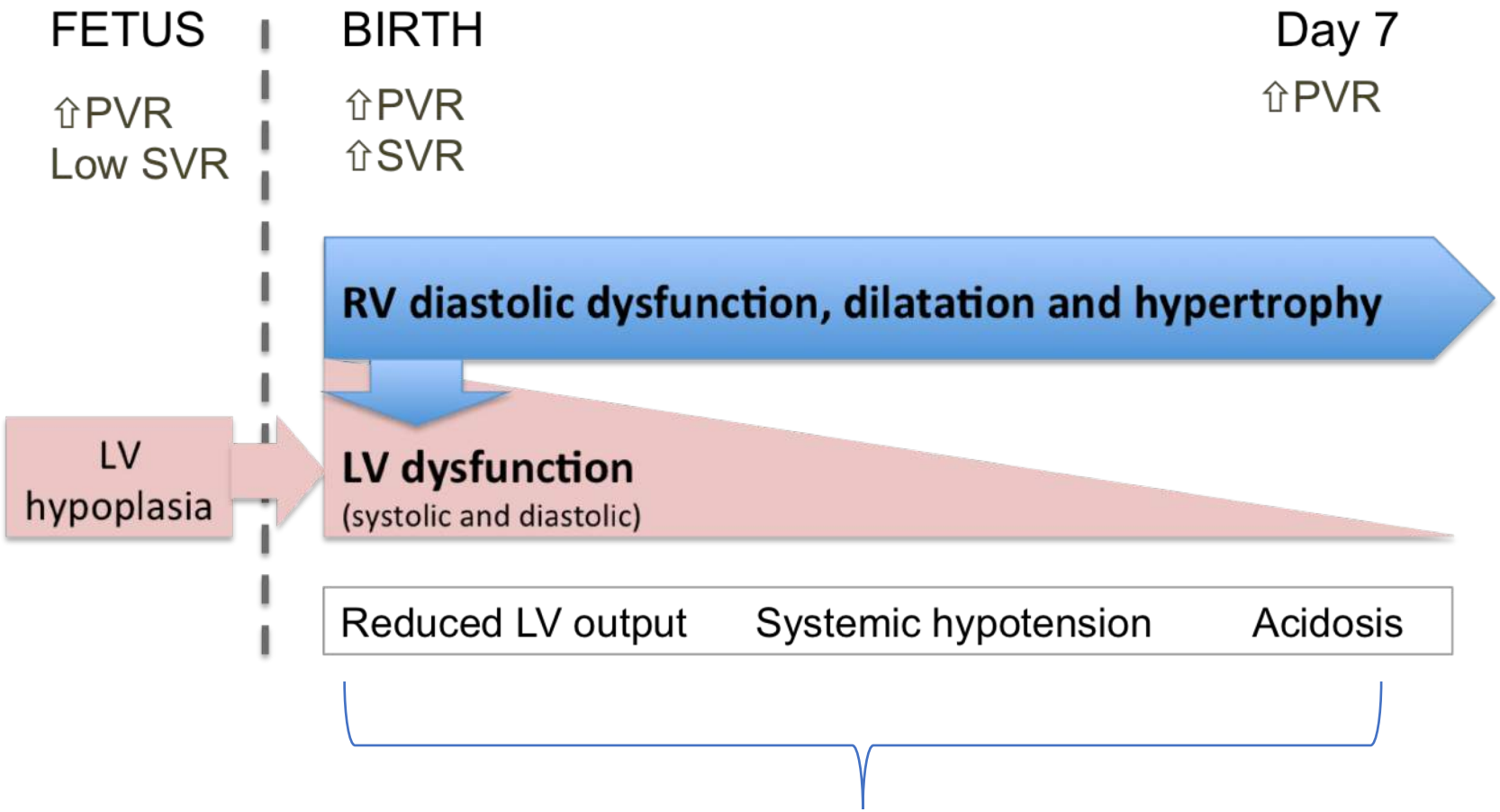


AJRCCM 2019, in press



Associated with outcomes:

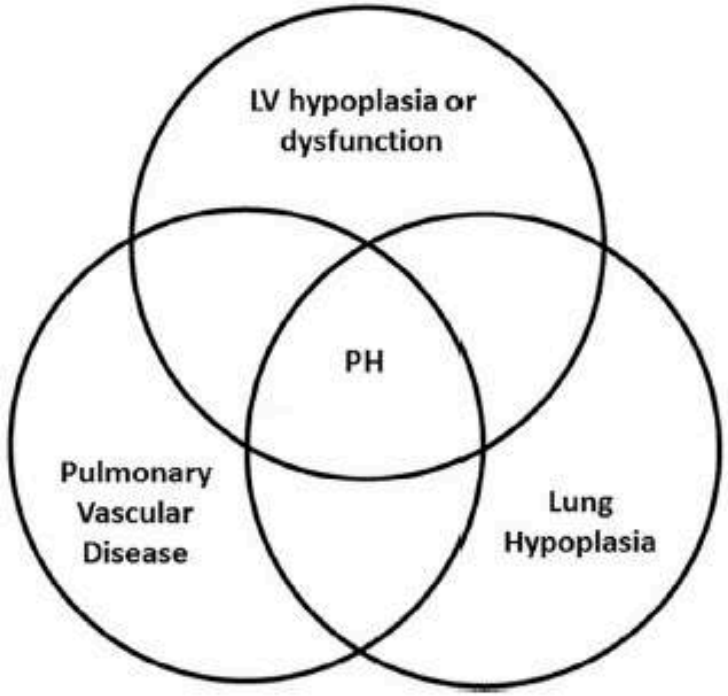
- Duration ventilation
- Length of stay
- Survival
- ECMO

N. Patel, F. Kipfmueller / Seminars in Pediatric Surgery 26 (2017)

The Left Ventricle in Congenital Diaphragmatic Hernia: Implications for the Management of Pulmonary Hypertension

John P. Kinsella, MD[1], Robin H. Steinhorn, MD[2], Mary P. Mullen, MD[3], Rachel K. Hopper, MD[4], Roberta L. Keller, MD[5], D. Dunbar Ivy, MD[6], Eric D. Austin, MD[7], Usha S. Krishnan, MD[8], Erika B. Rosenzweig, MD[8], Jeffrey R. Fineman, MD[9], Allen D. Everett, MD[10], Brian D. Hanna, MD[11], Tilman Humpl, MD[12], J. Usha Raj, MD[13], and Steven H. Abman, MD[14], on behalf of the Pediatric Pulmonary Hypertension Network (PPHNet)

- Pulmonary Venous Hypertension
- Decreased cardiac output
- Pulmonary edema, worsened with PH drug therapy



- High tone and abnormal reactivity;
- structural remodeling
- decreased vessel growth

- Decreased phasic lung stretch and/or compression of lung,
- decreased surface area for gas exchange,
- poor lung recruitment and lung injury from mechanical ventilation

Management of CDH: Assessment

PULMONARY HYPOPLASIA / RESPIRATORY FUNCTION	PVR / PAP	CARDIAC FUNCTION
Fetal measures lung volume. O:E LHR, O:E TFLV	Pre-post ductal saturations	Blood pressure analysis: pulse pressure
Blood gases, PaO2, PaCO2	Echocardiographic assessment: • Tricuspid regurgitation velocity • PDA shunting pattern • Time to peak velocity in pulmonary artery • Septal shape Challenging!	Echocardiographic assessment: • "Eyeballing" from 2d loops • Quantitative measures: ➢ Tissue Doppler imaging ➢ Speckle tracking echocardiography ? Cardiac dimensions?
Ventilation requirements		
(Chest x-ray)		

1. Assessment of PAP / cardiac function in CDH-PH

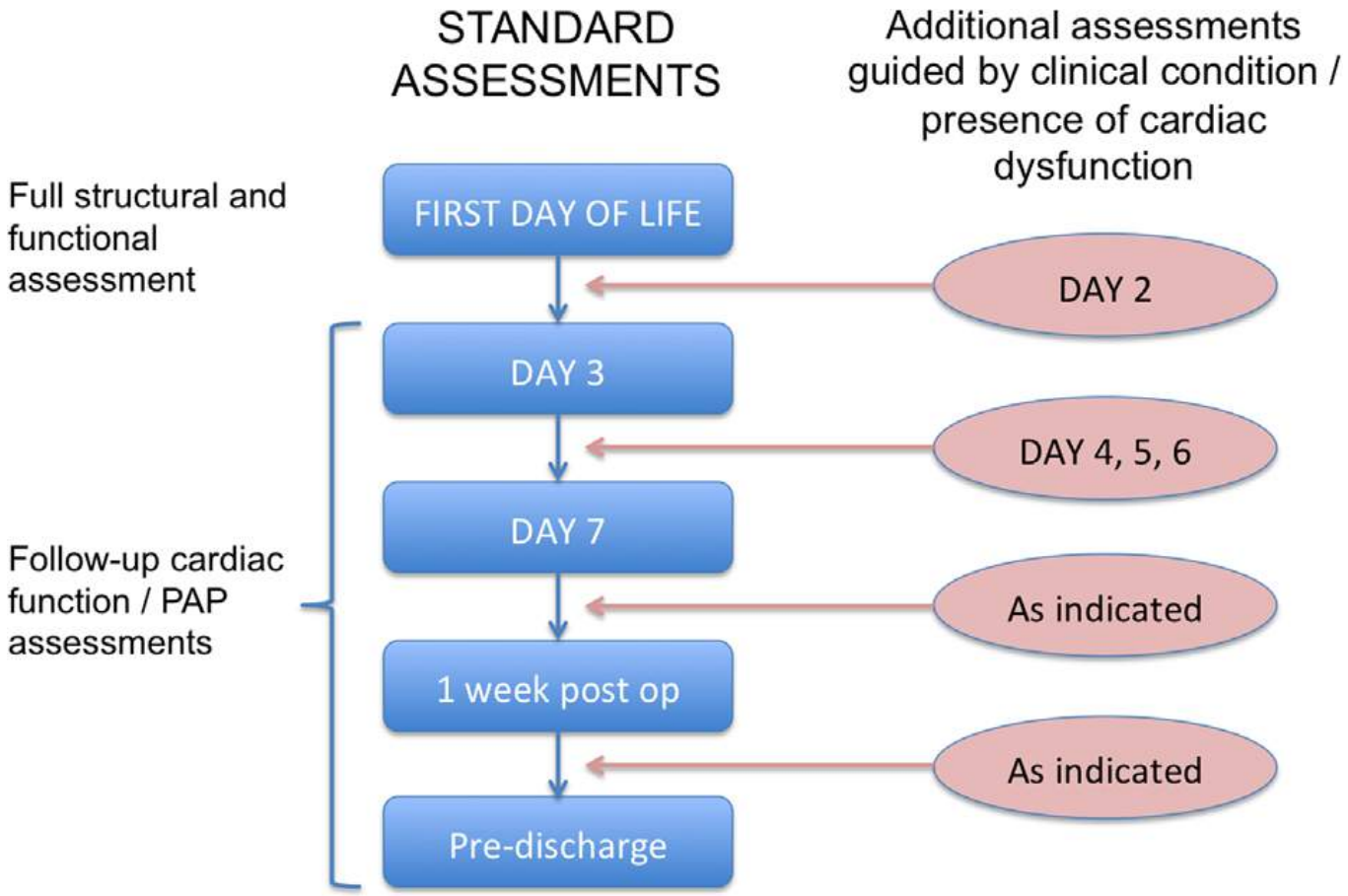
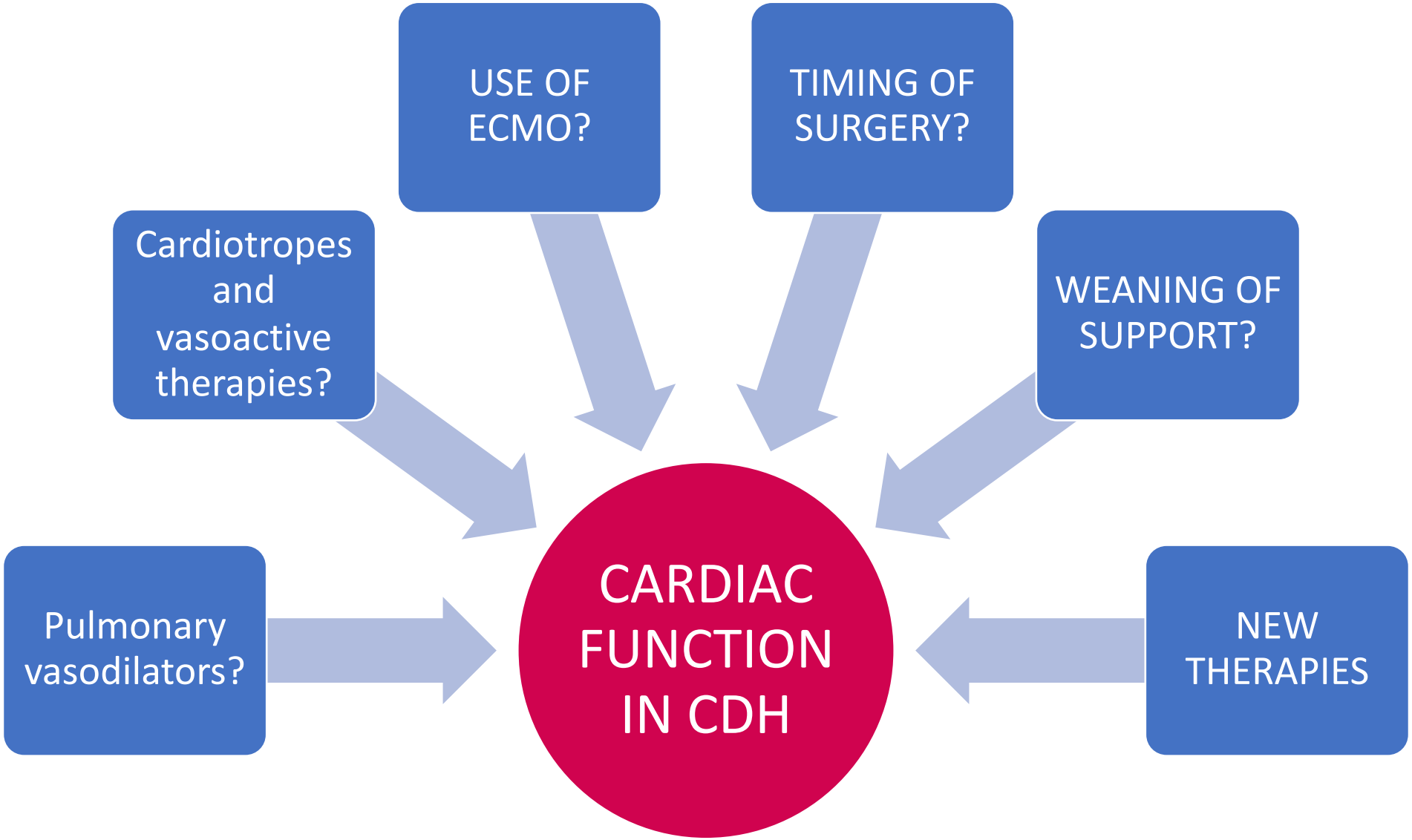
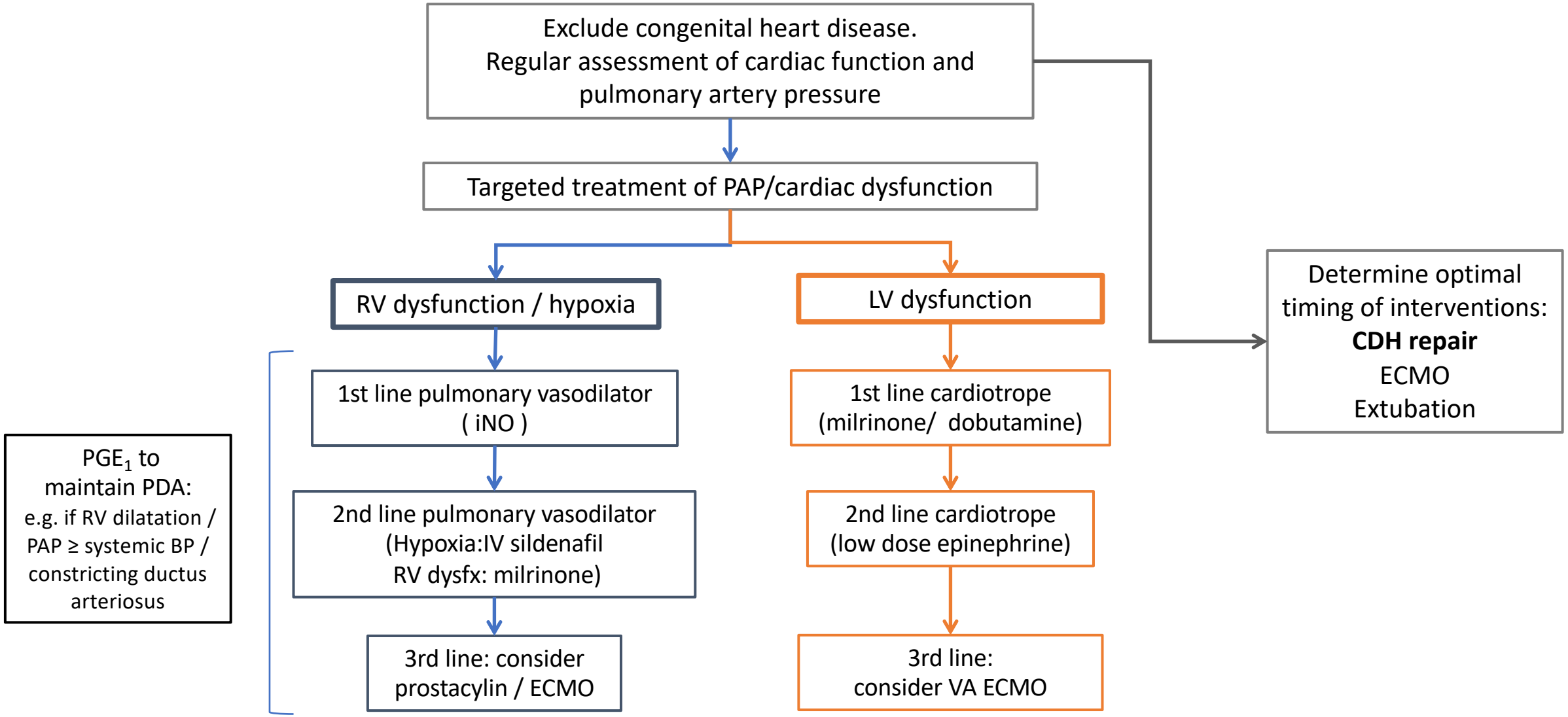


Fig. 3. Example protocol for timing of cardiac function assessment in CDH.

N. Patel, F. Kipfmueller / Seminars in Pediatric Surgery 26 (2017)


USE OF ECMO?
TIMING OF SURGERY?
Cardiotropes and vasoactive therapies?
WEANING OF SUPPORT?
Pulmonary vasodilators?
CARDIAC FUNCTION IN CDH
NEW THERAPIES

2. Targeted therapy of PH and cardiac dysfunction



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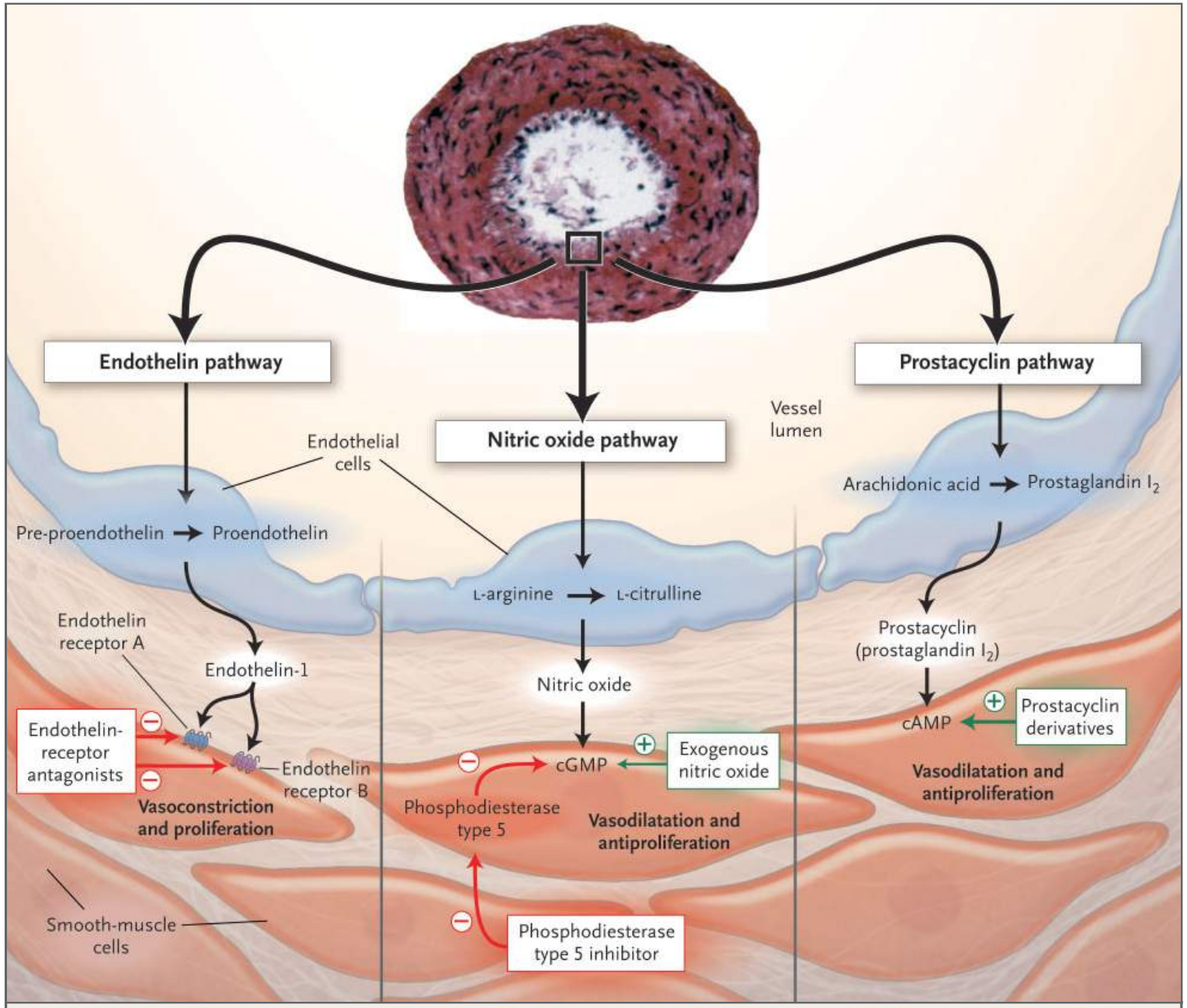
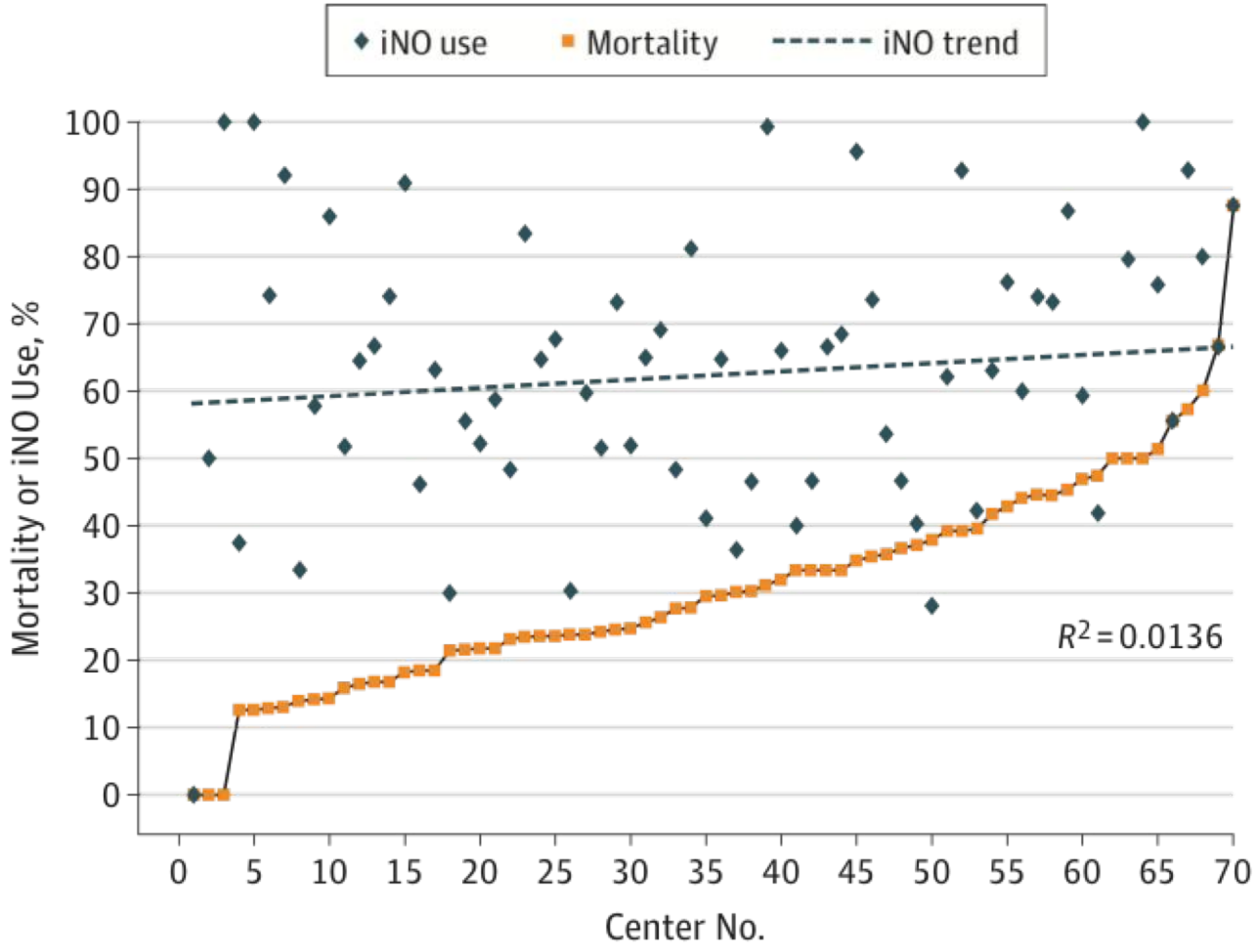


Figure 1. **Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.**

Naomi's 2010

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



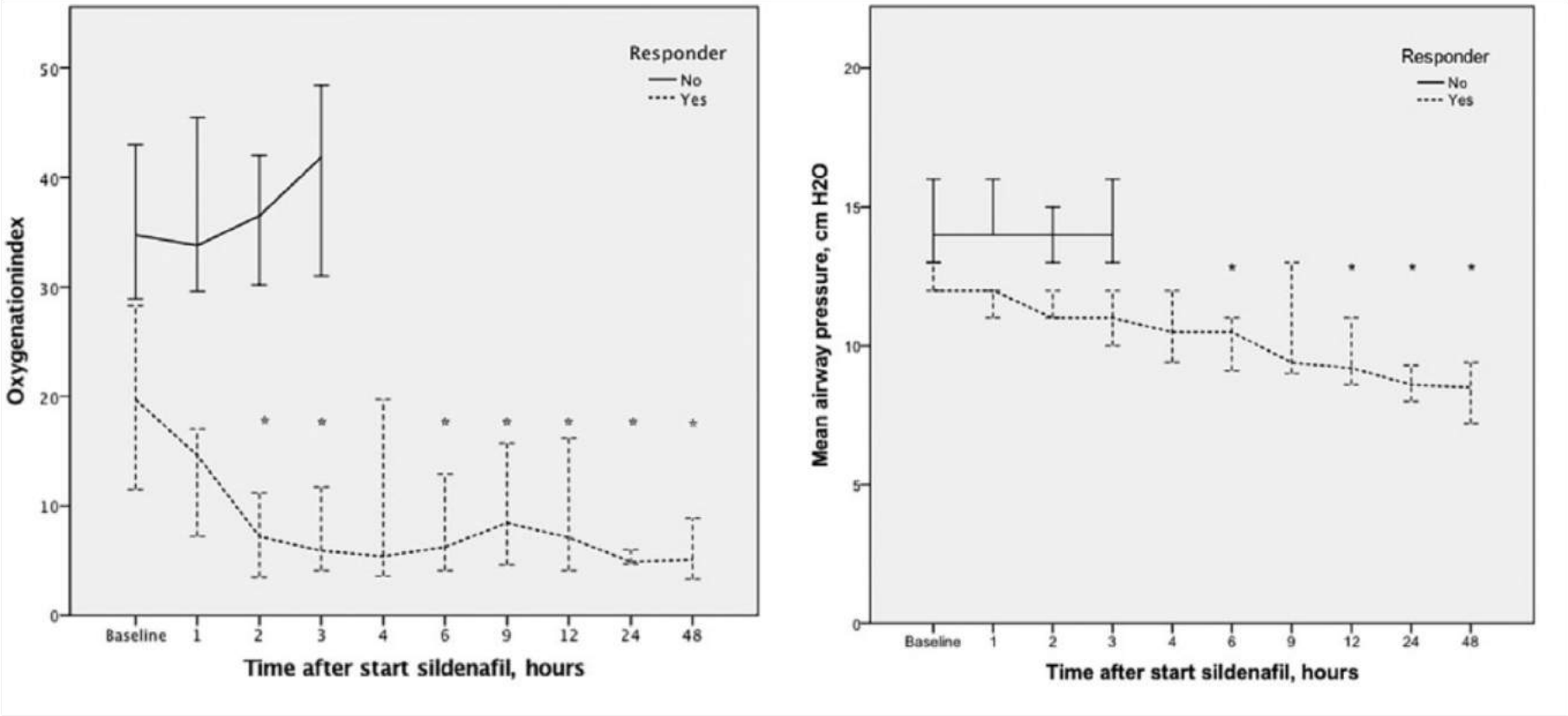
Overall, there was a positive association between the trend of iNO use and mortality by center.

Neonatus 2019

Putnam et al, JAMA Pediatr 2016

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;**53**:452–460.

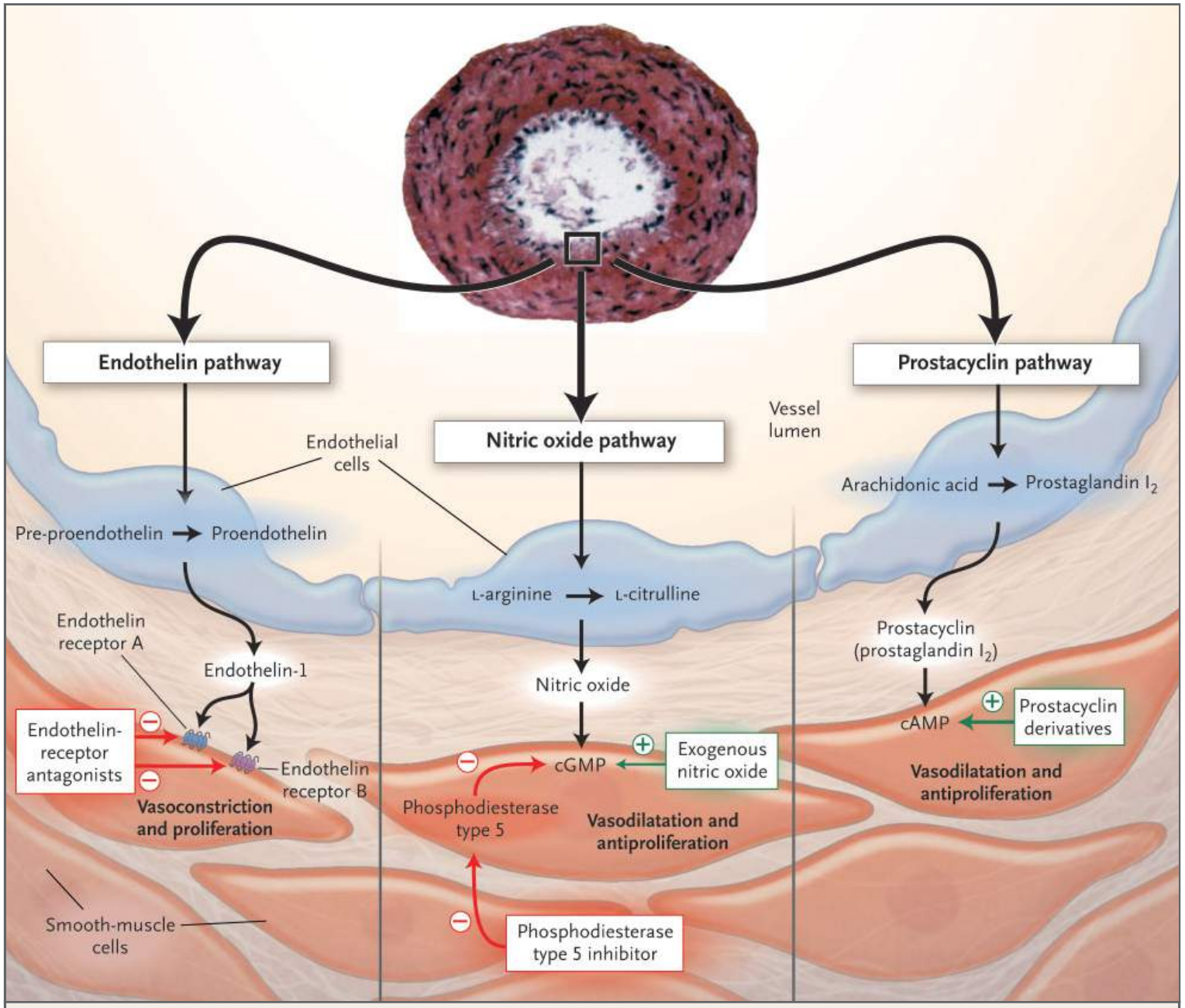


Figure 1. Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.

Neonatus 2019

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)

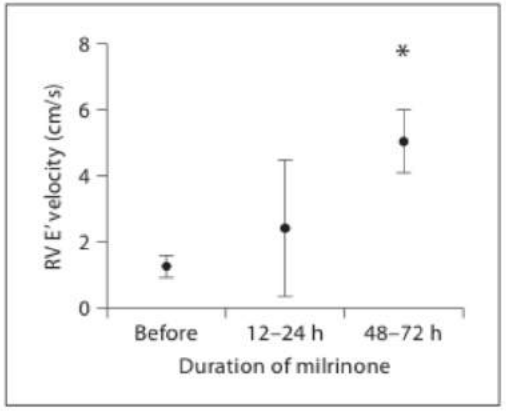


Fig. 1. Early diastolic velocities (E′) in the RV before and during milrinone therapy. Circles represent means, bars represent 95% CI. * $p < 0.05$.

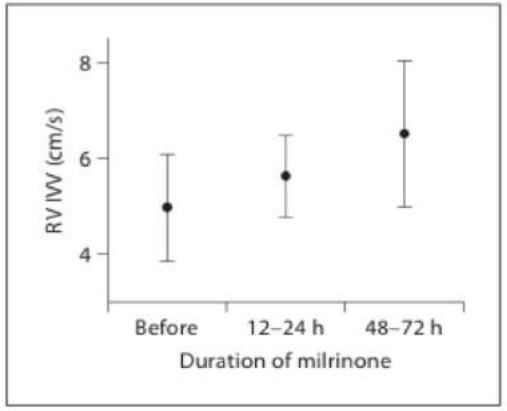


Fig. 2. Isovolumic contraction velocities (IVV) in the RV before and during milrinone therapy. Circles represent means, bars represent 95% CI.

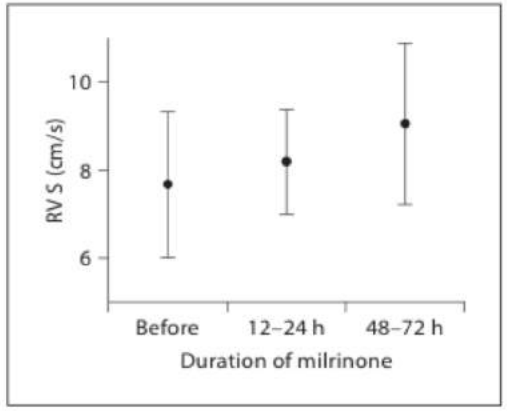
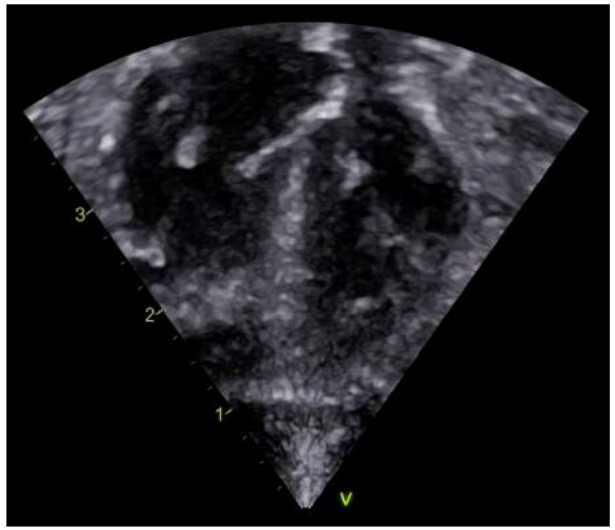


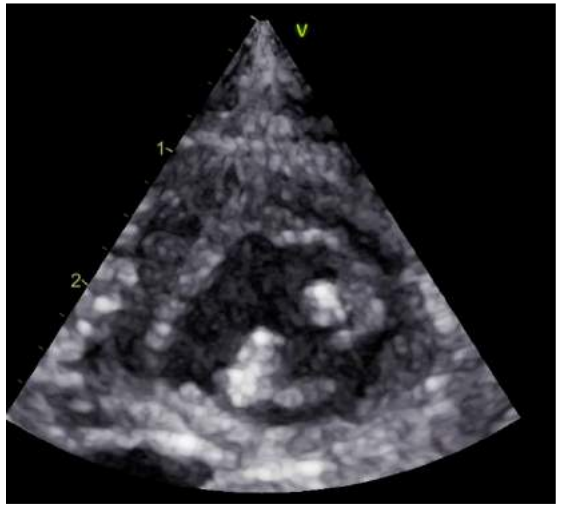
Fig. 3. Systolic ejection velocities (S) in the RV before and during milrinone therapy. Circles represent means, bars represent 95% CI.

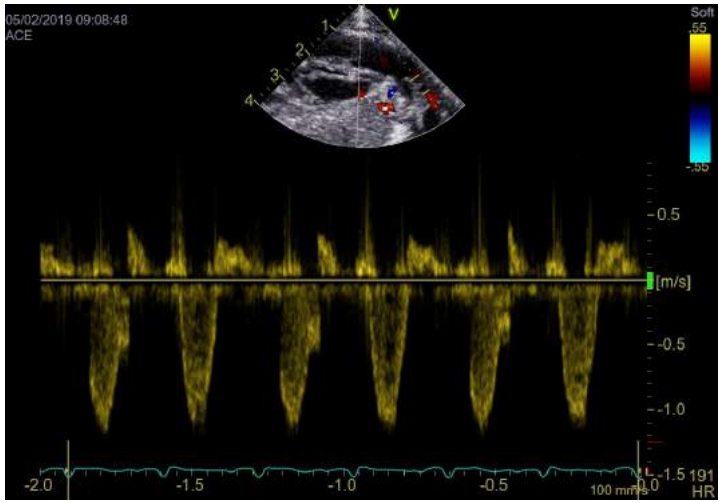
Neonatus 2019

Patel Neonatology 2012;102:130–136

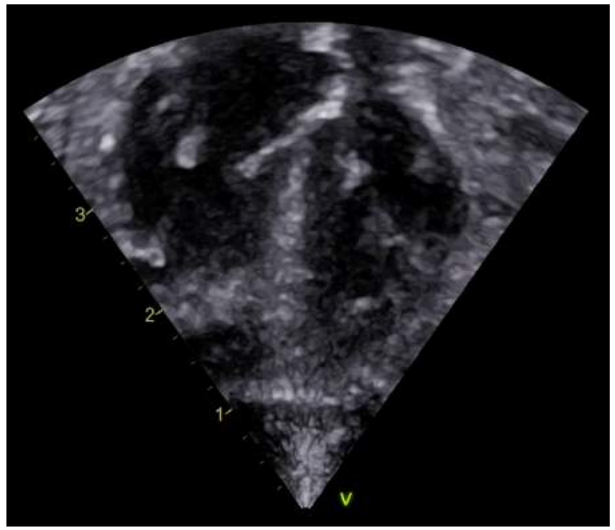
- 36/40. 2.8kg. L CDH. Day 1 of life
- Ventilation 26/6, FiO2 1.0. Sats 89 / 79%, BP 42/29 (34)mmHg. Lactate 3 mmol/L

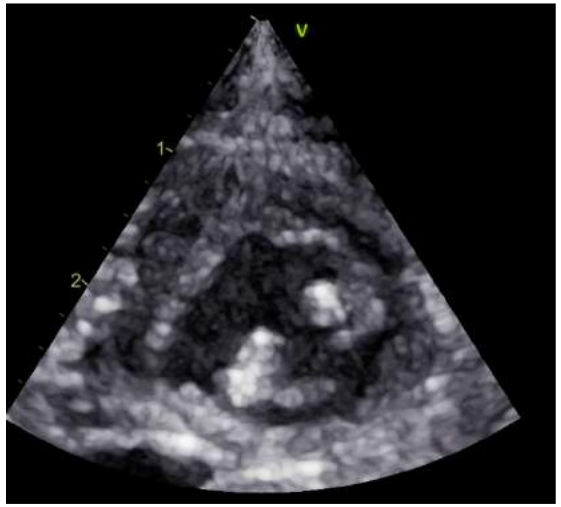


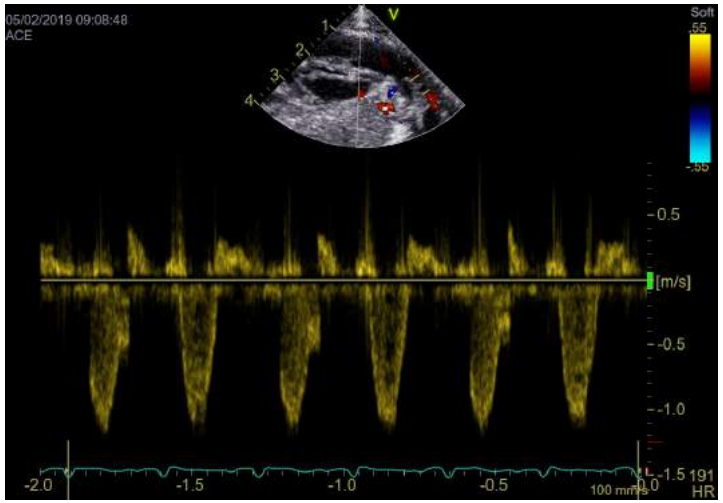




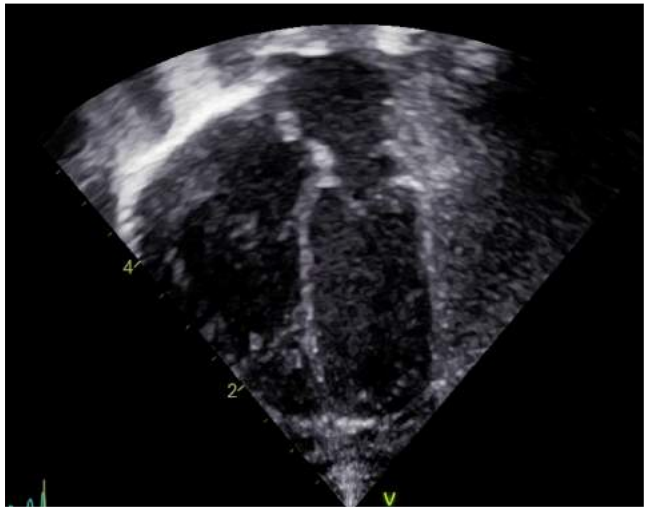
- 36/40. 2.8kg. L CDH. Day 1 of life
- Ventilation 26/6, FiO2 1.0. Sats 92 / 79%, BP 42/29 (34)mmHg

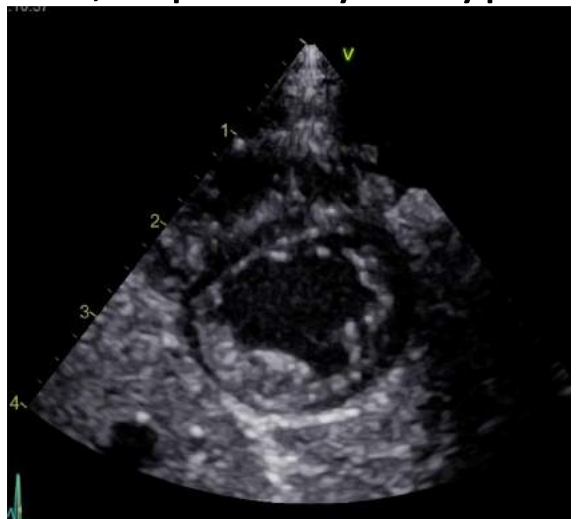


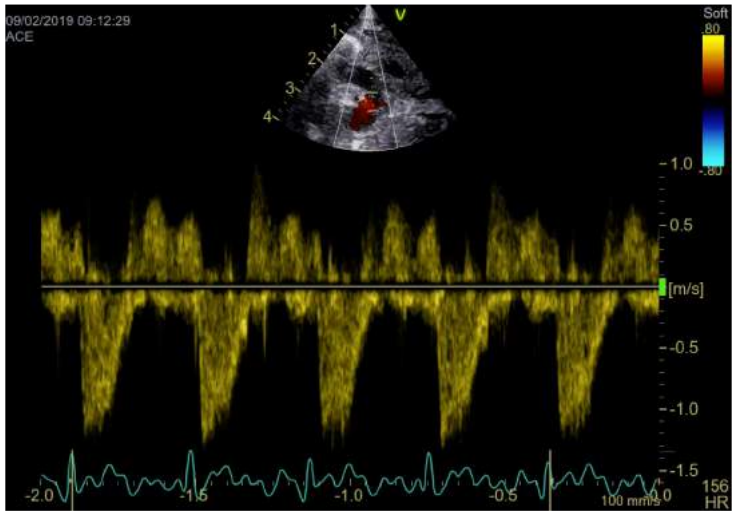




- Day 1: IV adrenaline (0.1mcg/kg/min), milrinone, IV sildenafil-→ VA ECMO
- Day 4: Decannulated from ECMO, repair day 5. Type C defect

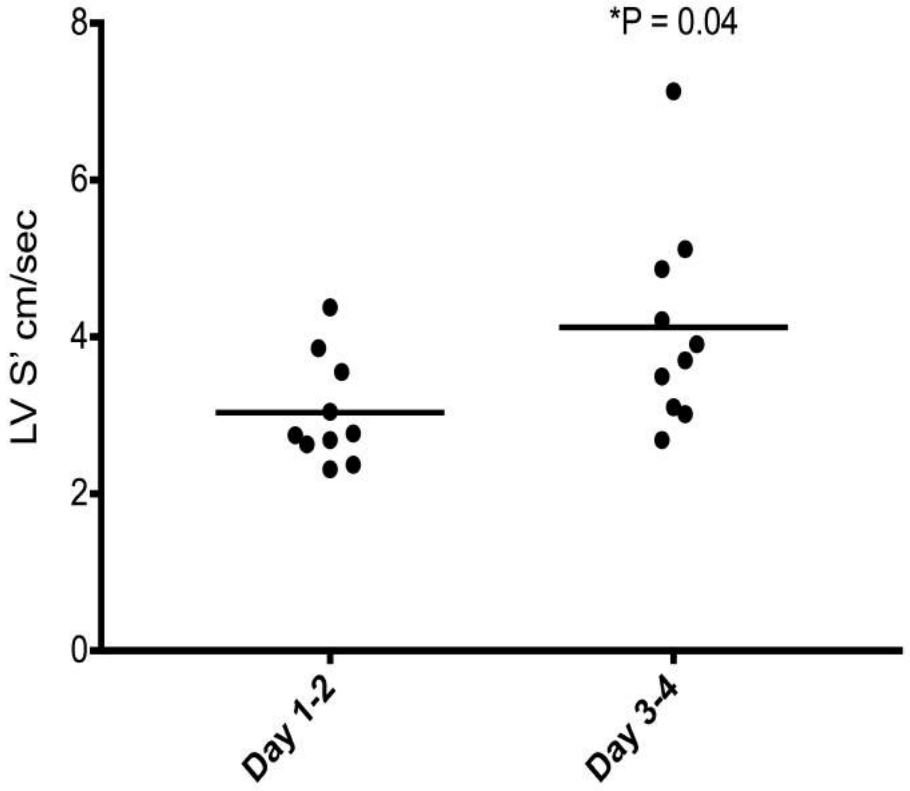




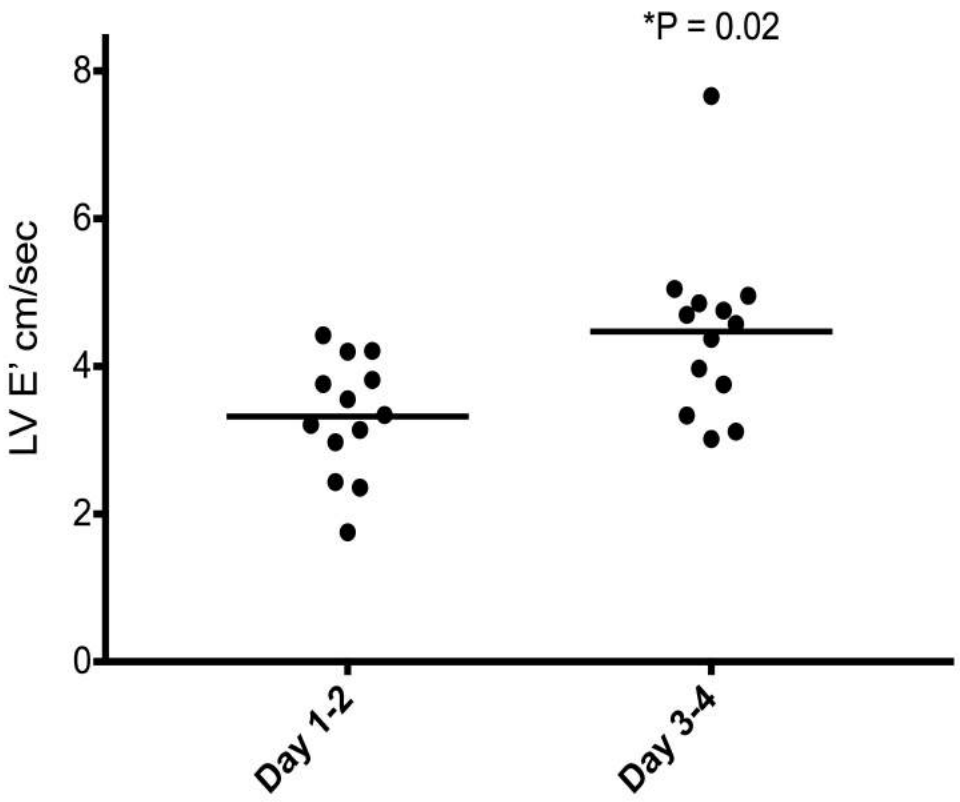


Early LV dysfunction improves in the first days of life

Systolic TDI velocities (LV S')



Diastolic TDI velocities (LV E')



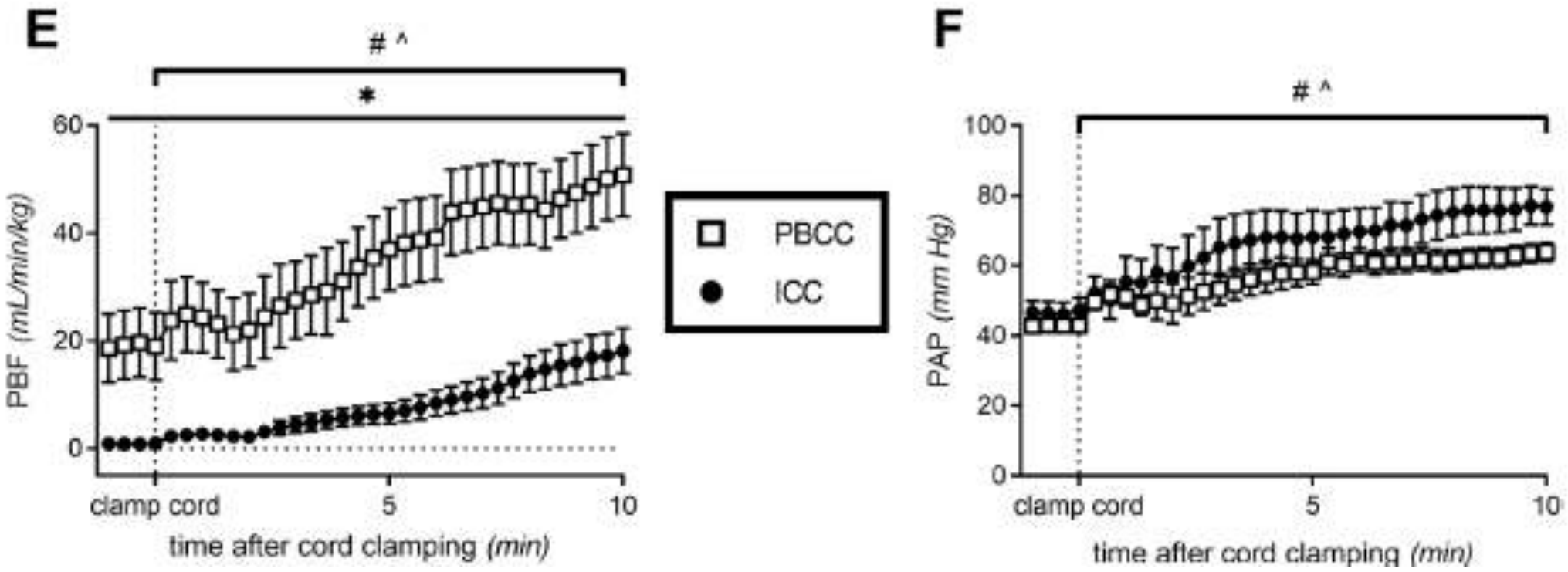
N. Patel, F. Kipfmueller / Seminars in Pediatric Surgery 26 (2017)

New therapies in CDH: Physiological based cord clamping?

NHS Greater Glasgow and Clyde | 70 YEARS #nhsscot70

Physiologically based cord clamping improves cardiopulmonary haemodynamics in lambs with a diaphragmatic hernia

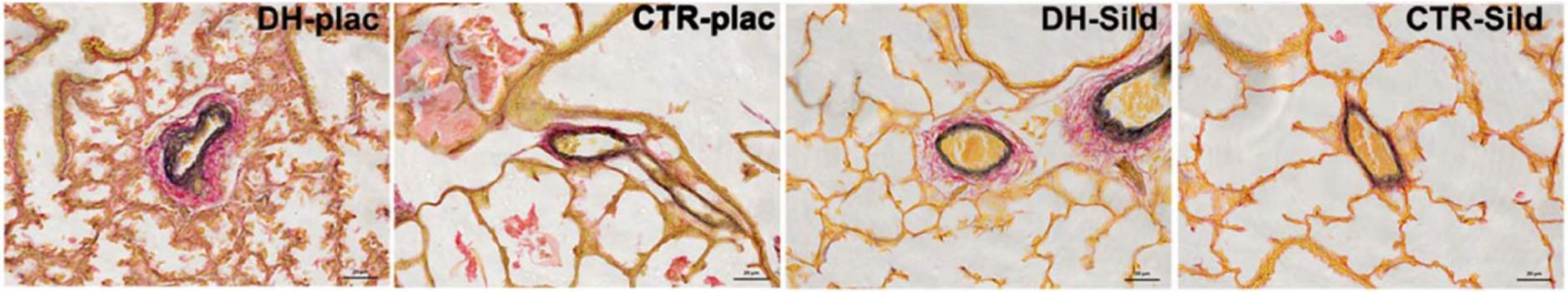
Aidan J Kashyap,[1,2] Ryan J Hodges,[1,3] Marta Thio,[4,5] Karyn A Rodgers,[1,2] Ben J Amberg,[1,2] Erin V McGillick,[1,2] Stuart B Hooper,[2,6] Kelly J Crossley,[1,2] Philip L J DeKoninck[6,7]



Neonatus 2019

New therapies in CDH: Prenatal therapies?

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



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

Thanks to

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CDH Euroconsortium

CDH International Registry