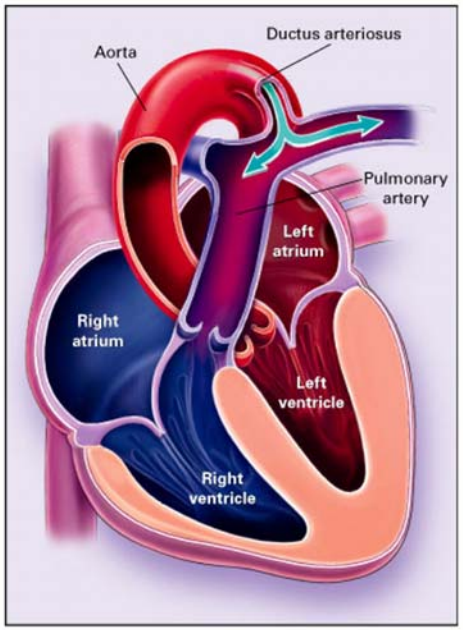
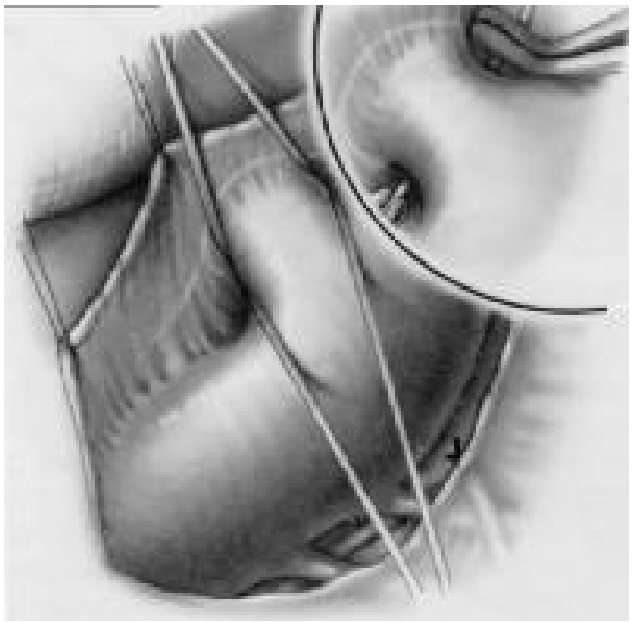
Understanding the Ductus Arteriosus. Are we hemodynamically naive?





Patrick J McNamara
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Closure of the patent ductus arteriosus with ligation and indomethacin: A consecutive experience

This report summarizes a consecutive experience with 59 preterm infants with clinical, radiographic, and echocardiographic findings of a large patent ductus arteriosus. Thirty-five infants who met defined criteria received indomethacin, and 24 infants underwent PDA ligation. Analysis of the clinical course of these infants revealed no selective indomethacin morbidity and suggests that infants undergoing ligation require more prolonged ventilator therapy with increased exposure to $Fi_{O_2} \geq 0.3$. Mortality rates between ligated and pharmacologically treated groups were similar. This study documents that inhibition of prostaglandin synthesis to constrict and close the PDA in the premature infant is an effective alternative to operative closure.

T. Allen Merritt, M.D., Thomas G. DiSessa, M.D., Bernard H. Feldman, M.D., M.P.H., Stanely E. Kirkpatrick, M.D., Louis Gluck, M.D., and William F. Friedman, M.D.,* *San Diego Calif., and Las Vegas, Nev.*

SINCE THE FIRST REPORT by Powell[1] in 1963 of closure of the patent ductus arteriosus in the preterm infant with the respiratory distress syndrome, controversy has existed regarding the optimal management of these infants. A substantial left-to-right shunt through the PDA

Merrit J Pediatr 1978

PDA Ligation & Outcome

Table III. Risk of adverse outcomes after surgical closure of PDA

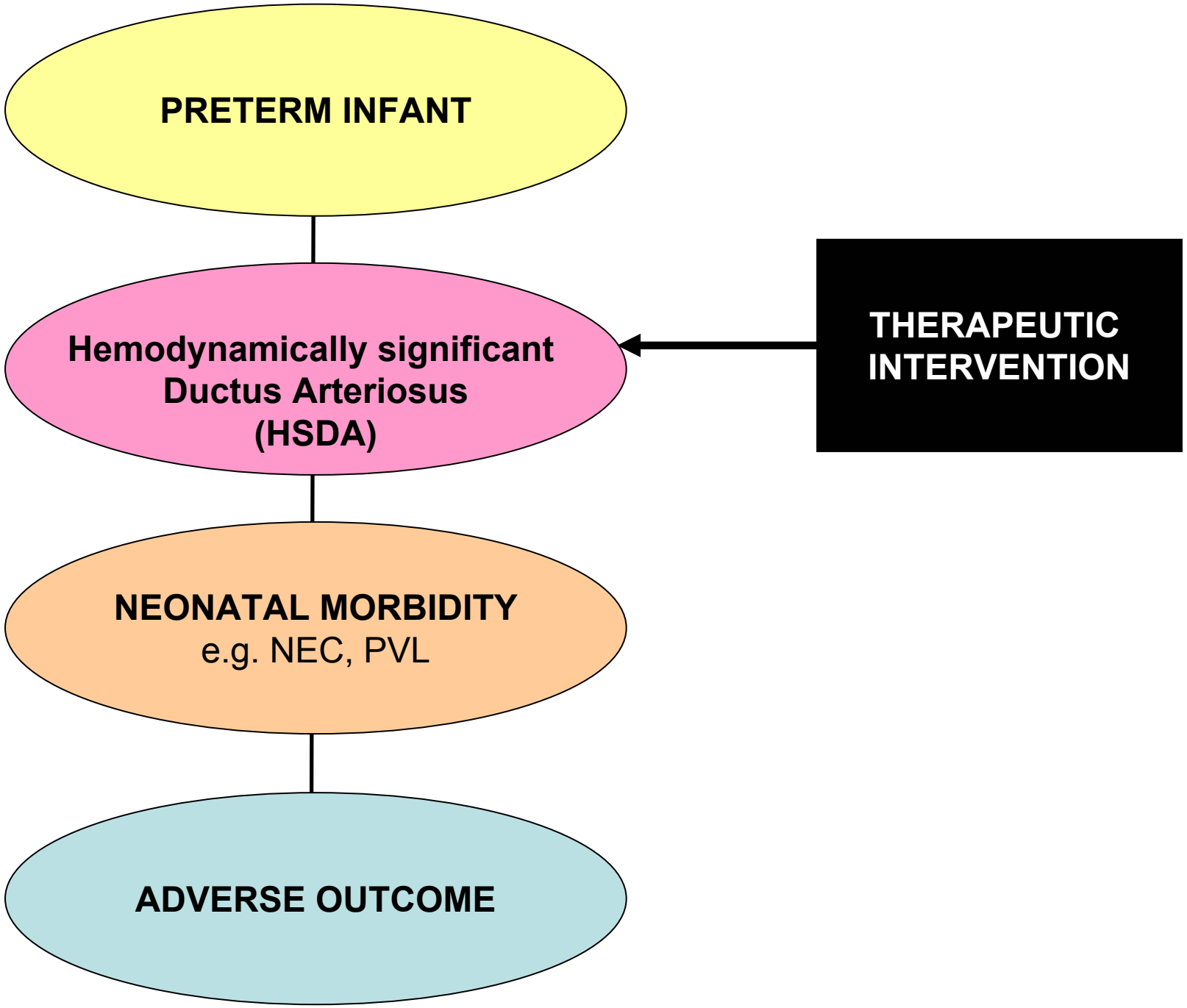
Outcome	PDA subgroup	Event rate	Unadjusted		Adjusted analyses*	
			Odds ratio	*P* value	Odds ratio (95% CI)	*P* value
BPD	PDA-no surgery	127/251 (51%)				
	PDA-surgical closure	67/100 (67%)	1.98	.0057	1.81 (1.09-3.03)	.023
Severe ROP	PDA-no surgery	32/251 (13%)				
	PDA-surgical closure	27/100 (27%)	2.53	.0016	2.20 (1.19-4.07)	.012
Death or neurosensory impairment at 18 months	PDA-no surgery	155/316 (49%)				
	PDA-surgical closure	65/110 (59%)	1.50	.07	1.55 (0.97-2.50)	.069
Death before 18 months	PDA-no surgery	71/316 (22%)				
	PDA-surgical closure	15/110 (14%)	0.55	.049	0.56 (0.29-1.10)	.095
Neurosensory impairment at 18 months	PDA-no surgery	84/245 (34%)				
	PDA-surgical closure	50/95 (53%)	2.13	.0021	1.98 (1.18-3.30)	.0093
Cognitive delay	PDA-no surgery	66/239 (28%)				
	PDA-surgical closure	41/92 (45%)	2.11	.0034	1.96 (1.14-3.35)	.015
Cerebral palsy	PDA-no surgery	35/245 (14%)				
	PDA-surgical closure	18/95 (19%)	1.40	.29	1.22 (0.64-2.33)	.55

*Analysis adjusted for the use of antenatal steroids, gestational age at birth, sex, multiple births, mother's education, and total dose of indomethacin received per kg bodyweight between

Kabra 2007 J Pediatrics

PDA-Related Variables	Risk of CLD			
	Model 1: Unadjusted OR (95% CI)	Model 2: Adjusted for Gestational Age, OR (95% CI)	Model 3: Adjusted for Perinatal and Neonatal Factors, OR (95% CI)[a]	Model 4: Adjusted for Gestational Age and Ligation, OR (95% CI)
Indomethacin doses				
Prophylactic doses >3	2.09 (1.26–3.47)[b]	1.69 (1.00–2.86)	1.35 (0.75–2.44)	1.32 (0.71–2.45)
Total doses >3	1.83 (1.13–2.95)[b]	1.44 (.87–2.38)	1.23 (0.70–2.16)	1.02 (0.54–1.94)
Ductus patent after prophylactic indomethacin	2.33 (1.25–4.36)[b]	1.79 (0.93–3.45)	1.54 (0.75–3.18)	1.09 (0.44–2.70)
Symptomatic PDA	2.81 (1.65–4.78)[b]	1.54 (0.90–2.64)	1.55 (0.85–2.81)	0.45 (0.10–2.06)
Ligation	2.14 (1.29–3.55)[b]	1.97 (1.11–3.47)[b]	1.91 (1.02–3.57)[b]	—

Chorne 2007 Pediatrics


PRETERM INFANT
Hemodynamically significant Ductus Arteriosus (HSDA)
THERAPEUTIC INTERVENTION
NEONATAL MORBIDITY
e.g. NEC, PVL
ADVERSE OUTCOME

Myths of the Modern Era

1. “PATENT” ductus arteriosus
=
“PROBLEMATIC” ductus arteriosus

2. “All ducti are equal”

3. Murmur = ductus

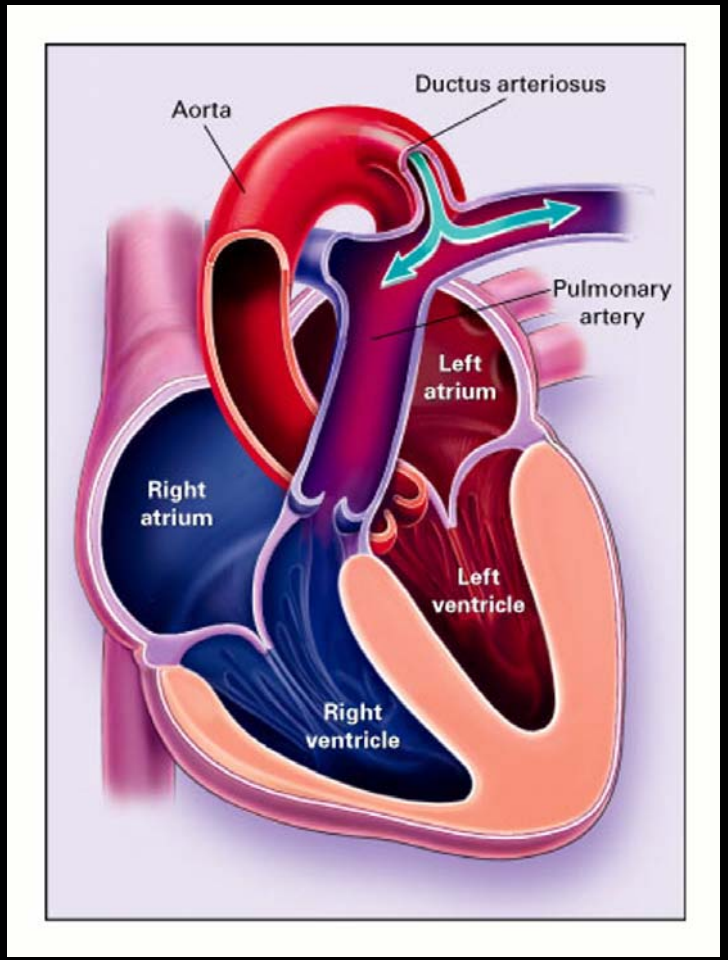
Oversimplification of Ductal Disease as an All or None Phenomenon

Issues…..

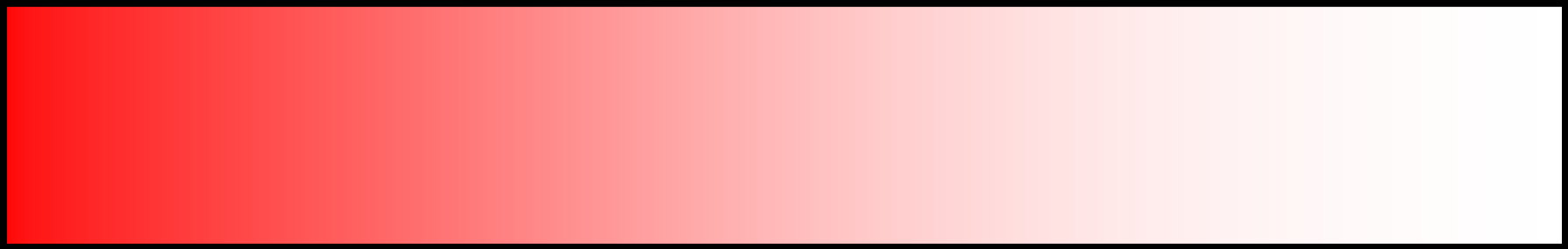
- Variable role of the Ductus arteriosus
- Challenges of making the **diagnosis**
  - **Clinical confounders**
  - **Echocardiography confounders**
- Failure to streamline those patients where the ductus arteriosus is an innocent bystander from a **hemodynamically significant ductus arteriosus** (HSDA)
- Oversimplification of study designs and remoteness of long term outcomes

Role of the Ductus Arteriosus

- Transitional Physiology
- PPHN, RV dysfunction
- Duct dependant cardiac lesions
- Systemic-pulmonary shunting



Ductal Continuum



INNOCENT BYSTANDER

3.0 mm DA, urL-R flow

Full feeds

Room air

PATHOPHYSIOLOGY

3.0 mm DA, urL-R flow

HFOV [MAP 16, FiO2 0.8]

Pulmonary hemorrhage

Systemic Hypotension

Anuria, Creatinine 360

Abdominal distension

Is their hemodynamic impact?

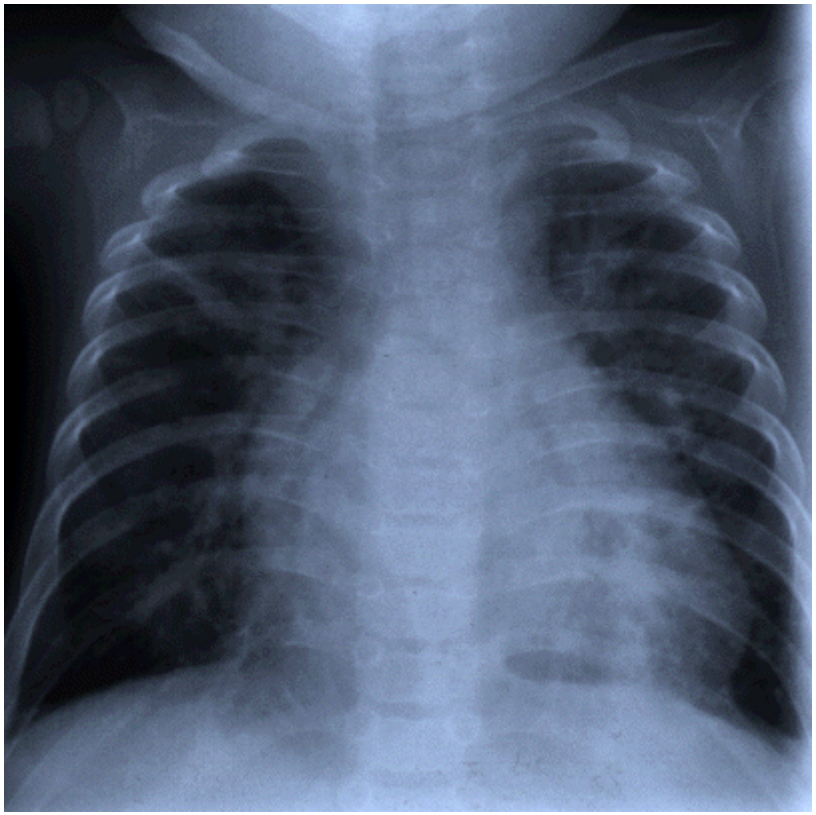
- Is the clinical and/or physiologic instability related to increased ductal severity?

- Does the clinical and/or physiologic alteration resolve after ductal treatment?

If YES, then the DA is likely to be contributing to ongoing patient instability

Early clinical findings ……

- Classical signs absent
- Hypotension (day 2-3) - inotropes
- Increased ventilator requirements
- Persistent metabolic acidosis –volume, bicarbonate



Eur J Pediatr (2009) 168:907–914
DOI 10.1007/s00431-009-0983-3

REVIEW

Does echocardiography facilitate determination of hemodynamic significance attributable to the ductus arteriosus?

Arvind Sehgal · Patrick J. McNamara

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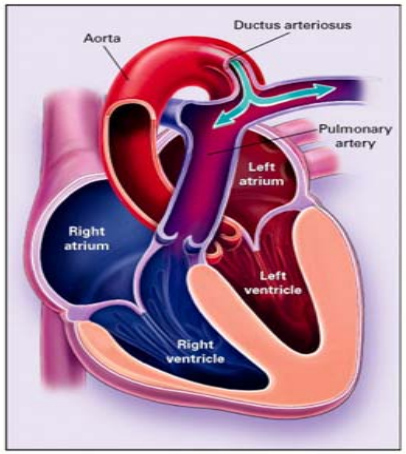
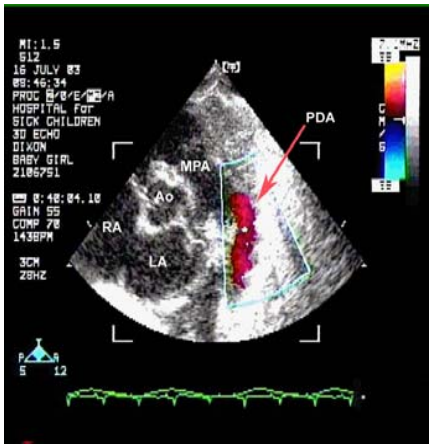
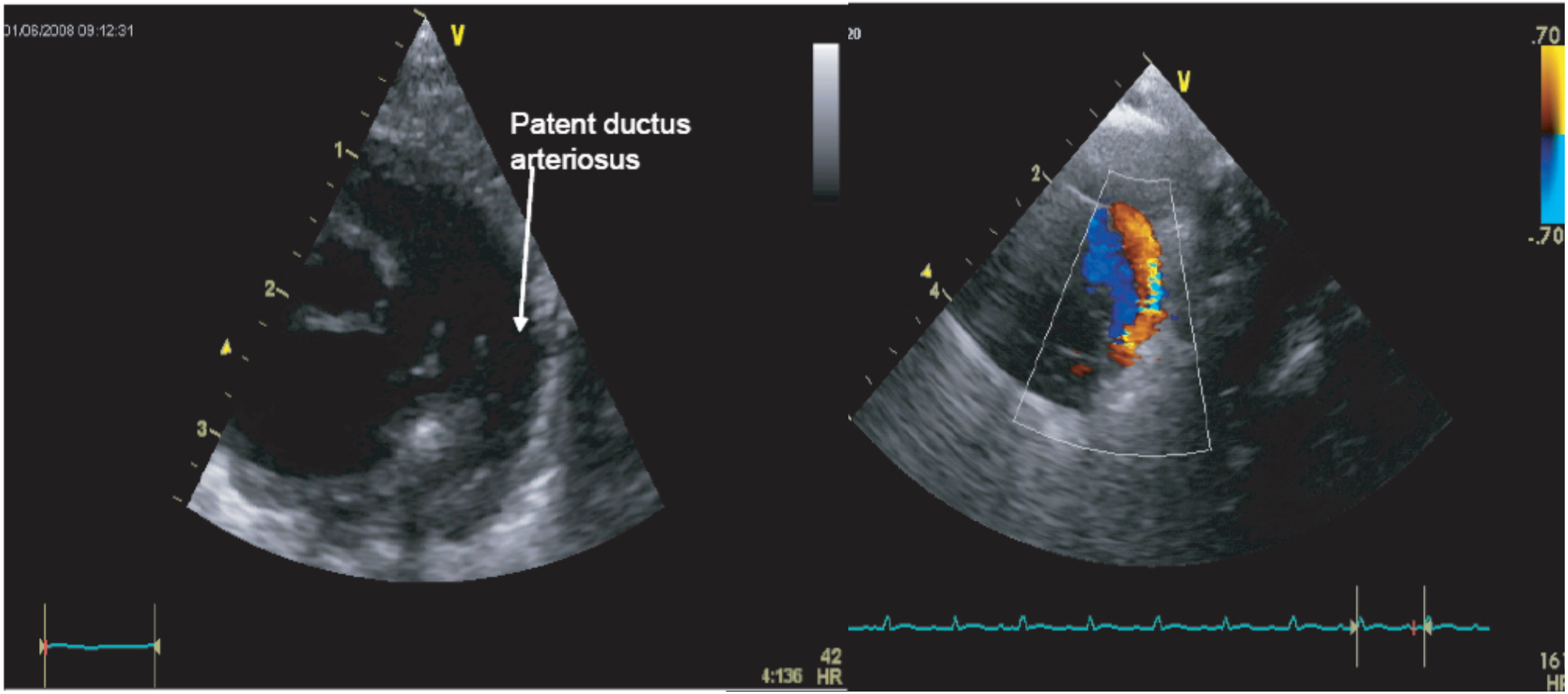




Quantification of the volume of blood flow across the Ductus Arteriosus would provide the best measure of hemodynamic significant

Is the ductus patent?

What is transductal diameter?



Issues: Measurement error, Variability in architecture and longitudinal diameter of the ductus arteriosus, Size is **NOT STATIC**

Diagnosis of HSDA

Transductal Diameter > 1.5 mm

AND

Unrestrictive L-R flow

AND

Clinical signs of pulmonary overcirculation ± systemic hypoperfusion

AND

Echocardiography signs of pulmonary overcirculation ± systemic hypoperfusion

HSDA

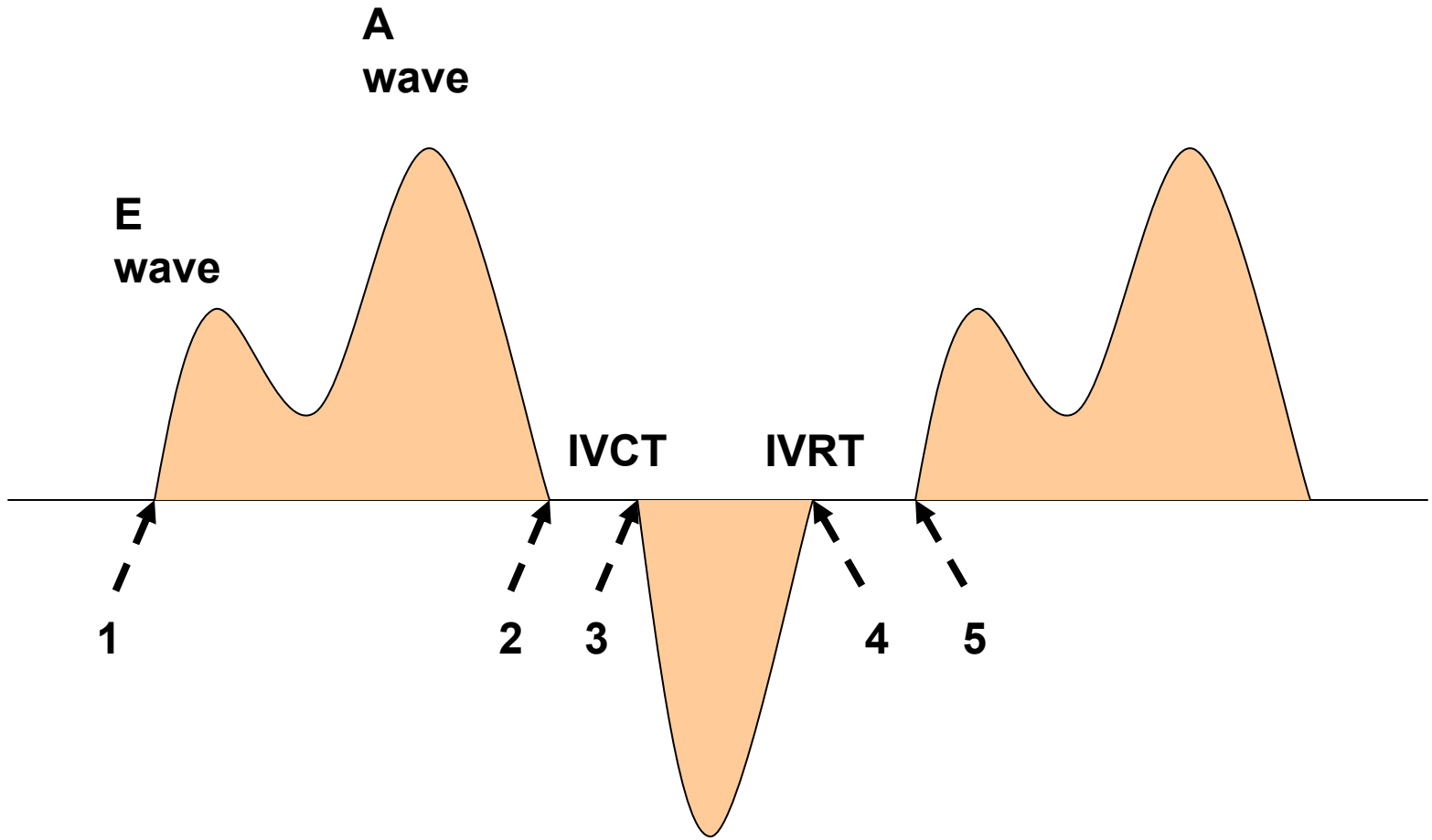
Ductal Evaluation
PDA – size, flow direction
& quality

Pulmonary Overcirculation
- LA:Ao, E:A ratio, IVRT
- ASD size & flow
- LPA diastolic flow

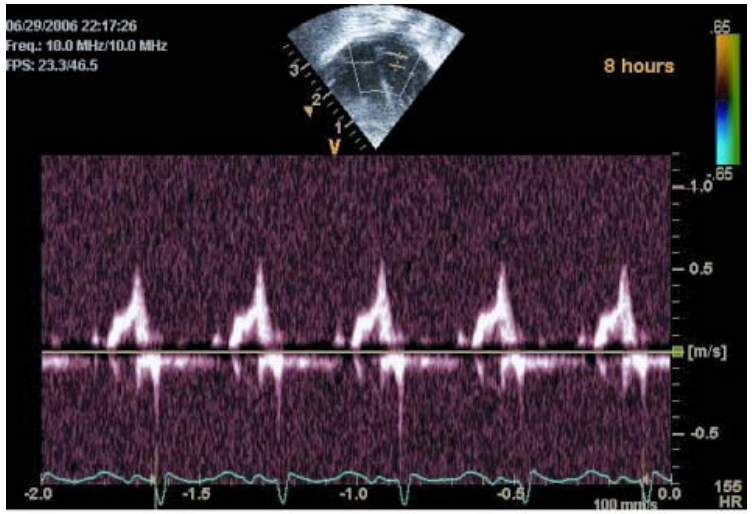
Systemic Hypoperfusion
- LVO or LVO:SVC flow
- Desc Ao Doppler
- End-organ Dopplers
(*MCA, celiac, renal*)

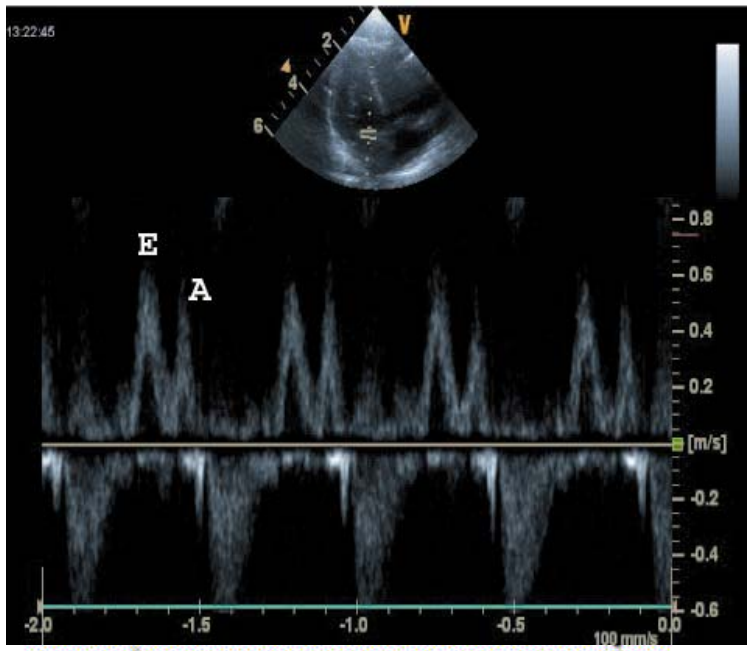
ANATOMICAL REVIEW

Transmitral Flow



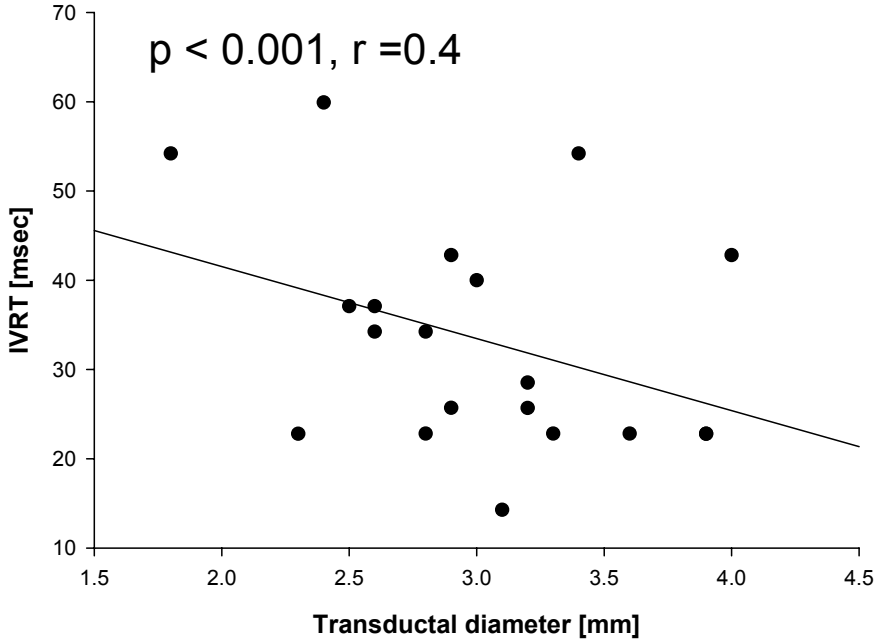
TRANSMITRAL FLOW



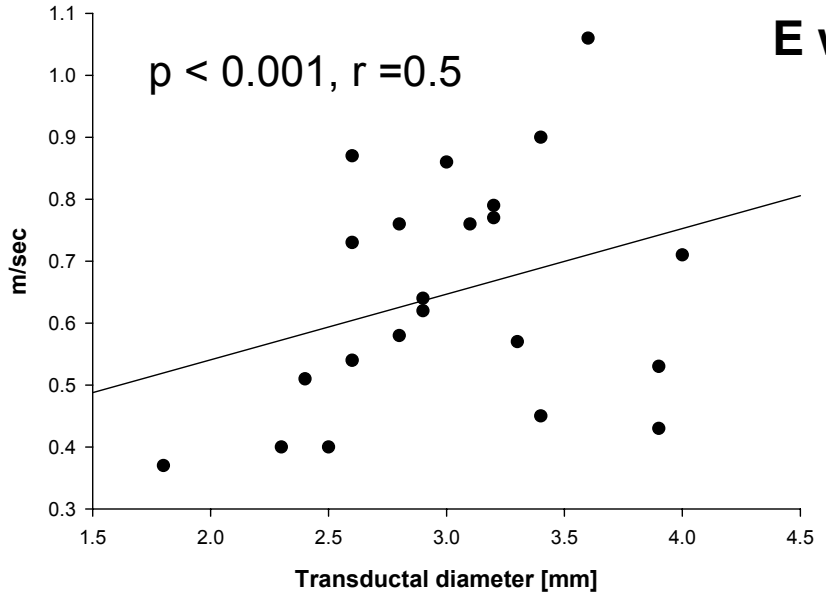


Sehgal 2007 E-PAS

IVRT

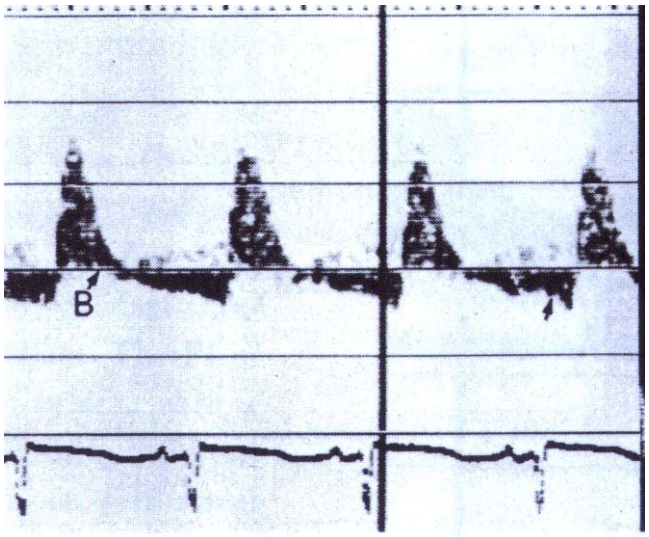


E wave



End-organ flow and Ductal size

Middle Cerebral Artery



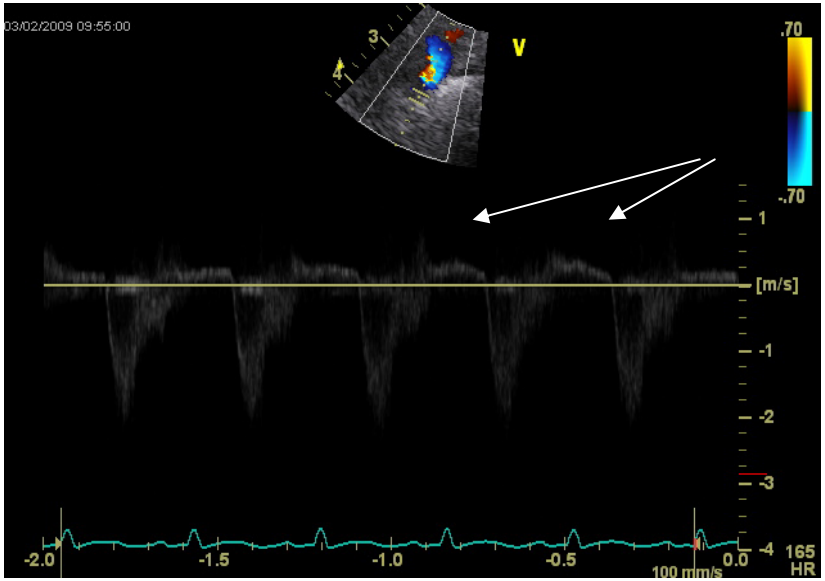
Lipman 1982 Pediatrics

Size (mm)	Anterograde	Retrograde
< 1.5	58/61(95%)	0
>1.7	1/58(1.7%)	50/58(86.3%)

Evans 1995 Arch Dis Child

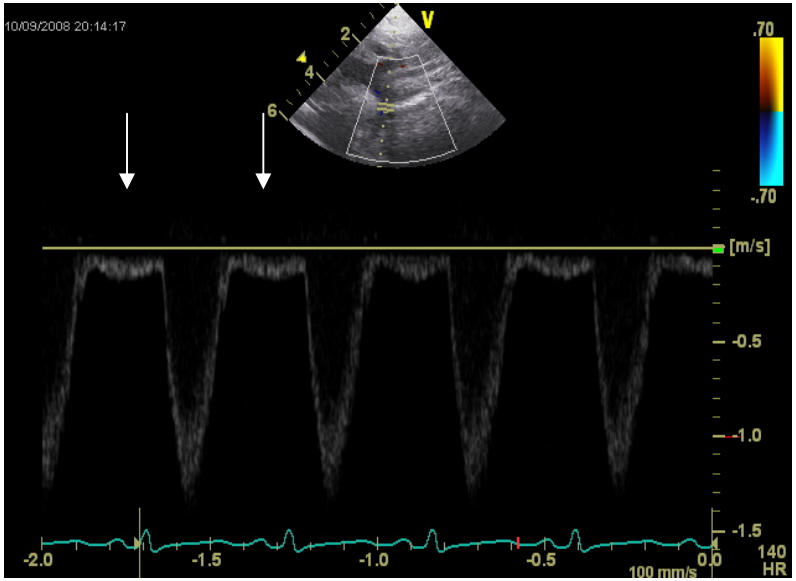
Increased transductal diameter leads to **absence or reversal** of diastolic flow to vital organs

HSDA

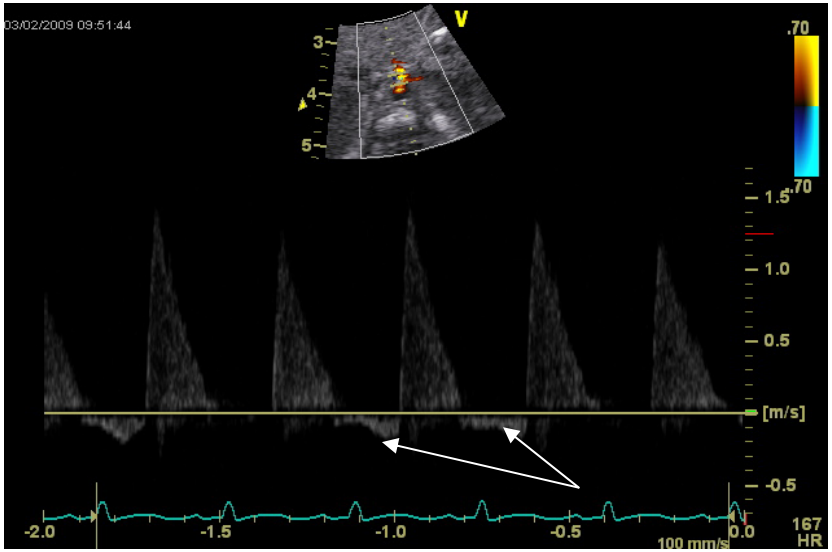


Reversed EDF in post-ductal aorta

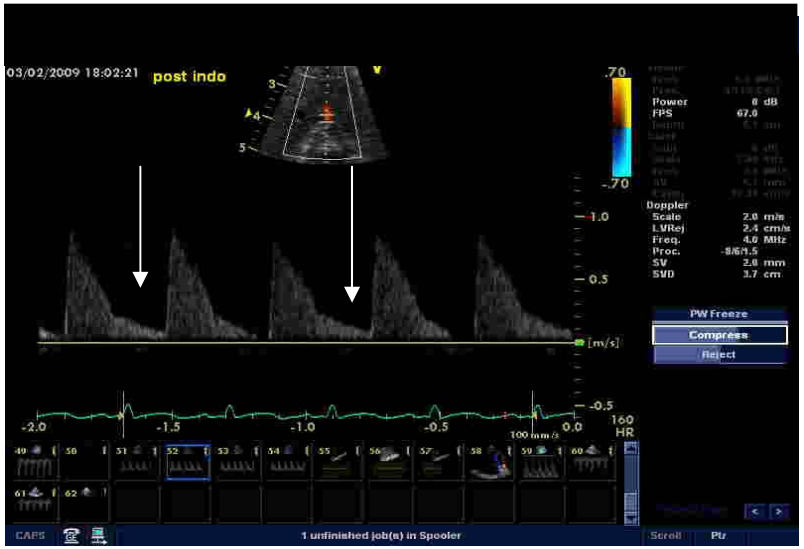
Closed DA



Normal EDF in post-ductal aorta

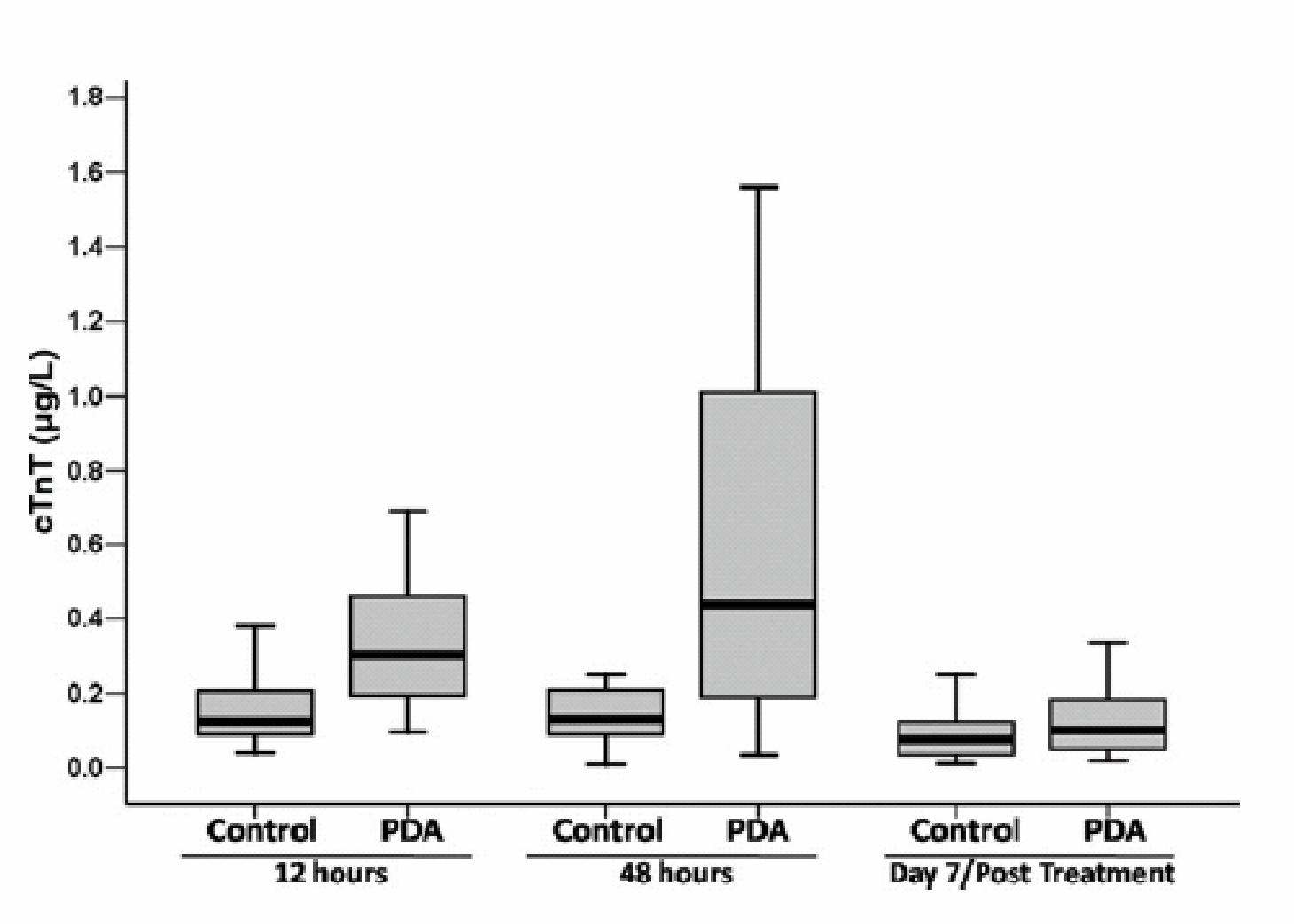


Reverse EDF in SMA



Normal EDF in SMA

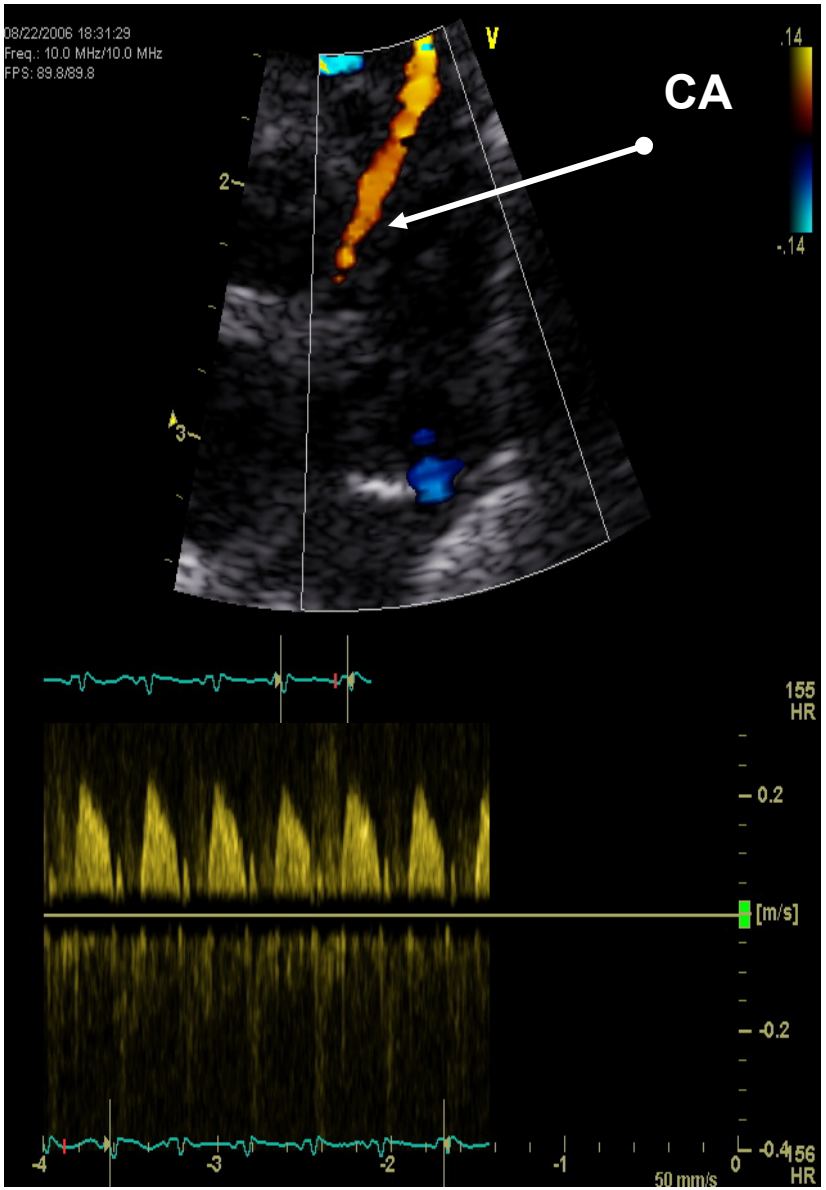
Troponin & HSDA

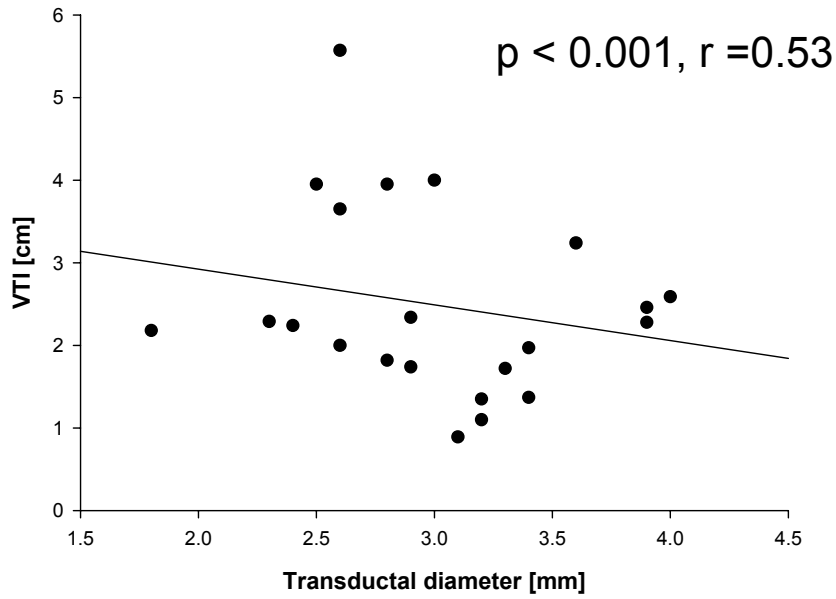


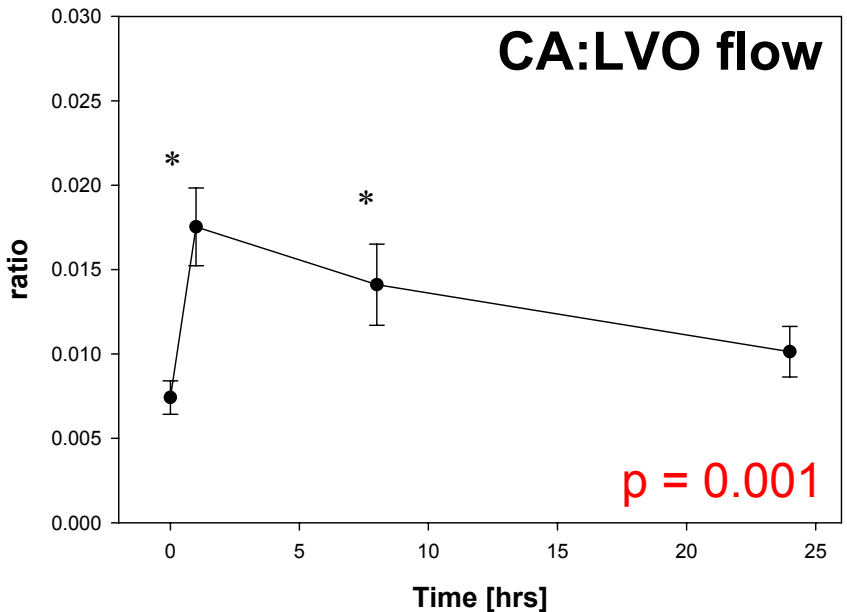
Al Khuffash 2008 Arch Dis Child

CORONARY ARTERY FLOW and HSDA

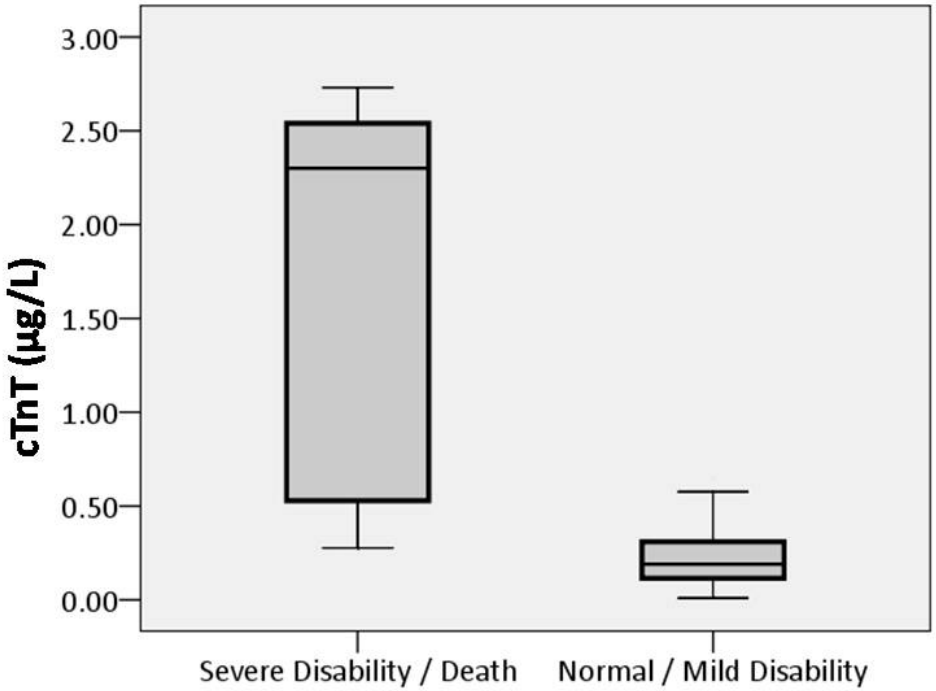
Sehgal 2007 E-PAS

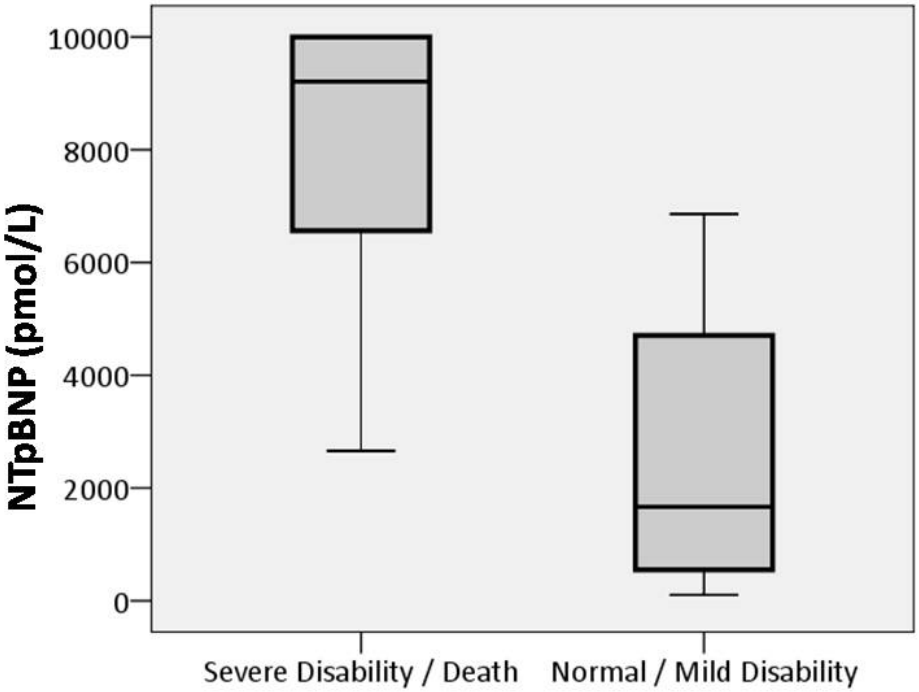






Plasma cTnT and NTpBNP in first 48 hours of life

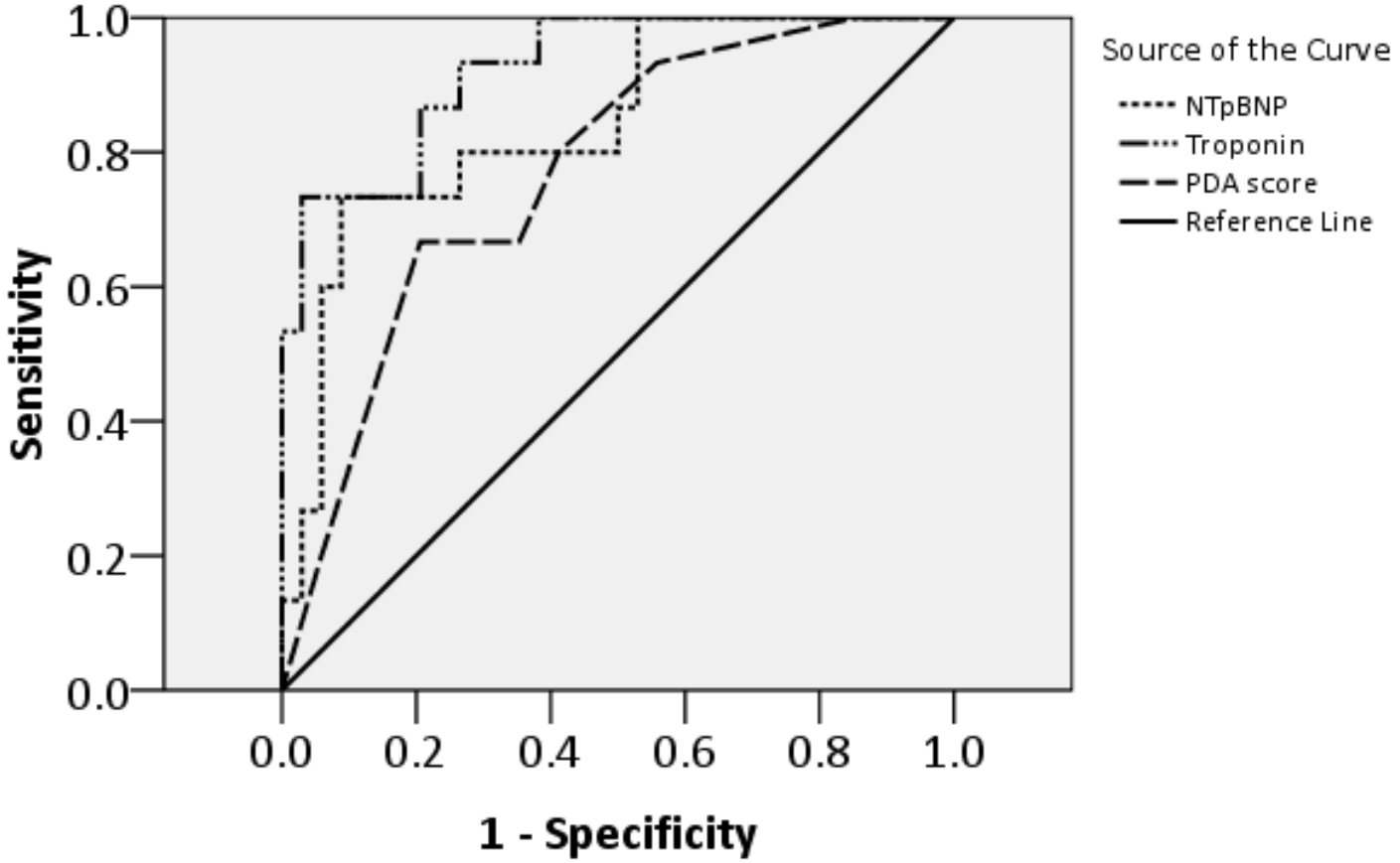




El-Khuffash Arch Dis Child (In press)

Figure 2: ROC for cTnT, NTpBNP and PDA score in predicting outcome

El-Khuffash Arch Dis Child (In press)



	Area	p value	95% CI	Cut off	Sensitivity	Specificity
NTpBNP	0.84	< 0.001	0.72 – 0.93	5200	80%	75%
cTnT	0.92	< 0.001	0.85 – 0.99	0.49	87%	79%
PDA Score	0.77	0.003	0.63 – 0.91	4	67%	79%

Ductal Staging *McNamara 2007 Arch Dis Child*

Table 1 Proposed staging system (adapted from McNamara and Hellman, unpublished clinical triaging system for ligation of a patent ductus arteriosus (PDA)) for determining the magnitude of the haemodynamically significant ductus arteriosus (HSDA), which is based on clinical and echocardiographic criteria

Clinical	Echocardiography
C1 Asymptomatic	E1 No evidence of ductal flow on two-dimensional or Doppler interrogation
C2 Mild Oxygenation difficulty (OI <6) Occasional (<6) episodes of oxygen desaturation, bradycardia or apnoea Need for respiratory support (nCPAP) or mechanical ventilation (MAP <8) Feeding intolerance (>20% gastric aspirates) Radiologic evidence of increased pulmonary vascularity	E2 Small non-significant ductus arteriosus Transductal diameter <1.5 mm Restrictive continuous transductal flow (DA V_{max} >2.0 cm/s) No signs of left heart volume loading (eg, mitral regurgitant jet >2.0 cm/s or LA:Ao ratio >1.5:1) No signs of left heart pressure loading (eg, E/A ratio >1.0 or IVRT >50) Normal end-organ (eg, superior mesenteric, middle cerebral) arterial diastolic flow
C3 Moderate Oxygenation difficulty (OI 7–14) Frequent (hourly) episodes of oxygen desaturation, bradycardia or apnoea Increasing ventilation requirements (MAP 9–12) Inability to feed due to marked abdominal distension or emesis Oliguria with mild elevation in plasma creatinine Systemic hypotension (low mean or diastolic BP) requiring a single cardiotropic agent Radiological evidence of cardiomegaly or pulmonary oedema Mild metabolic acidosis (pH 7.1–7.25 and/or base deficit −7 to −12.0)	E3 Moderate HSDA Transductal diameter 1.5–3.0 mm Unrestrictive pulsatile transductal flow (DA V_{max}<2.0 cm/s) Mild-moderate left heart volume loading (eg, LA:Ao ratio 1.5 to 2:1) Mild-moderate left heart pressure loading (eg, E/A ratio >1.0 or IVRT 50–60) Decreased or absent diastolic flow in superior mesenteric artery, Middle cerebral artery or renal artery
C4 Severe Oxygenation difficulty (OI >15) High ventilation requirements (MAP >12) or need for high-frequency modes of ventilation Profound or recurrent pulmonary haemorrhage "NEC-like" abdominal distension with tenderness or erythema Acute renal failure Haemodynamic instability requiring >1 cardiotropic agent Moderate-severe metabolic acidosis (pH<7.1) or base deficit >−12.0	E4 Large HSDA Transductal diameter >3.0 mm Unrestrictive pulsatile transductal flow Severe left heart volume loading (eg, LA:Ao ratio >2:1, mitral regurgitant jet >2.0 cm/s) Severe left heart pressure loading (eg, E/A ratio >1.5 or IVRT >60) Reversal of end-diastolic flow in superior mesenteric artery, middle cerebral artery or renal artery

Benefits of this approach

- Streamline Innocent bystanders from Pathological cases
  - ↓ ligation rates [82/year (2005) to 38 /year (2009)]
  - Prevent transfers or cancellations

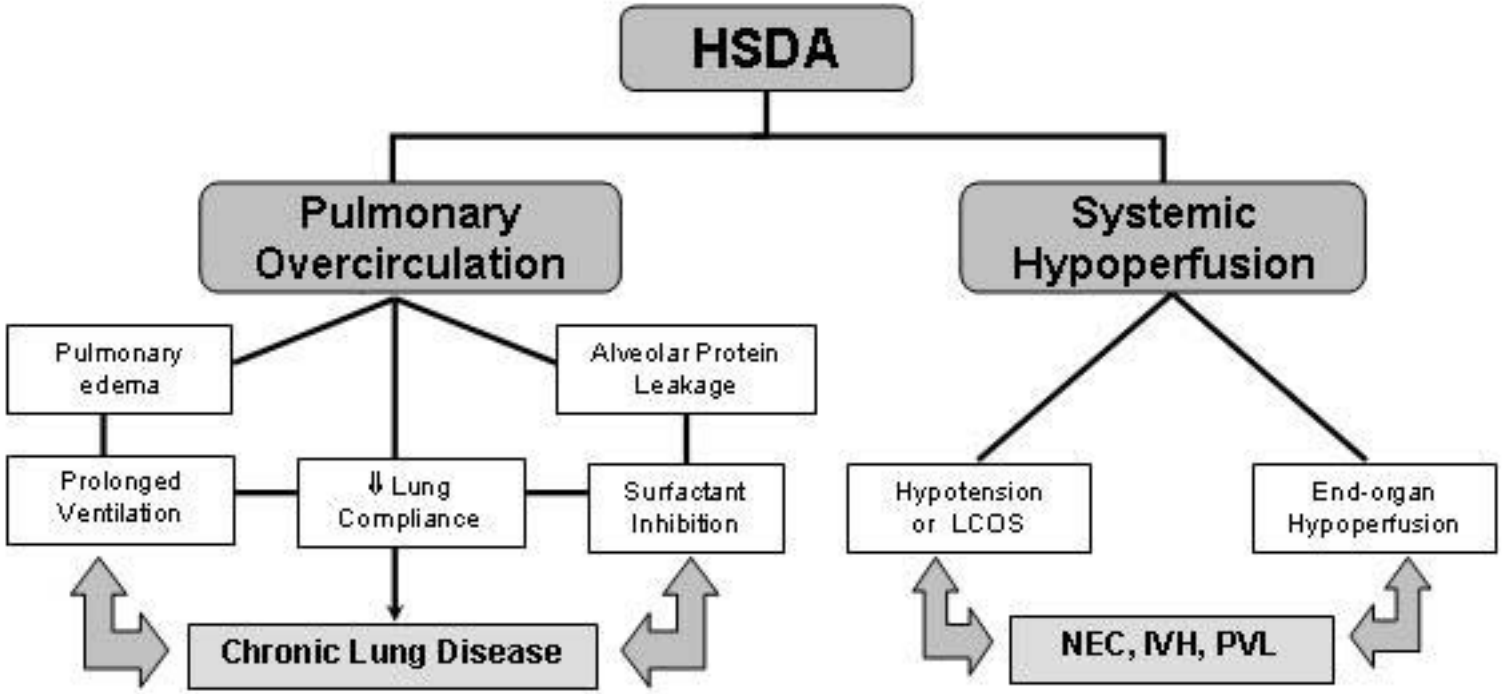
- Categorization & Prioritization
  - determine urgency and level of intervention

- Facilitates a more physiologic approach

- Evaluate response to therapy and better define responders

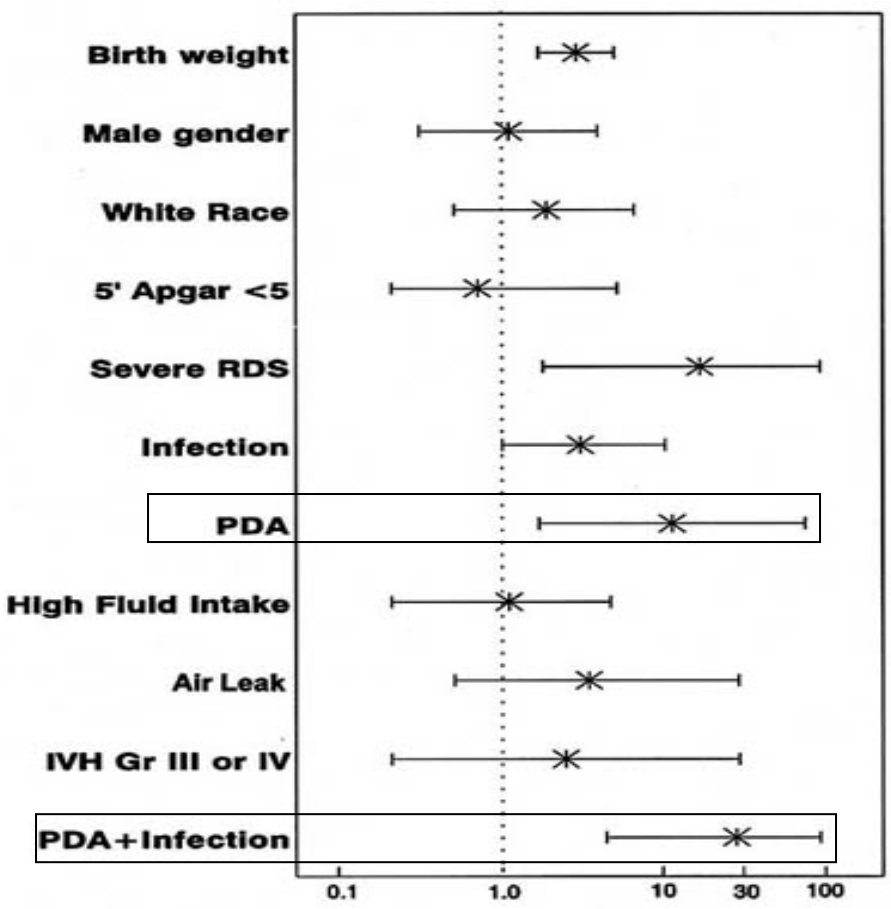
A hemodynamically significant ductus arteriosus is associated with **acute reversible physiologic disturbance**……

- BUT what about neonatal morbidities?



Teixeira 2006 Acta Paed

HSDA and increased Respiratory morbidity…..



Gonzalez 1996 J Pediatr

- Increased risk of CLD with combination of sepsis and HSDA
  [OR 29.6 (4.5, >100)]
- PDA is a risk factor for wheezing in children at 1 year of age
  [OR 1.7 (1.0, 3.1)]

Palta 2001 Am J Perinat

Ductal stage and Respiratory outcomes

	Low grade (n=10)	Intermediate grade (n=16)	High grade (n=18)	p
Duration of oxygen (d)	60.2 ± 40.6 #	79.9 ± 38.2 #	124.9 ± 61.9	**0.009**
Home oxygen (n)	0 *	0 *	8	**0.009**
CLD (n, %)	5 (50%)	7 (44%)	14 (78%)	**0.09**

*# p <0.05 vs group I, *p< 0.05 vs III*

Sehgal 2010 Am J Perinat

HSDA & increased risk of NEC…

	Adjusted OR (95% CI) All gestational ages (N = 6135)	Adjusted OR (95% CI) 24–27 weeks gestation (N = 1476)	Adjusted OR (95% CI) 28–34 weeks gestation (N = 4659)
PDA and indomethacin therapy			
Neither	1.0	1.0	1.0
Indomethacin only	0.72 (0.25–1.66)	0.83 (0.24–2.15)	0.45 (0.02–2.14)
PDA only	1.85 (1.24–2.69)	1.77 (1.00–3.02)	2.05 (1.16–3.44)
PDA + indomethacin	1.53 (1.15–2.02)	1.47 (1.01–2.16)	1.66 (1.08–2.51)

Odds ratios adjusted for maternal hypertensive disorder, gestational age; small for gestational age, multiple pregnancy and respiratory disorders.
NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; OR = odds ratios; CI = confidence interval.

Prospective data collected from Israel Neonatal Network

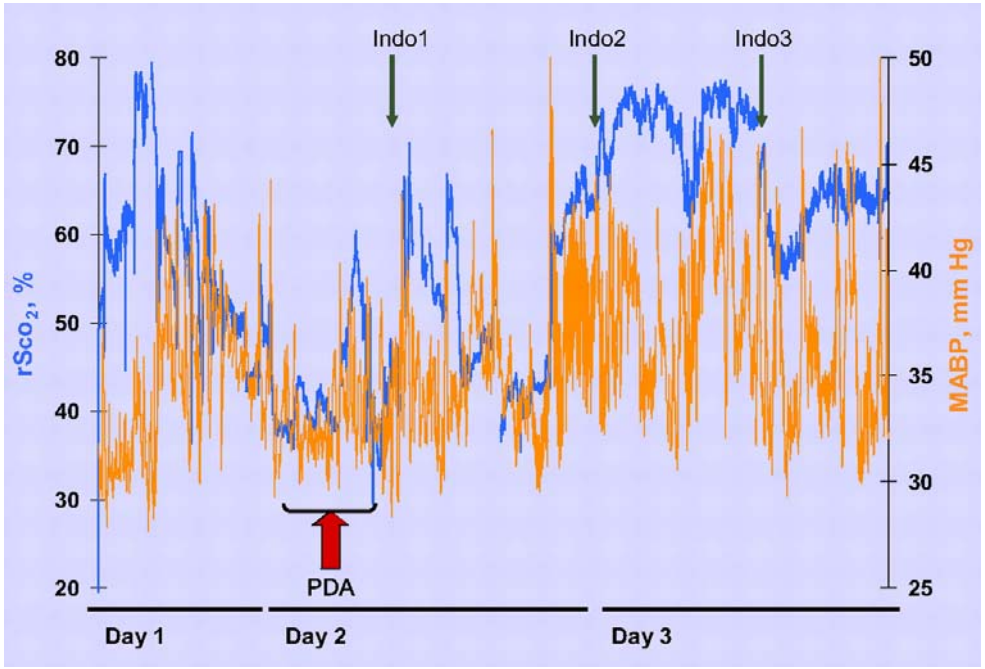
NEC rate 5.5% (all) & 9.4% of neonates with a PDA

Dollberg 2005 J Pediatr Gastro & Nutrition

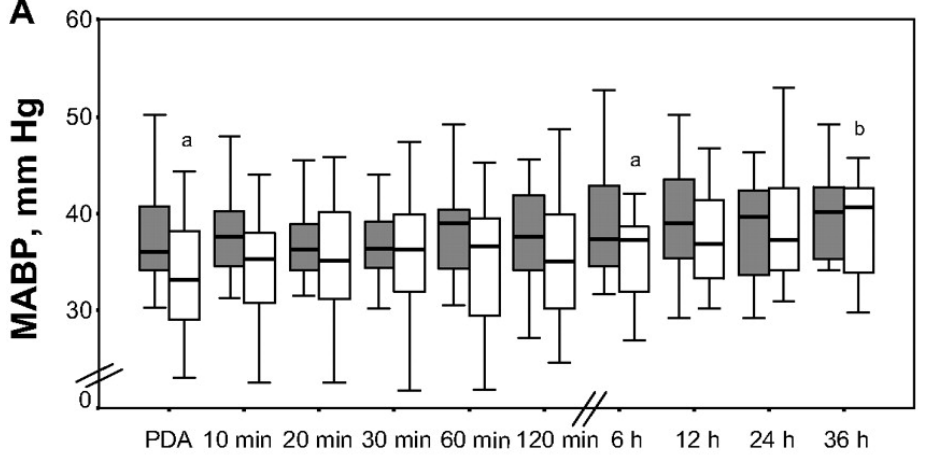
NEC rate 23% in neonates requiring PDA Ligation

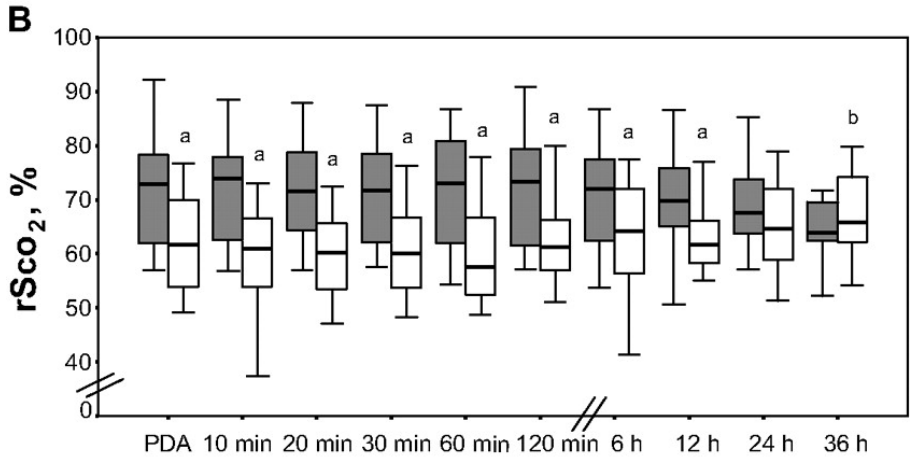
Teixeira 2008 J Perinat

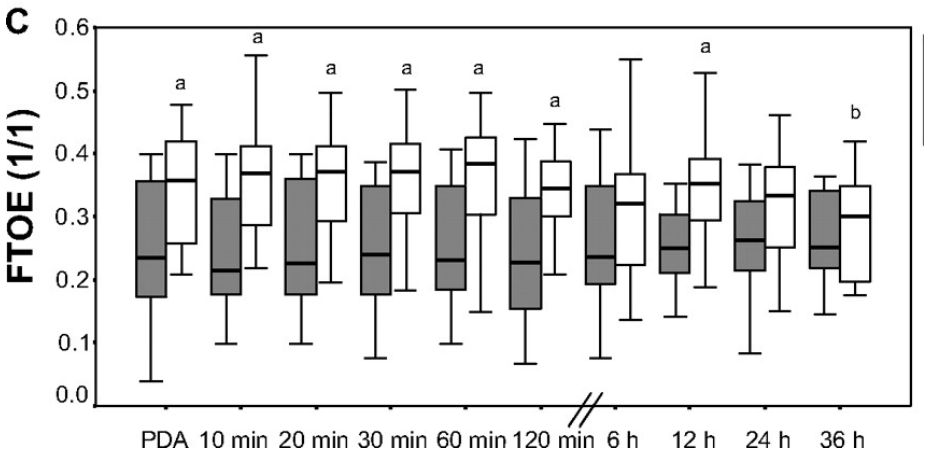
Mesenteric Tissue Oxygenation



Lemmers 2008 Pediatrics







Is there evidence that intervention is beneficial?

The viewpoint of the "permissivist"

"there is NO evidence that treatment of the DA improves long term outcomes"

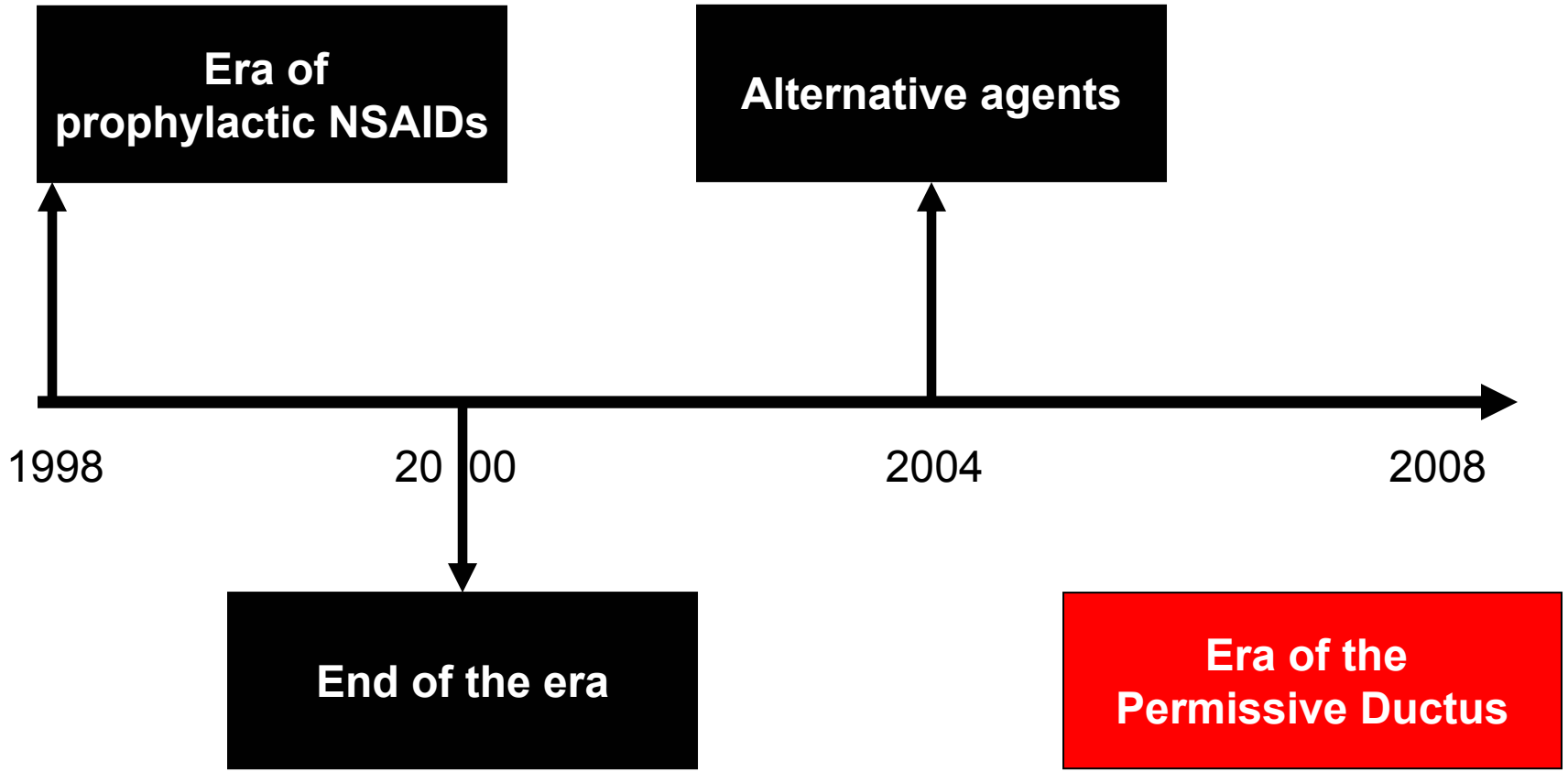
No placebo controlled trials of therapeutic intervention

Effect of Medical Treatment

	Proph vs. Early (17)	Early vs. Late (8)
Number	264	1580
Ligation	0.37 (0.2-0.68) *	0.18 (0.08-0.41) *
Pulmonary Morbidity	1.04 (0.81-1.31)	0.39 (0.21-0.76) *
NEC	1.39 (0.76-2.51)	0.24 (0.06-0.96) *
Pulmonary Hemorrhage	0.54 (0.3-0.96)	

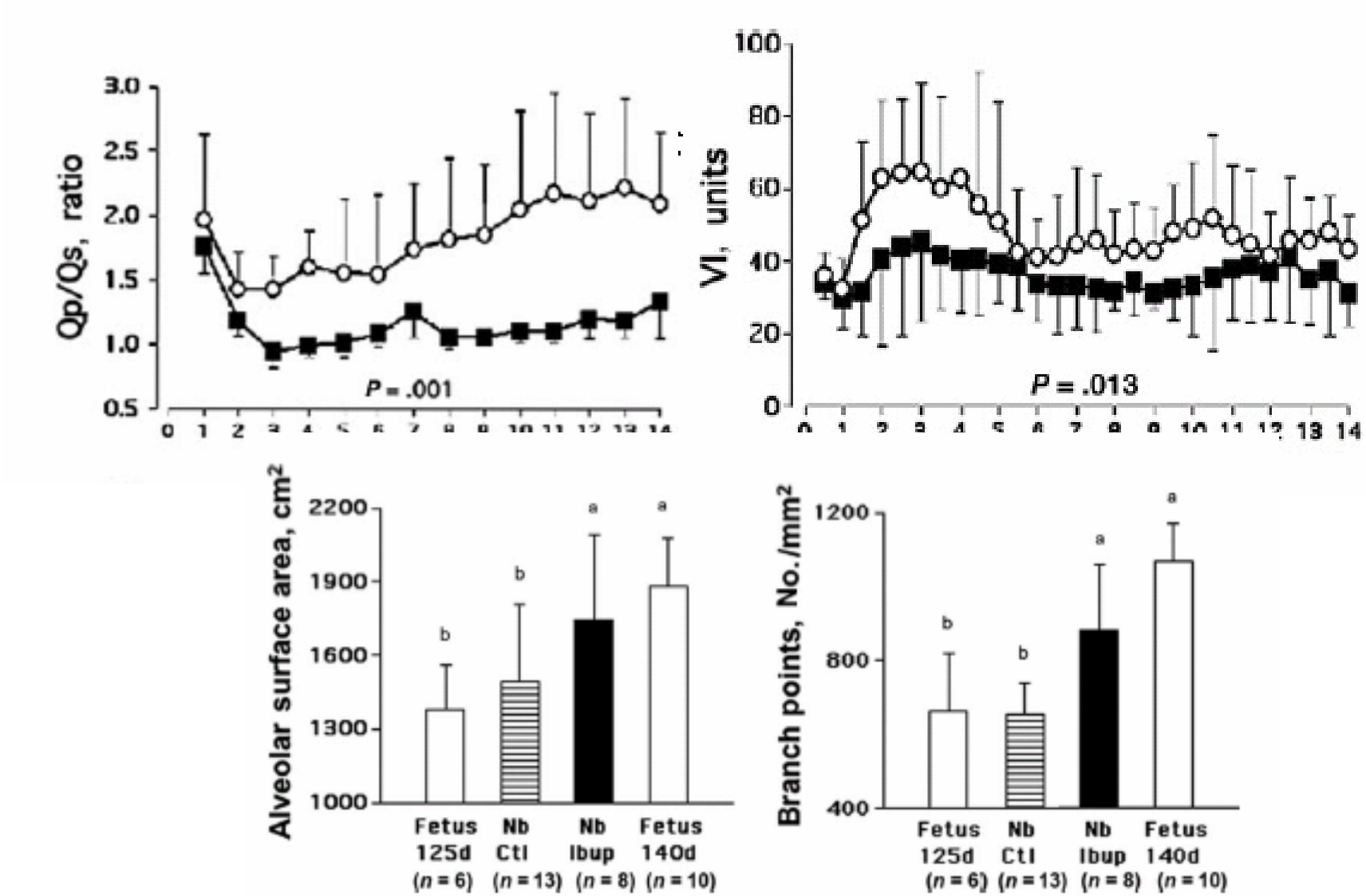
Clyman 1996 J Pediatr

Trends in Ductal Care



NSAIDs vs Placebo: *acute physiology*

McCurnin 2008 Pediatrics



SUPPORTIVE ICU CARE

Surfactant

Hypocapnia

Oxygen or Nitric oxide

Hypocapnia / Alkalosis

Pressors

Oxygen

Hypothermia

PVR
+

PDA

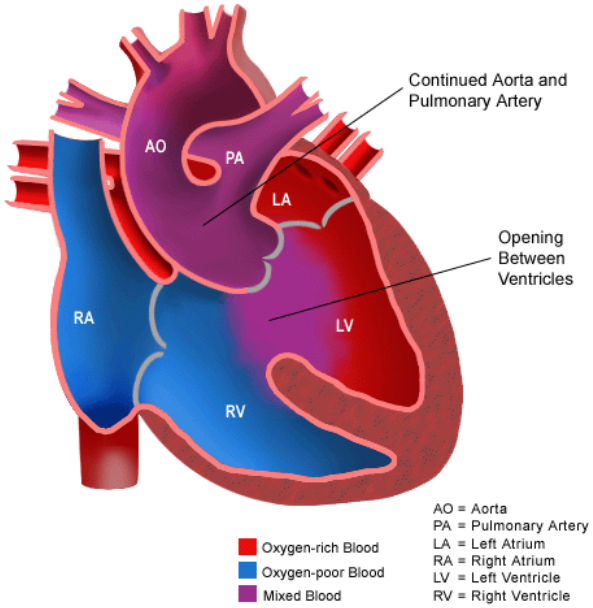
Ao

SVR
+++++
+++

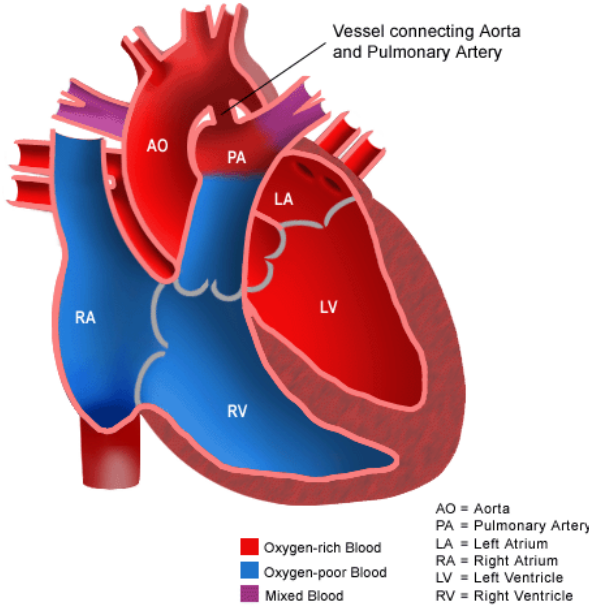
Ao

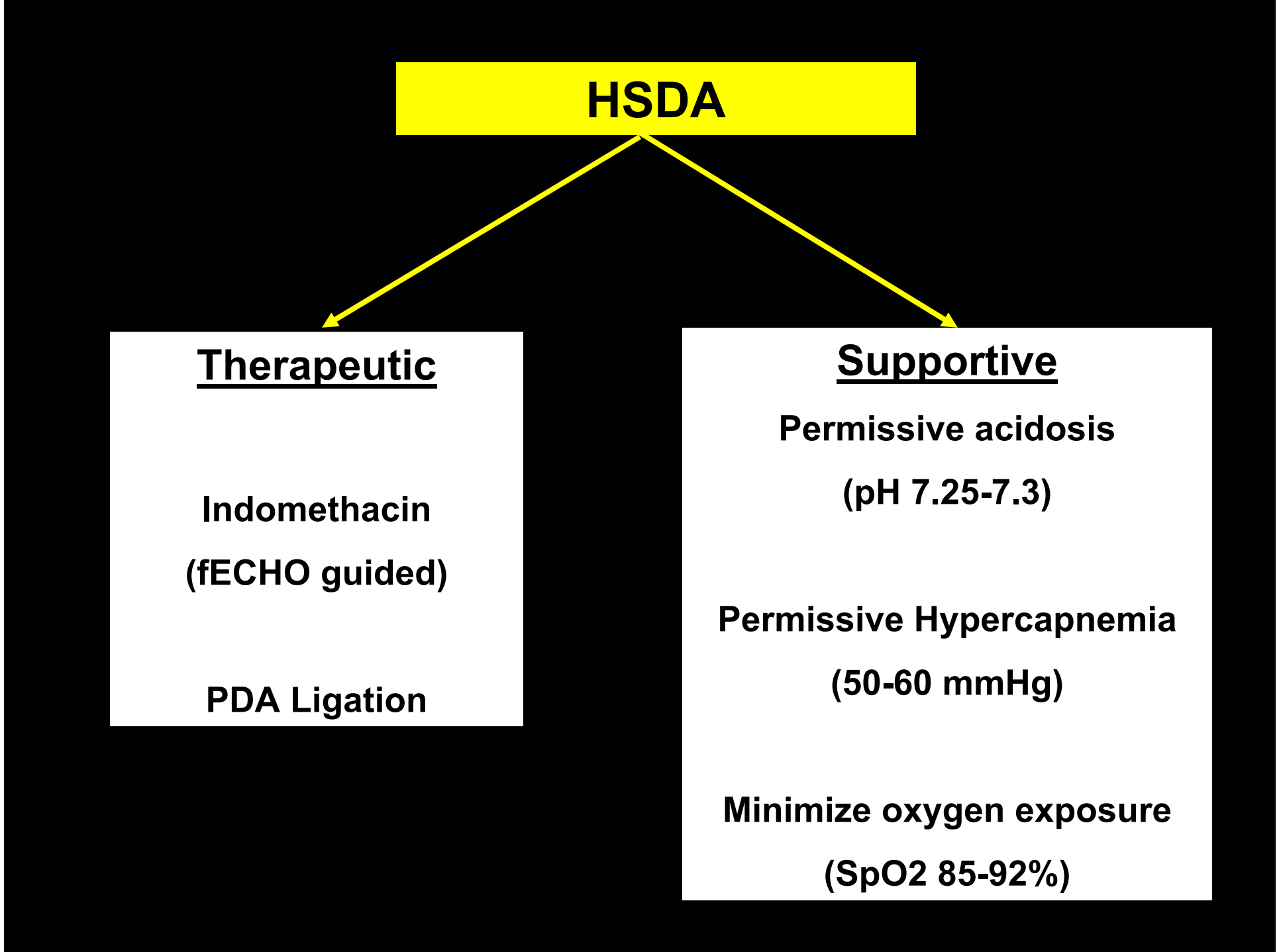
Left Ventricle

Truncus Arteriosus



Patent Ductus Arteriosus (PDA)




HSDA
Therapeutic
Indomethacin
(fECHO guided)
PDA Ligation
Supportive
Permissive acidosis
(pH 7.25-7.3)
Permissive Hypercapnemia
(50-60 mmHg)
Minimize oxygen exposure
(SpO2 85-92%)

Fluid Restriction, Diuretics, Feeding & HSDA

- ***Fluid restriction*** not effective in reducing the rates of HSDA or improving outcomes

  Reller 1985 Ped Card

  – May compromise end-organ perfusion further by reducing LV stroke volume

- ***Furosemide*** stimulates renal production of PgE_2

  Sulyok 1980 Ped Res, Wong 1981 Am J Phy

- Limited data regarding feeding and HSDA

- Is surgical intervention preferable?

Scenario II

31 day old (27/40 weeks) referred for emergency PDA ligation

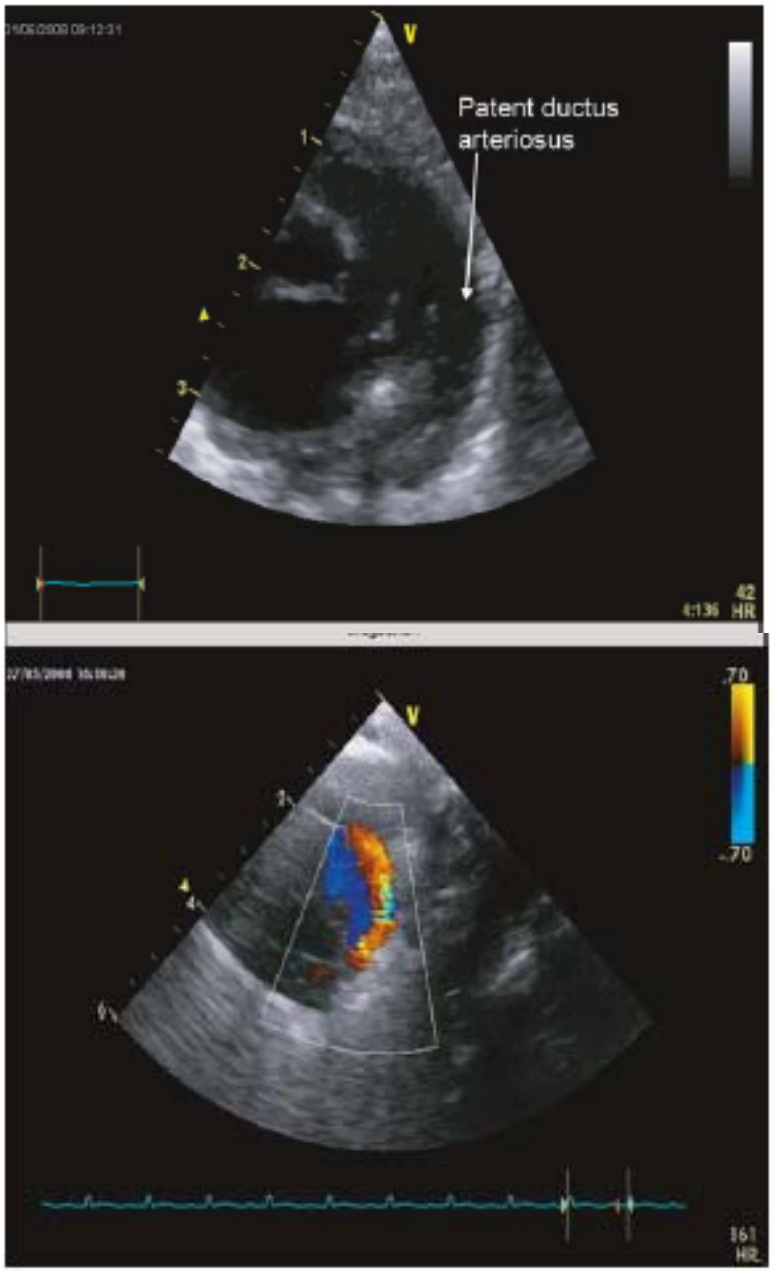
Issues: Oxygenation failure (HFOV) and hypotension (Dobutamine 20)

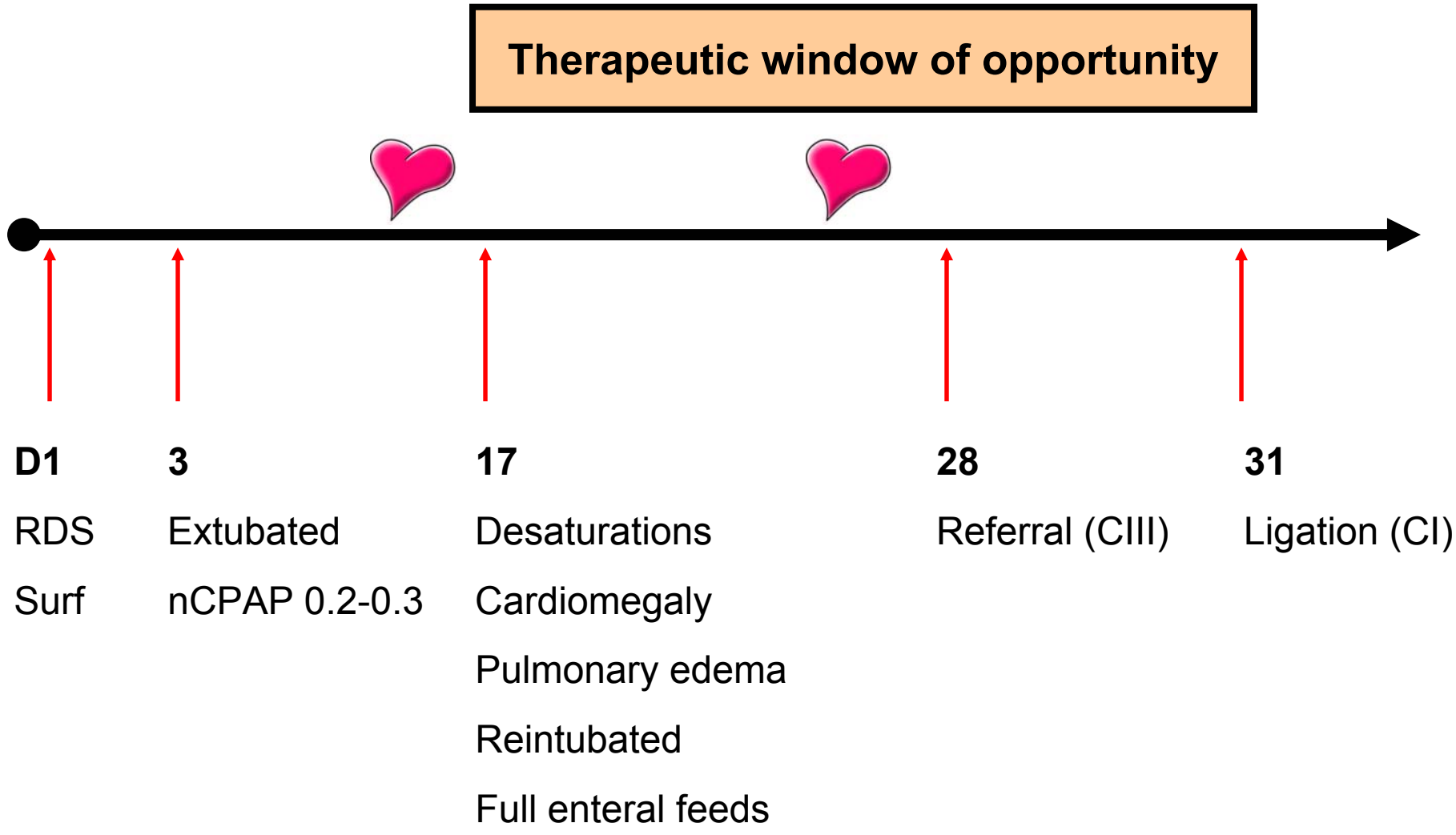
fECHO: 3.2 mm HSDA with L-R flow, dilated LA LV, LVO 420 mls/kg/min

Focused ICU care

- Prophylactic milrinone, hydrocortisone, serial fECHO

- Profound low cardiac output, MOF
- Radiological evidence of NEC
- Died day 2 postop




Therapeutic window of opportunity
D1
RDS
Surf
3
Extubated
nCPAP 0.2-0.3
17
Desaturations
Cardiomegaly
Pulmonary edema
Reintubated
Full enteral feeds
28
Referral (CIII)
31
Ligation (CI)

Lessons learned

- Hazards of an expectant approach and “All or none” approach to care
- Disconnect between clinical scenario and findings on 2D echo
- Intervention may have saved this life

Early Ligation - respiratory benefit

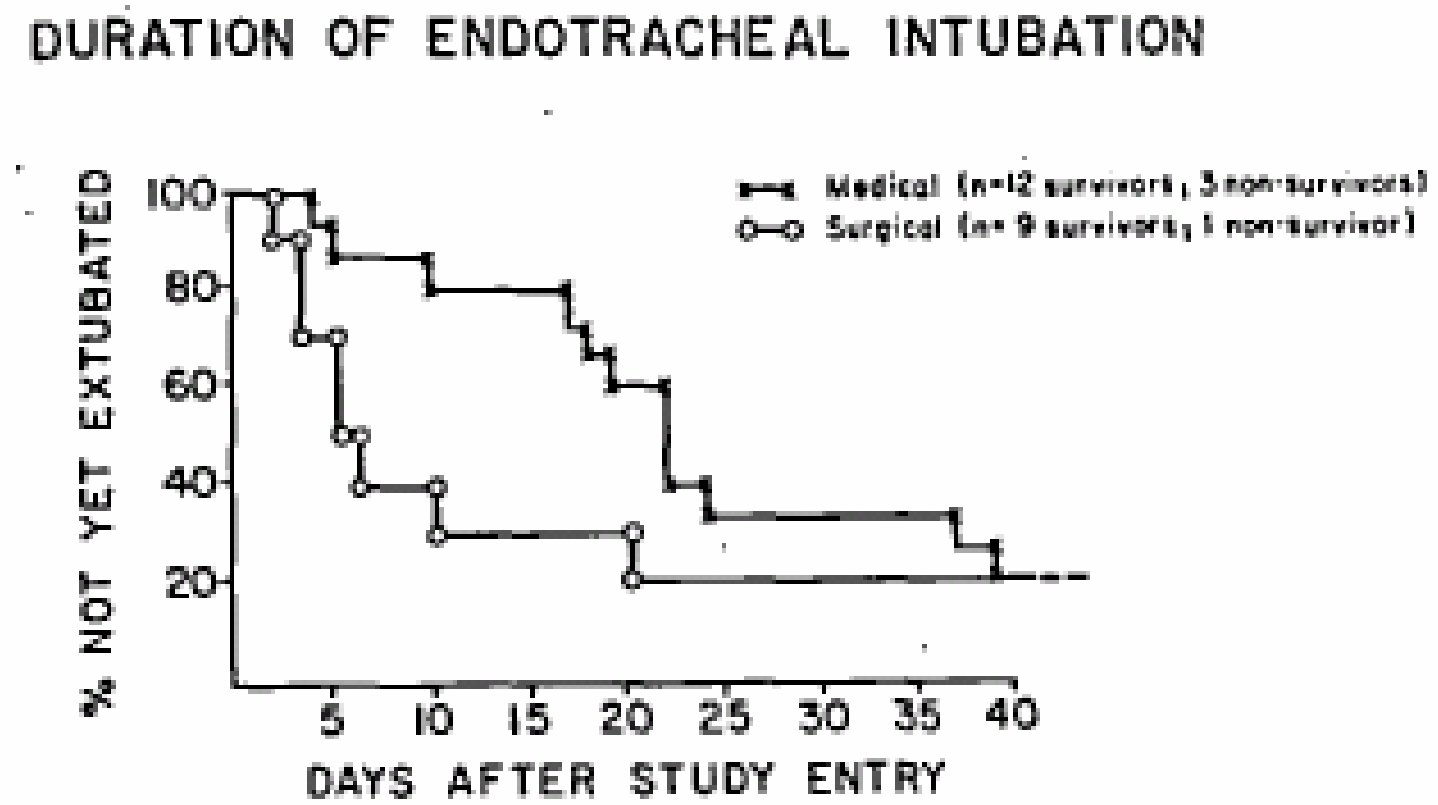


Fig. 1. Illustration of mechanical ventilator dependence of the study groups. The patients who died were considered never to have been successfully extubated.

Cotton 1978 J Pediatr

Early Ligation reduces NEC rates….

A RANDOMIZED, CONTROLLED TRIAL OF VERY EARLY PROPHYLACTIC LIGATION OF THE DUCTUS ARTERIOSUS IN BABIES WHO WEIGHED 1000 g OR LESS AT BIRTH

George Cassady, M.D., Dennis T. Crouse, M.D., John W. Kirklin, M.D., Martha J. Strange, M.D., Clinton H. Joiner, M.D., Ph.D., Guillermo Godoy, M.D., Gregory T. Odrezin, M.D., Gary R. Cutter, Ph.D., James K. Kirklin, M.D., Albert D. Pacifico, M.D., Monica V. Collins, M.S.N., William A. Lell, M.D., Celia Satterwhite, M.D., and Joseph B. Philips III, M.D.

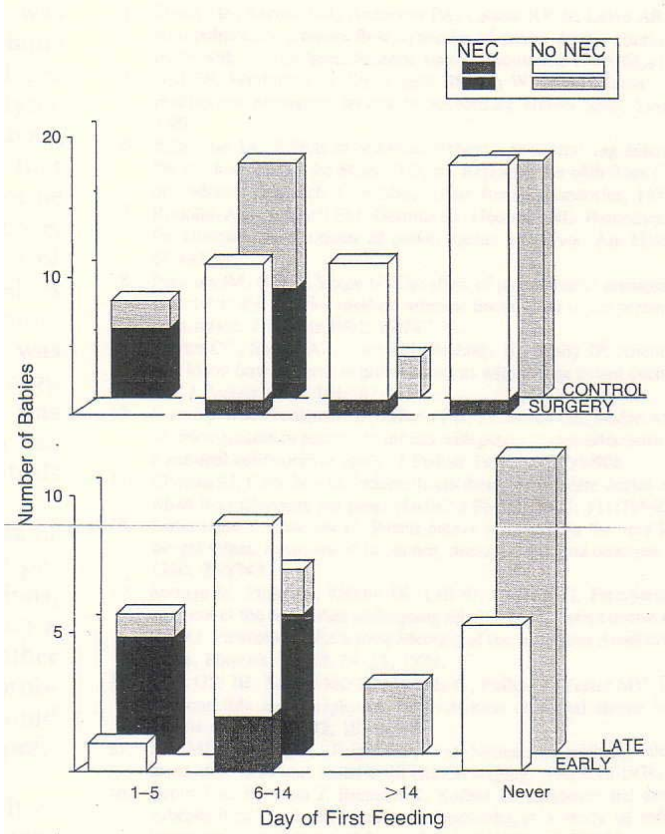


Figure 3. Relation of Necrotizing Enterocolitis (NEC) to the Day Enteral Feeding Began.

Neonates < 1000 g (n=84) with ⇓ rate of NEC (30 vs 8%)

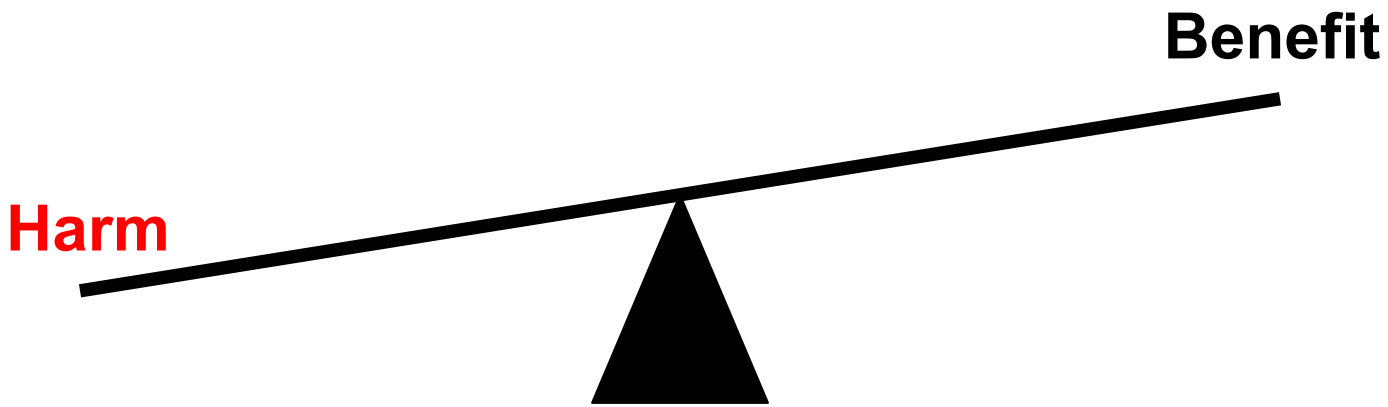
The hemodynamically significant ductus …..

- May lead to **acute physiological change**, hemodynamic disturbance and clinical instability
- is associated with important **neonatal morbidities** and mortality
- May require **early therapeutic intervention** to minimize morbidity and improve patient outcomes

Treatment is BAD?

Treatment doesn’t work!

THERAPEUTIC POLARITY



Demographics	Day 3: 25/40 gestation, 650 grams	
Clinical problem	Oxygenation failure SpO_2 85%, FiO_2 1.0	Systemic hypotension Respiratory failure SpO_2 95%, FiO_2 0.5
Laboratory findings	pH 7.28, pCO2 42, pO2 38, Bxs -7.0, Lac 3.1	pH 7.12, pCO2 65, pO2 68, Bxs -8.0, Lac 4.1
2D Echo	3.0 mm DA with R-L flow RVSP 65 mmHg Hypokinetic RV	3.0 mm DA with L-R flow LVO: SVC flow ratio 6:1 E:A 1.3, LA:Ao 2.5:1, rEDF SMA

Scenario II

7 day old (24/40 weeks) referred for PDA ligation

Issues

- Anuric, creatinine 260 mmol/l
- Refractory shock (Dobutamine 20 & Dopamine10 μg/kg/min)
- Metabolic acidosis (7.0-7.15) with ↑ lactate 6-10 mmol/l

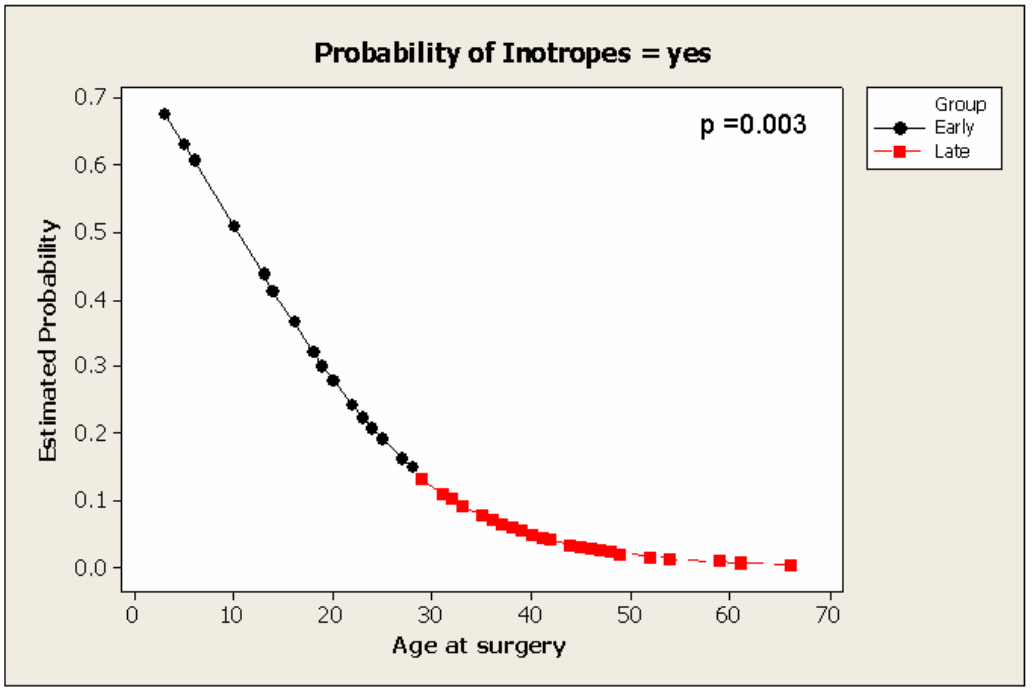
2d ECHO

- 3.8 mm HSDA with unrestrictive L-R flow
- Dilated LA and LV, cardiac output 380 mls/kgmin
- Reversed end-diastolic flow in SMA, MCA & renal artery

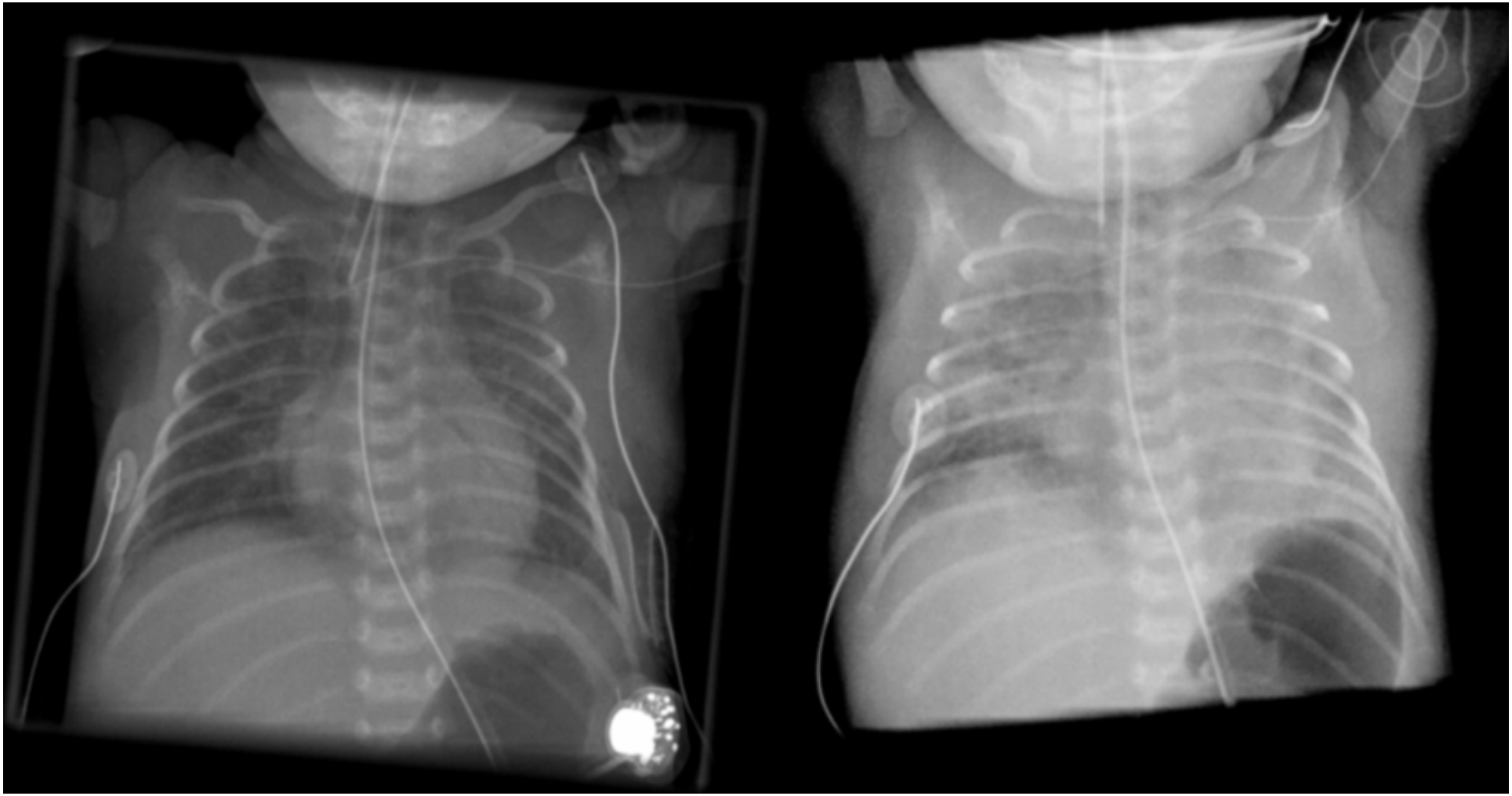
Post-Ligation Cardiac Syndrome (PLCS)

Clinical deterioration with **predictable onset** at 8-12 hours characterized by:

- Oxygenation Failure
  - ↑ 20% < 1000g (p<0.01)
- Systolic Hypotension
  - X 8 fold increase < 1000g
- Need for cardiotropes

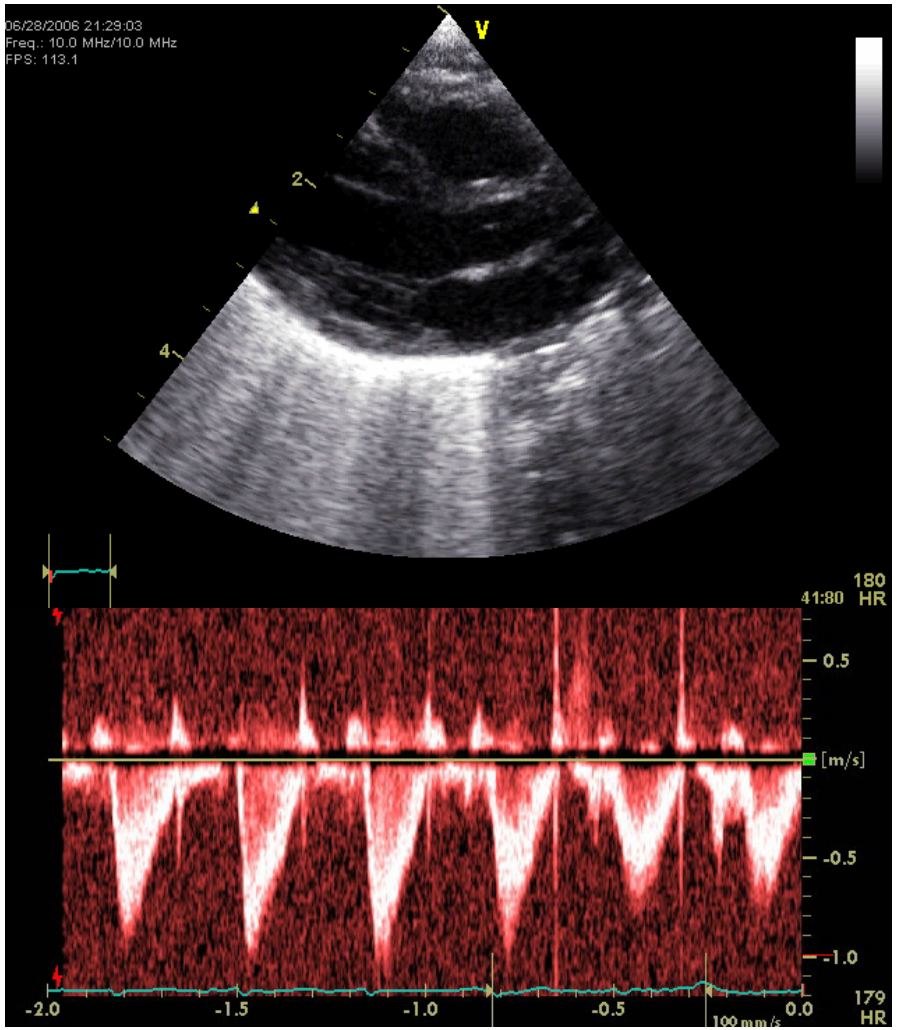


Teixeira et al. J Perinat 2008



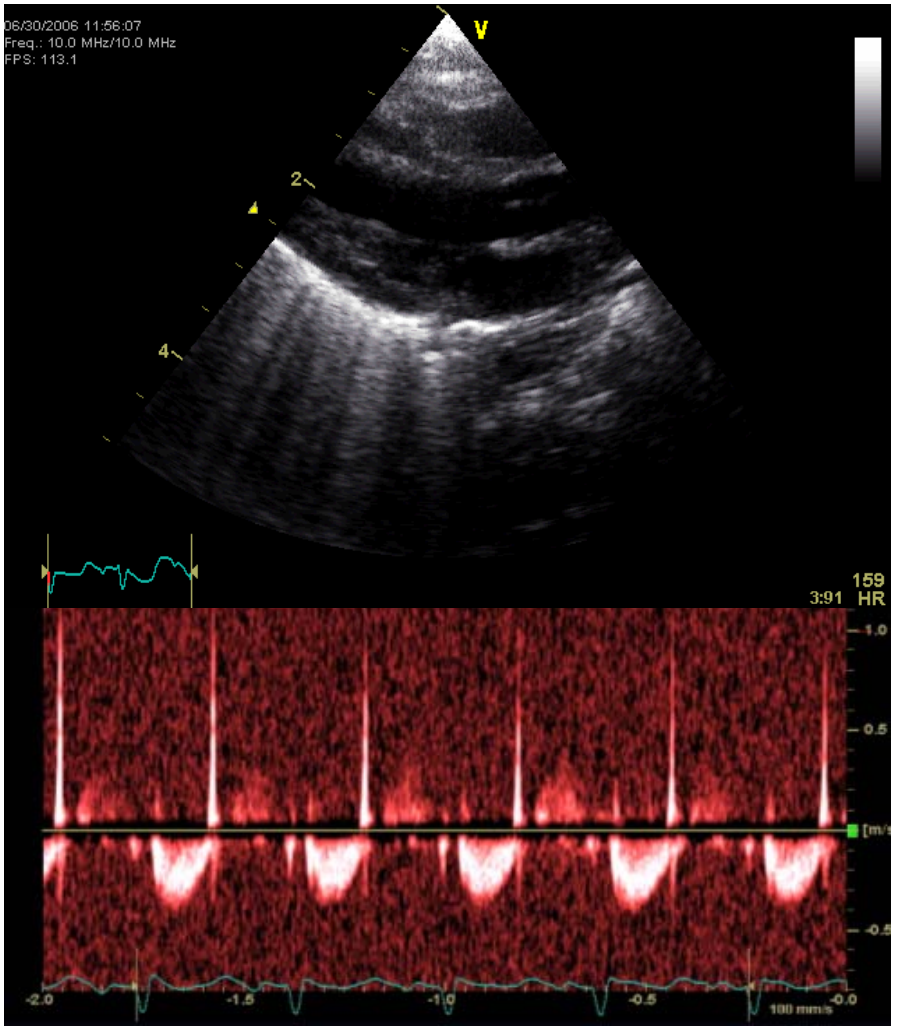
	Pre-Ligation	Post-Ligation
FiO2	30%	50%
MAP	7	11

Systemic blood flow



PRE-OP

[Normal]



8 HOURS

[Impaired LV function]

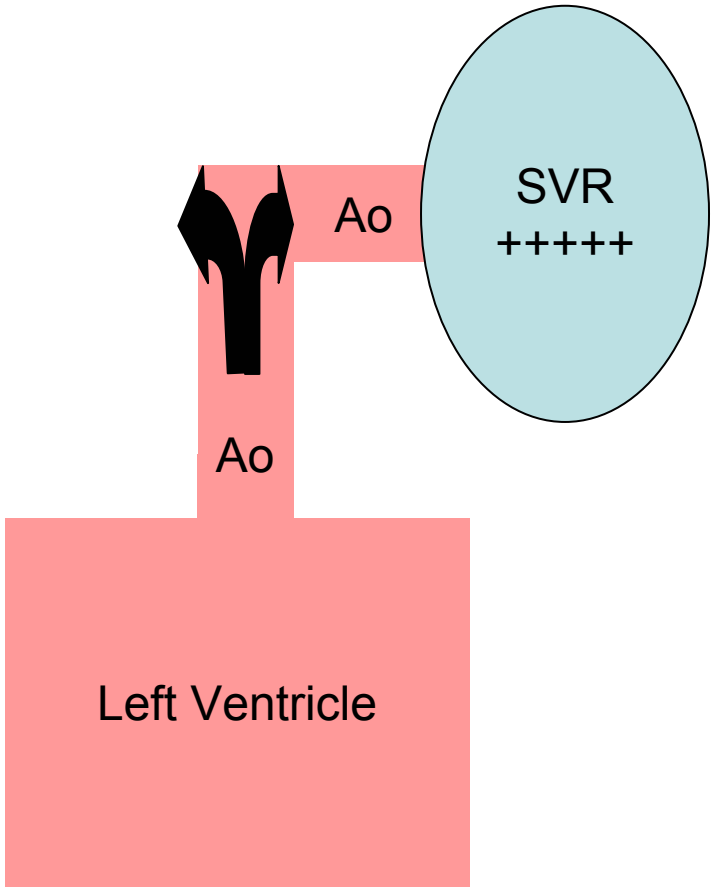
Hypothesis I

Is this an effect of

LV exposed afterload on myocardial performance?

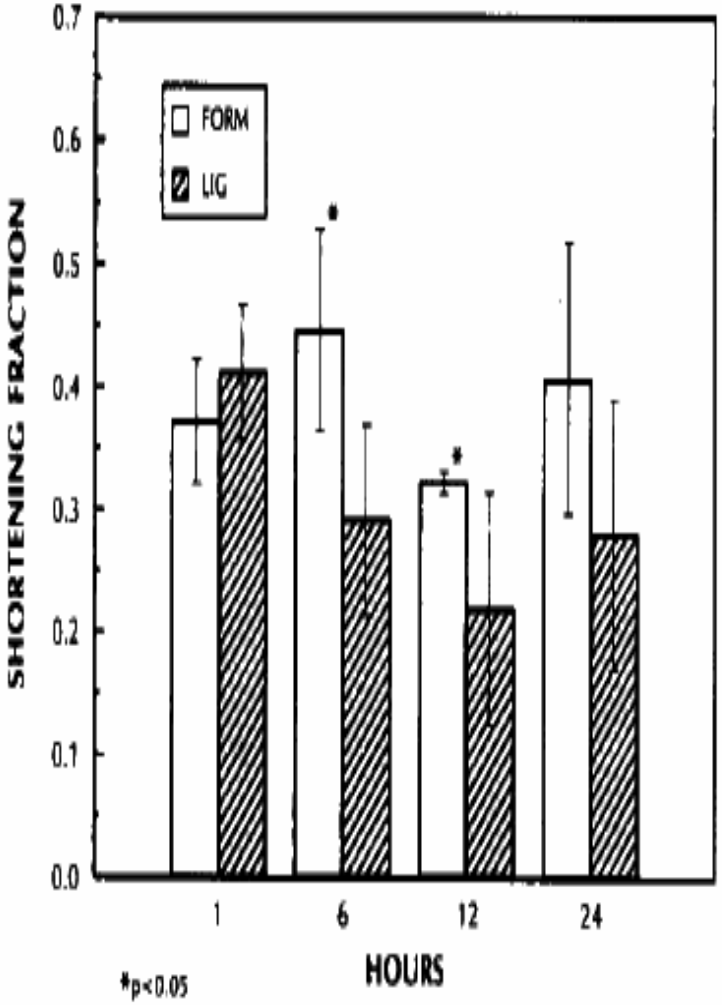
Hypothesis: Increased LVE-VR (*Left ventricle exposed vascular resistance*), after PDA ligation, was associated with impaired myocardial performance

Left Ventricle Exposed Vascular Resistance (LVER)

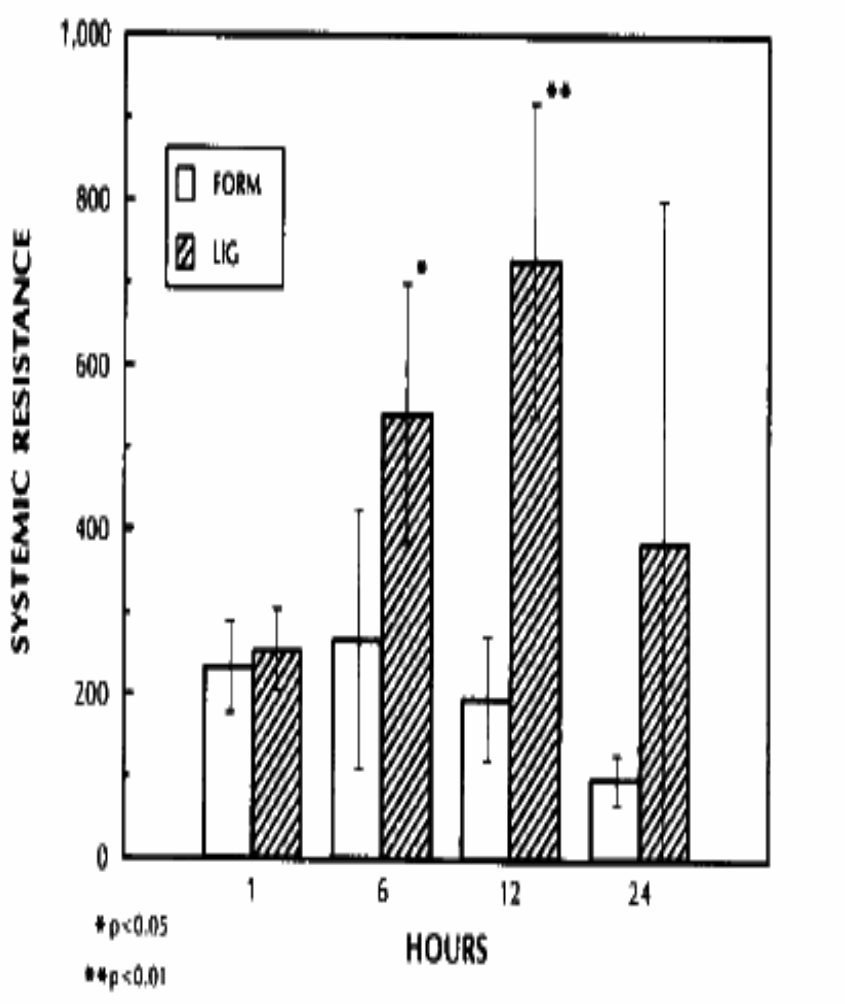


LV dysfunction after PDA ligation in preterm baboon

Taylor 1990 J Surg Res



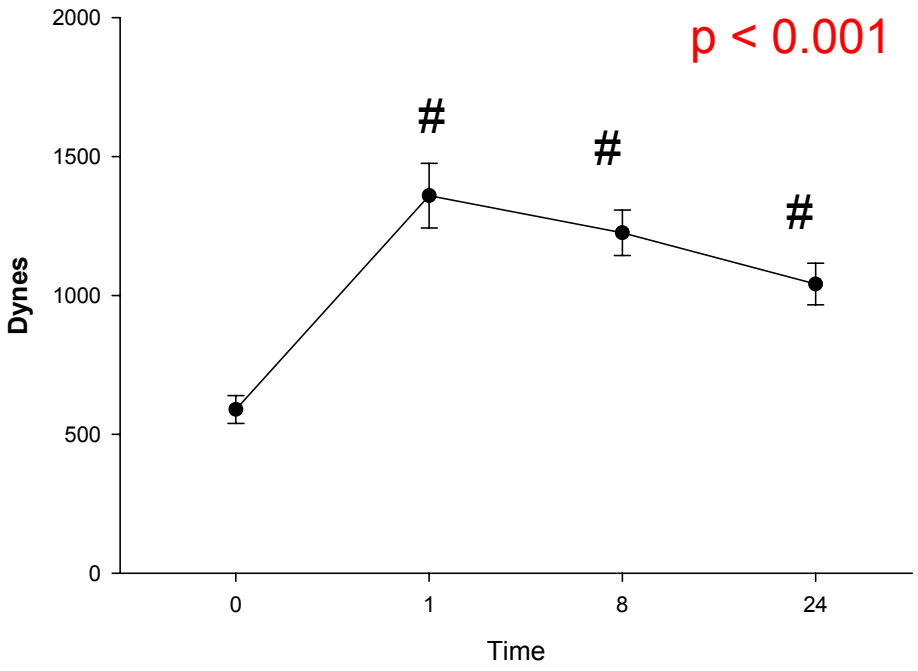
SF



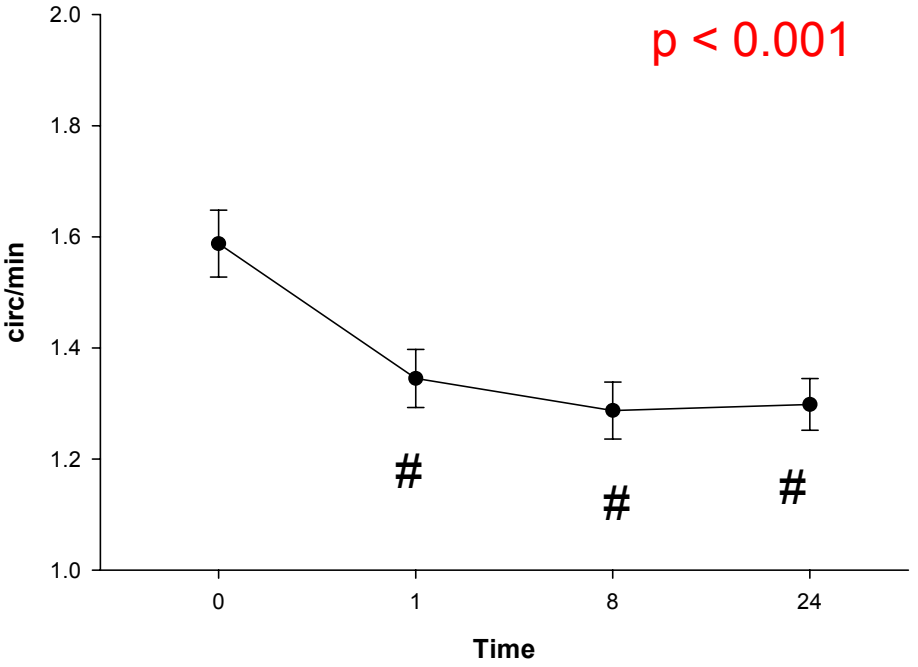
SVR

Myocardial Performance

LV Exposed Vascular Resistance



mVCFc



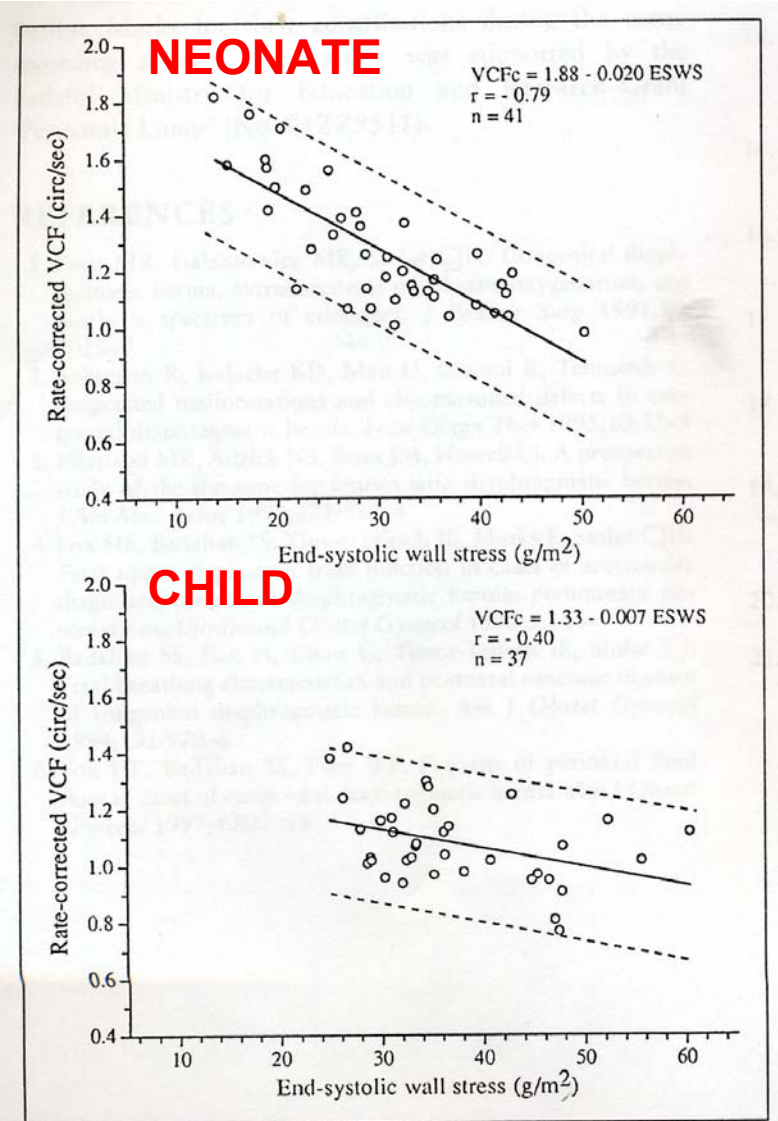
# p < 0.05 vs baseline

McNamara, 2010 J Thorac Cardiovasc Surg

	< 1000 g n= 23	> 1000 g n= 23	p
LVO < 170 mls/kg			
0	1 (4.3)	0 (0)	1.0
1	3 (13)	4 (17.4)	1.0
8	7 (30.4)	2 (8.7)	0.03
24	1 (4.3)	3 (13)	0.61
FS < 25%			
0	0 (0)	0 (0)	1.0
1	2 (8.7)	3 (13)	1.0
8	7 (30.4)	1 (4.3)	0.02 *
24	1 (4.3)	3 (13)	0.61

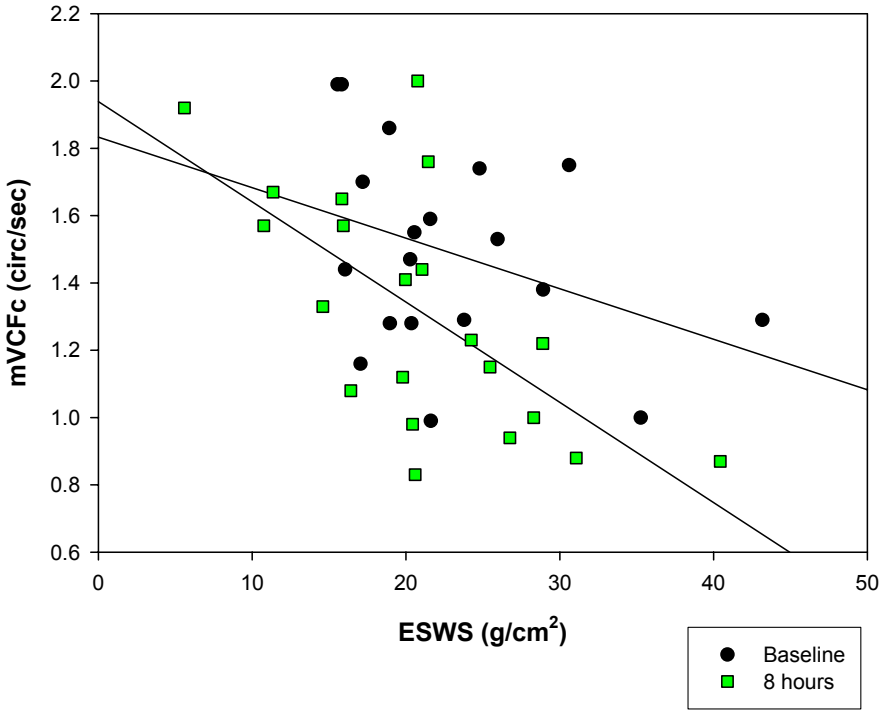
Data presented as number (%)

Stress-Velocity Relationship (*Afterload*)



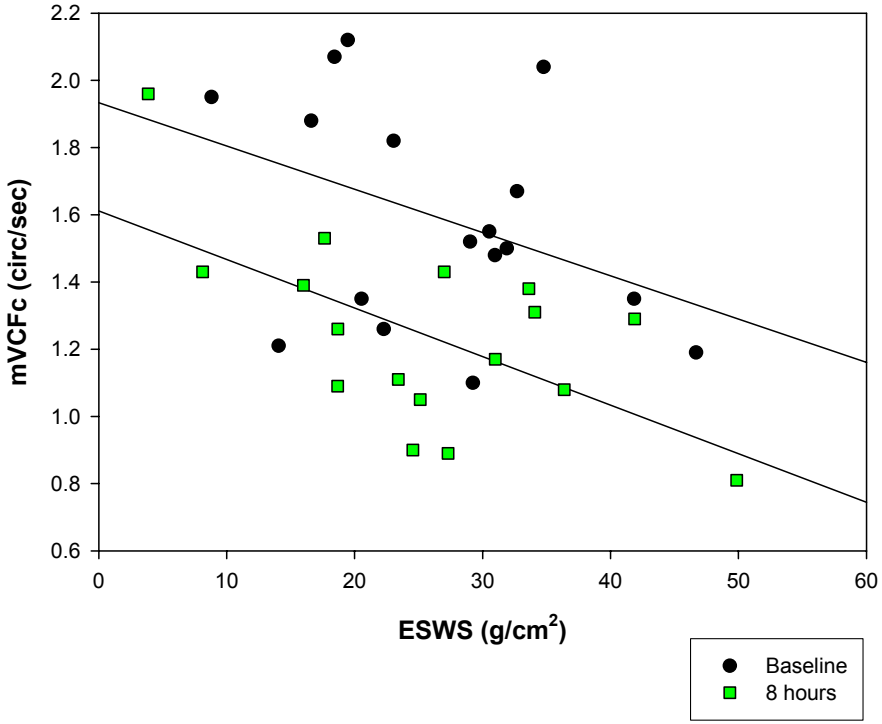
Rowland 1995 Am J Card

Stress-Velocity < 1000g

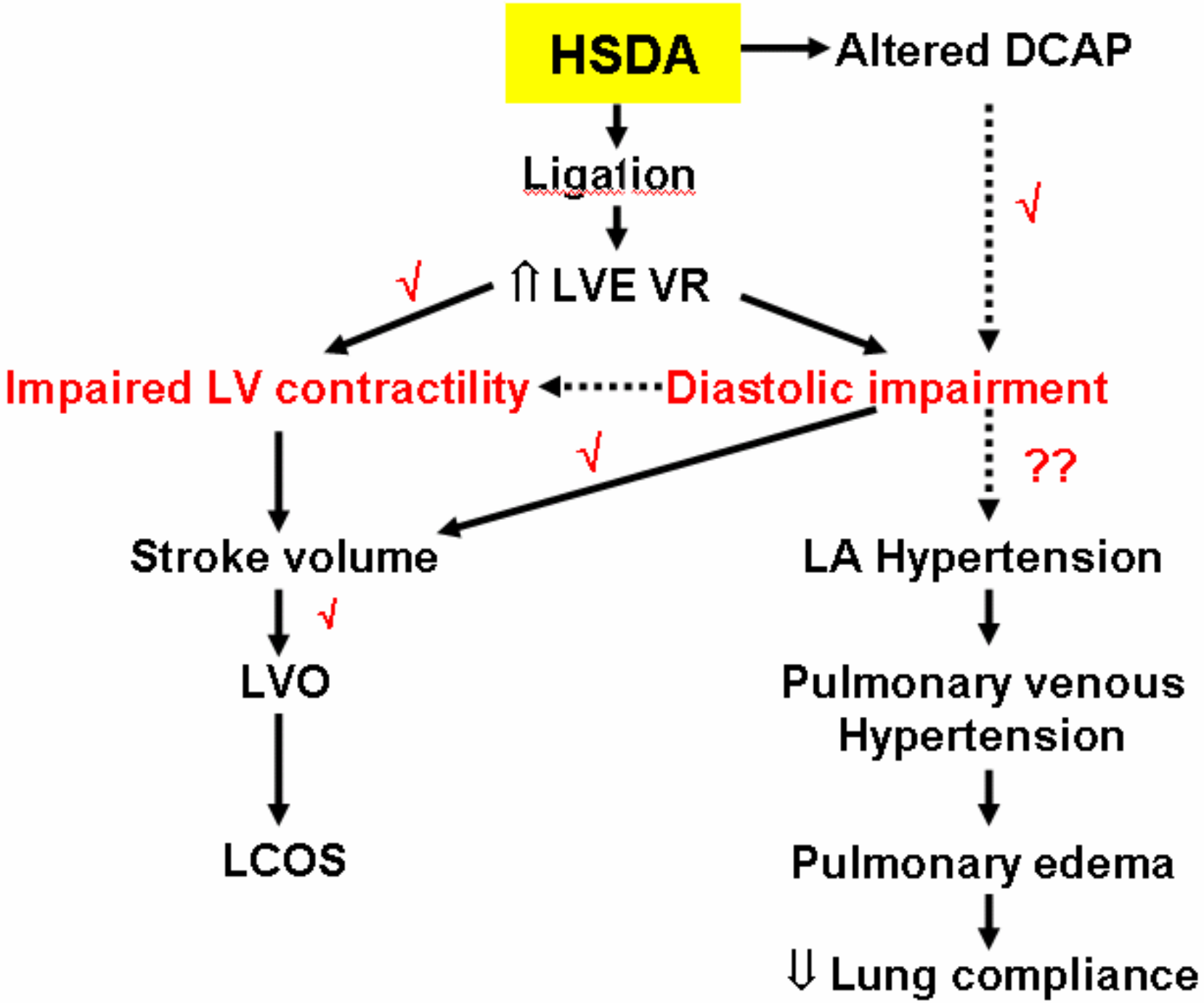


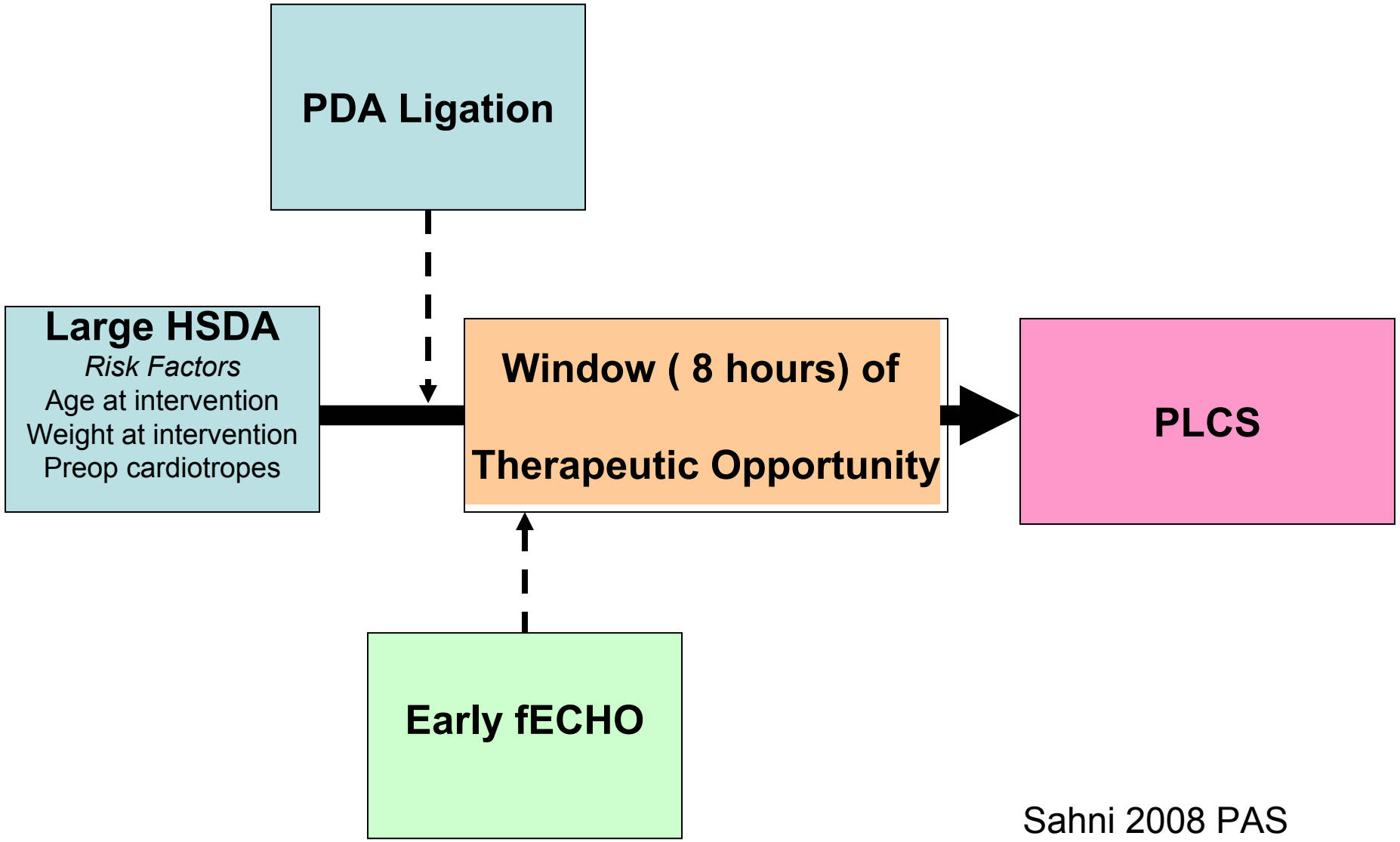
Time (h)	y	x	r
0	1.83	- 0.015	0.36
1	1.73	- 0.014	0.31
8	1.94	- 0.03 *	0.65
24	1.7	-0.013	0.37

Stress-Velocity > 1000g



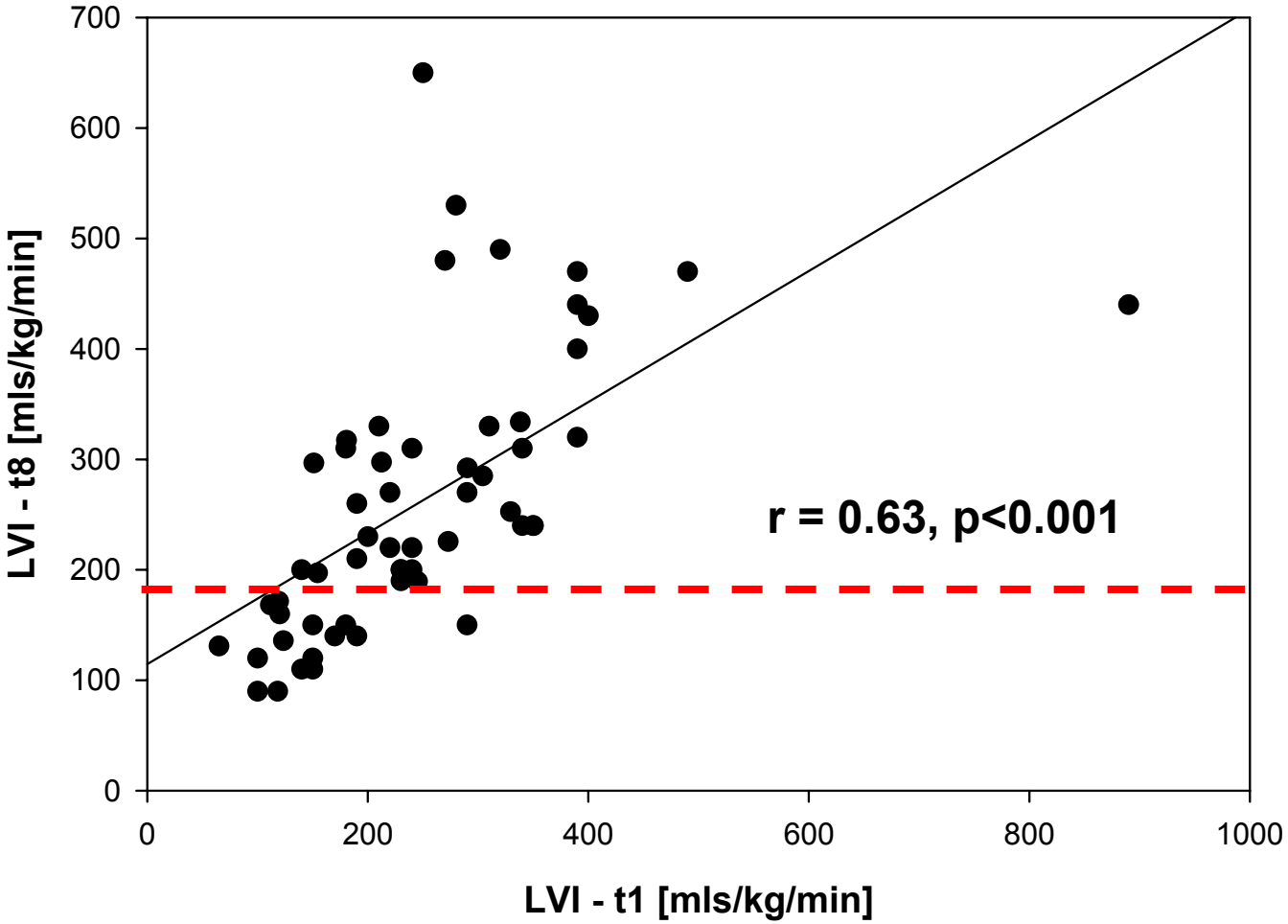
Time (h)	y	X	r
0	2.1	- 0.018	0.46
1	1.75	- 0.02	0.56
8	1.61	- 0.014	0.6
24	1.72	- 0.018	0.53


HSDA
Altered DCAP
Ligation
√
⇑ LVE VR
√
Impaired LV contractility
Diastolic impairment
√
??
Stroke volume
LA Hypertension
√
LVO
Pulmonary venous Hypertension
LCOS
Pulmonary edema
⇓ Lung compliance



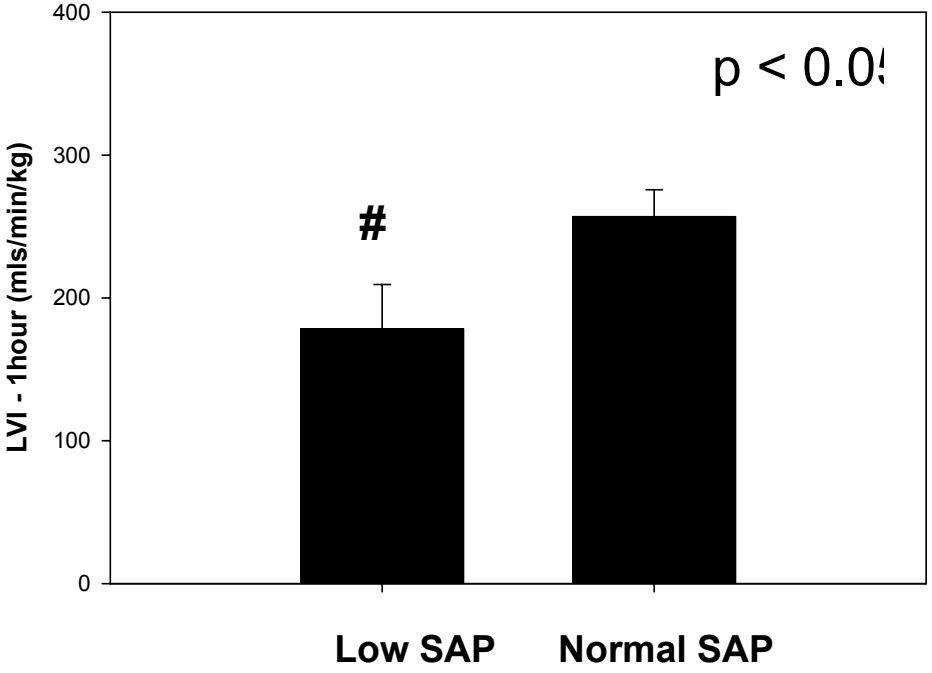
Sahni 2008 PAS

Left Ventricular Output

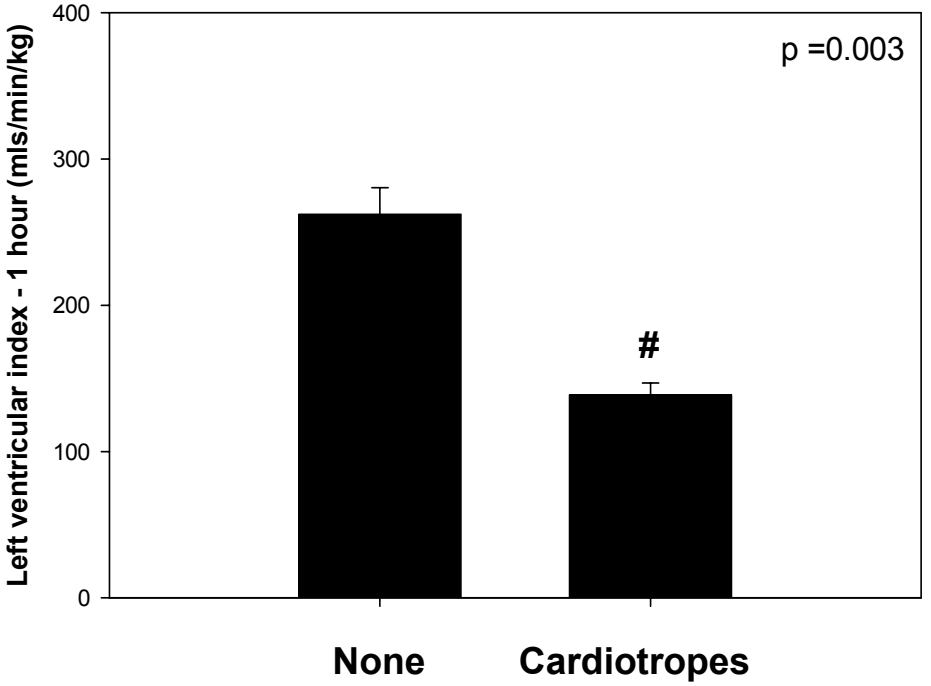


Sahni 2008 PAS

Systolic Pressure < 3rd Centile [8 hrs]



Need for Cardiotropes



Threshold of LVO < 200 mls/min/kg at 1- hour will identify

- 83% neonates who develop *SAP < 3rd centile* (Sensitivity = 83.3%, Specificity = 96.1%)

- 100% neonates who required *cardiotropes* (Sensitivity = 100%, Specificity = 100%)

Summary

- Early fECHO may help anticipate postoperative cardiorespiratory instability
- LVO < 200 mls/min/kg is the best marker of clinical and echo indices of PLCS

Targeted neonatal ECHO directed therapy program

- introduced in January 2009

Modifications since January 2009:

- ACTH stimulation test pre-operatively
- TnECHO at 1 hour post surgery
  - **LVO < 200 mls/min/kg → MILRINONE infusion at 0.33 mics/kg/min**
  - **LVO > 200 ml/min/kg → continue observation**

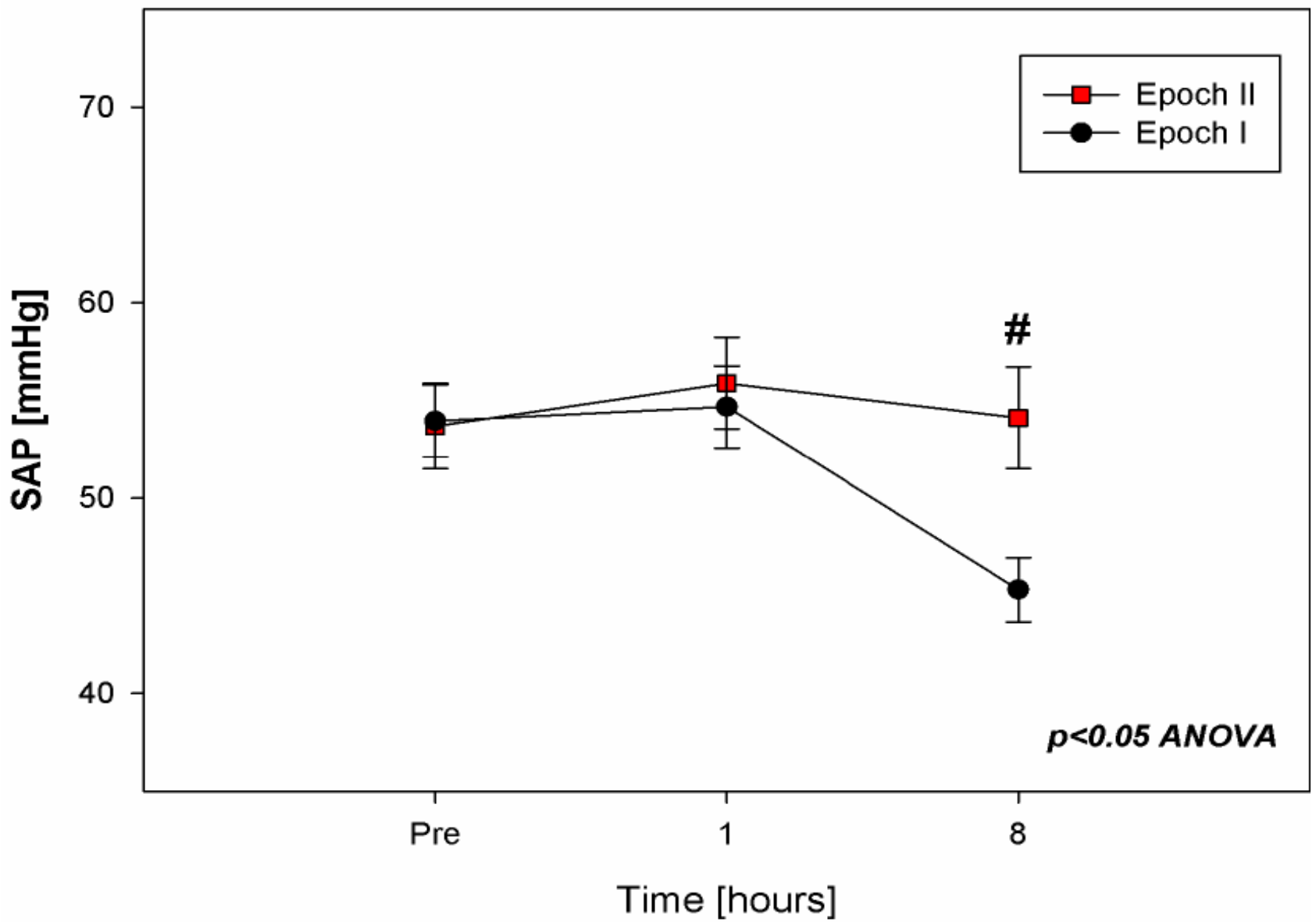
Guideline for cardiovascular intervention:

- SAP < 3rd centile & DAP > 3rd centile → **iv. DOBUTAMINE**
- SAP < 3rd centile & DAP < 3rd centile → **VOLUME or DOPAMINE**
- If failed ACTH stimulation test and refractory hypotension → consider **HYDROCORTISONE**

Study Objective

To compare the rate and components of PLCS in infants who have undergone PDA ligation **before** and **after** the introduction of targeted neonatal echocardiography (TnECHO) directed therapy program

Systolic Arterial Pressure



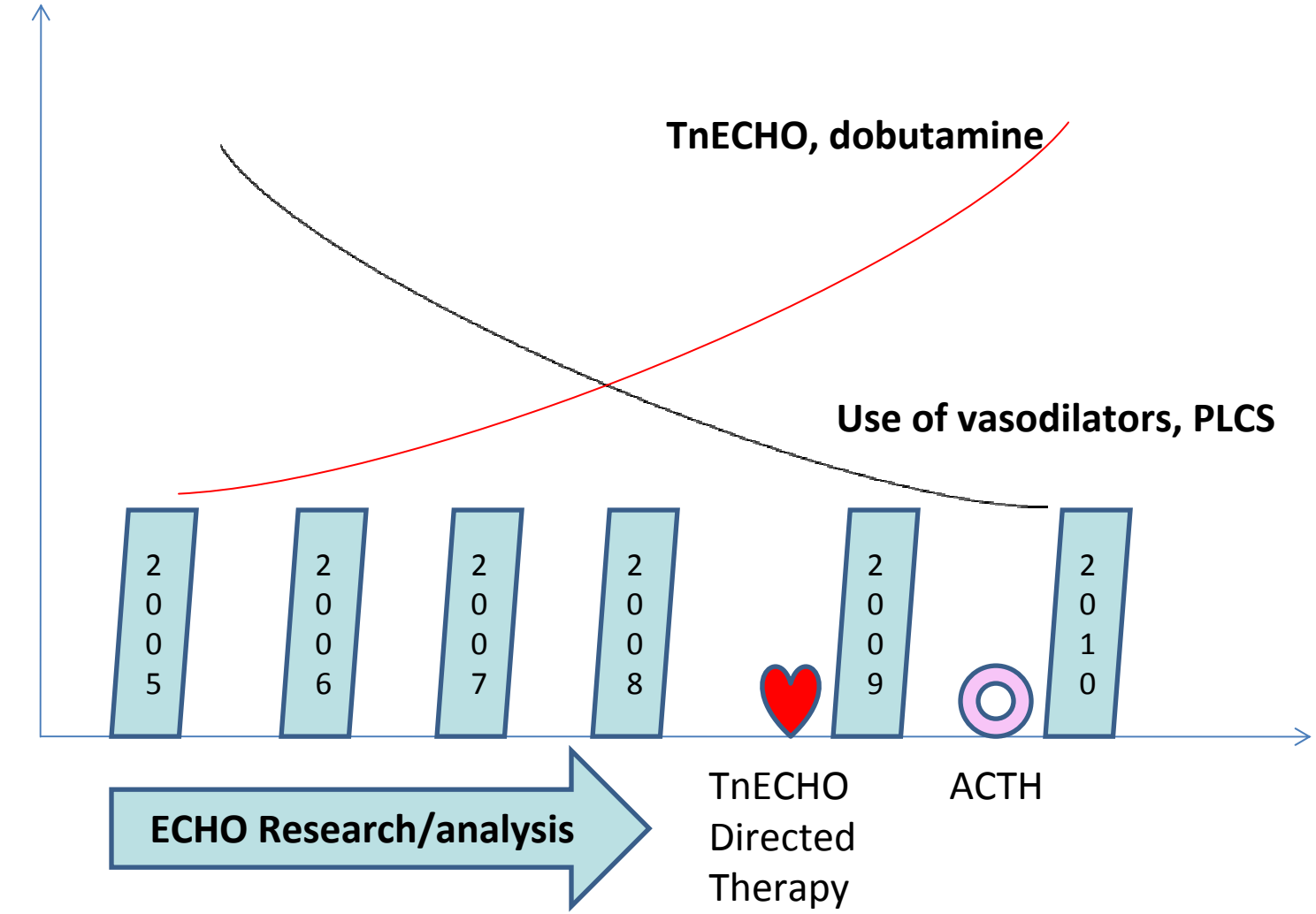
Outcomes

Outcome	Epoch I (N=25)	Epoch II (N=27)	P Value
PCLS (n)	64%	37%	**0.05**
Oxygenation failure (n)	56%	29%	0.09
Need for cardiotropes (n)	36%	14%	0.14
Oxygenation failure & need for cardiotropes (n)	28%	7.4%	0.07

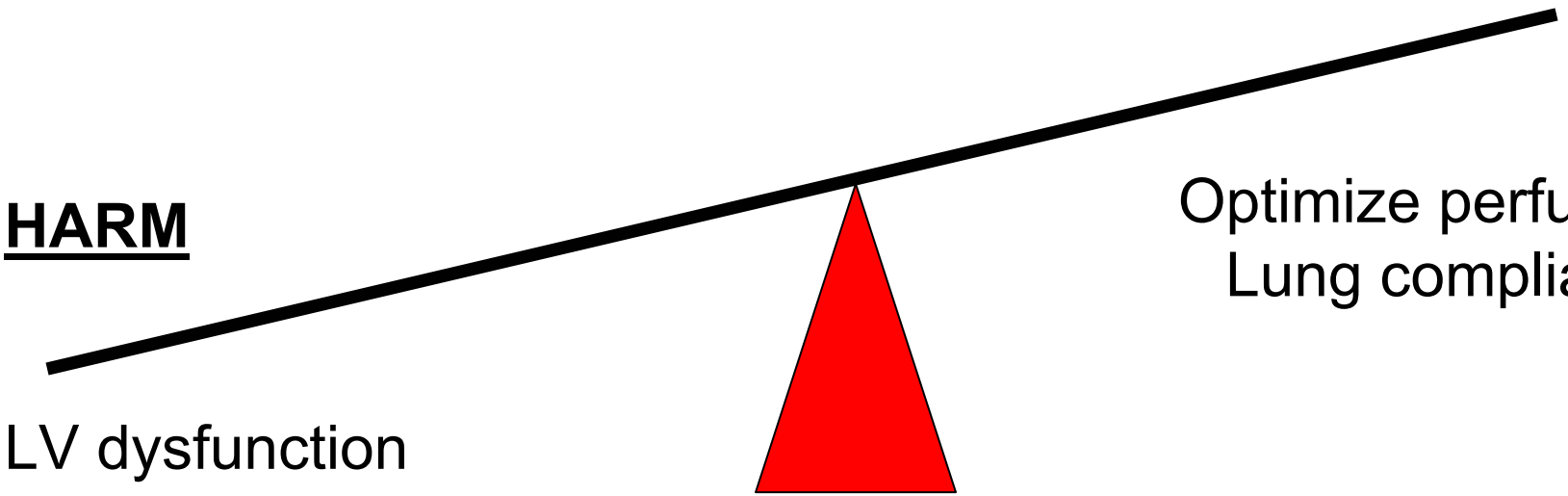
Only 1 case of need for inotropes in 2010

Jain 2010

Evolution of post-operative care



BENEFIT



HARM

Optimize perfusion
Lung compliance

LV dysfunction

Focused ICU care

- Prophylactic milrinone (afterload reduction)
- Serial functional echocardiography

Intermediary outcome

- Off cardiotropes within 72 hours
- Creatinine 125 within 12 hours of surgical intervention, normal by day 5
- Extubated 10 days after surgical intervention
- Uneventful neonatal course

Take Home Messages

- PDA is a **common** neonatal problem with significant physiologic and hemodynamic consequences

- HSDA is a **continuum** from physiological normality to a pathological disease state with clinical instability and differential effects on bodily organs

- **Ductal staging** may help elicit those patients at greatest risk of duct-related morbidity where treatment is most beneficial and monitor therapeutic effects

Take Home Messages

- Merits of intervention (benefit-harm) remains **controversia**l
- **Early screening & targeted intervention** guided by serial functional imaging is <u>probably</u> most desirable
- Current trial designs do not consider the heterogeneity of disease
  - Placebo controlled trial for early low grade DA (ANZAC, INDUCE)
  - Timing of intervention trial for high grade DA

Special Thanks

Neonatal Research Fellows

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Sandesh Shivananda

Lilian Teixeira

Emer Finan

Research Assistants

Wendy Mak

Derek Stephens (Statistical support)

Glen Van Arsdell & CVS team

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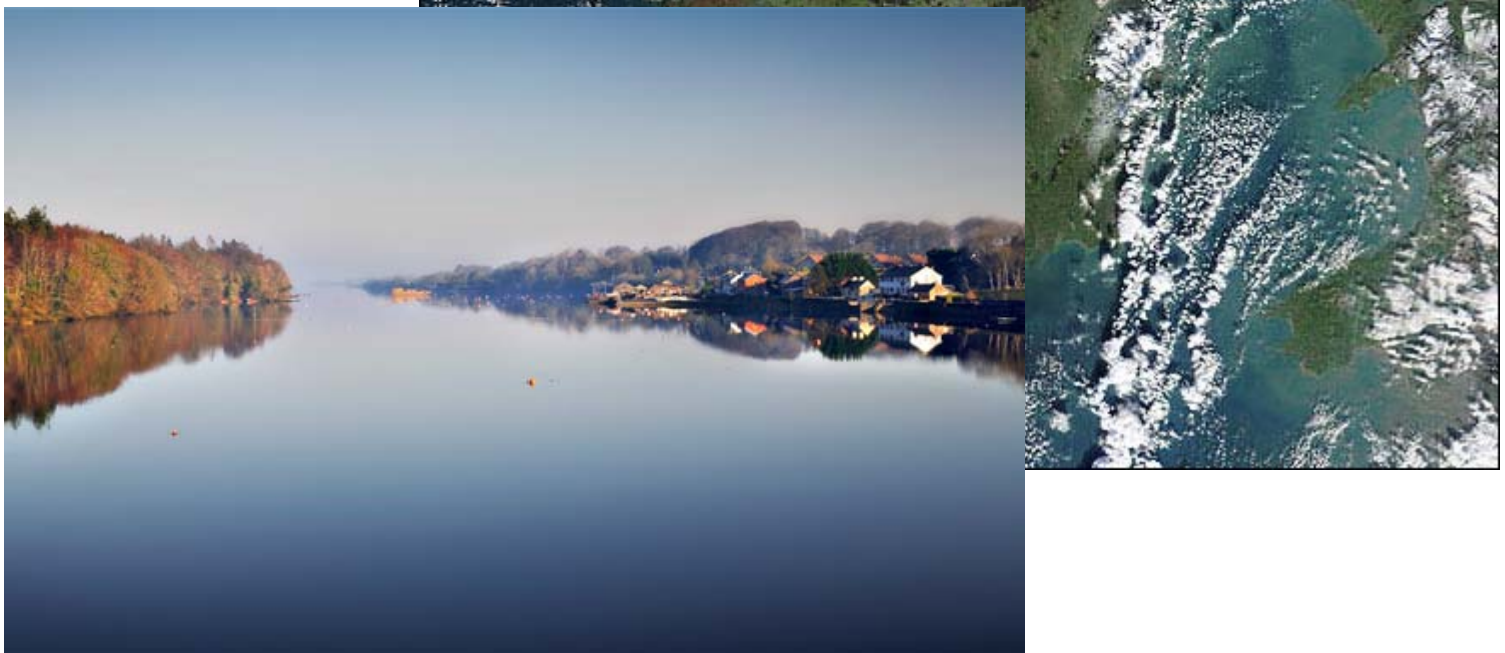


Request for PDA Ligation

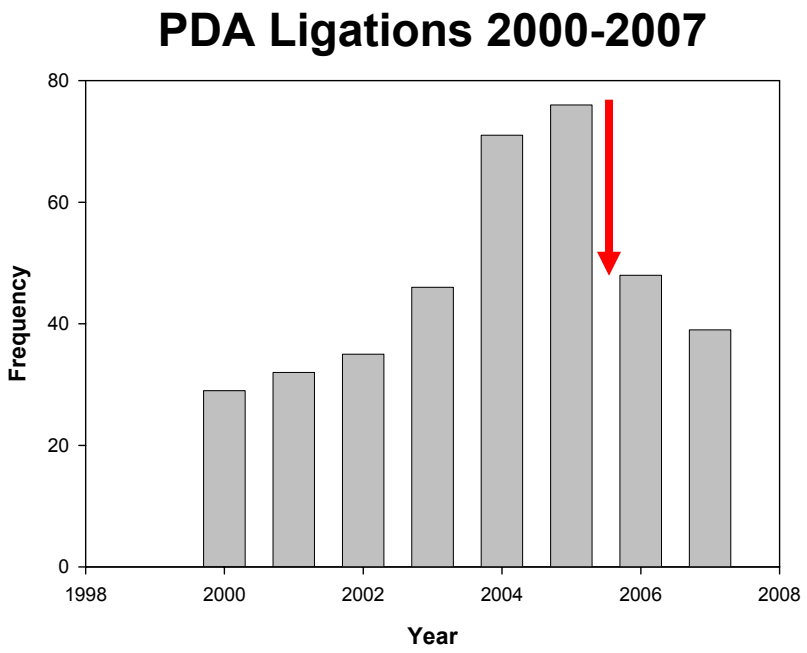
PDA Team

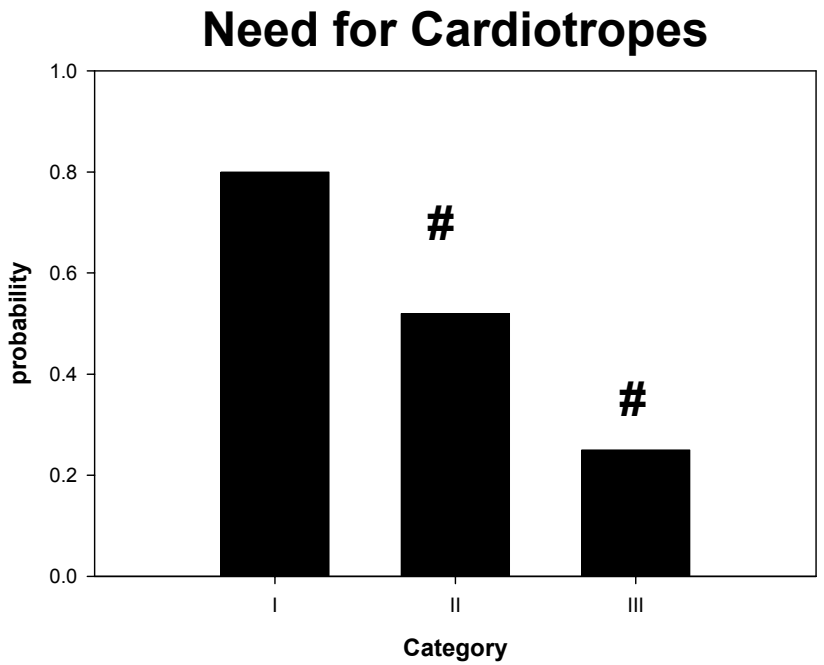
Case Triage

- Categorization (I-III)
- PLCS Risk Assignment
- Admission plan

Peri-operative Care Plan

- Consultation
- Monitoring (SBP,DBP)
- Intervention (choice of cardiotropes)
- Echo supported care





Mittal 2008 PAS

Category	Clinical Indication
I	a. Profound pulmonary hemorrhage with significant oxygenation difficulties (OI > 15 or MAP >12 & FiO2 > 50%) b. Low cardiac output syndrome or rapidly progressive cardiorespiratory failure requiring ≥ 2 inotropes
II	a. Deteriorating respiratory status (OI > 15 or MAP >12 & FiO2 > 50%) b. Preterm < 26 weeks with large HSDA & medical treatment is contra-indicated c. Low cardiac output syndrome or cardiorespiratory failure requiring ≥ 1 inotropes d. Neonate with NEC and large PDA which is felt to be contributing significantly to clinical instability
III	a. Inability to extubate or wean respiratory support b. Cardiac failure associated with failure to thrive

Table 1. Clinical indicators for categorization of neonates for PDA ligation

Early ligation improves feeding tolerance……..

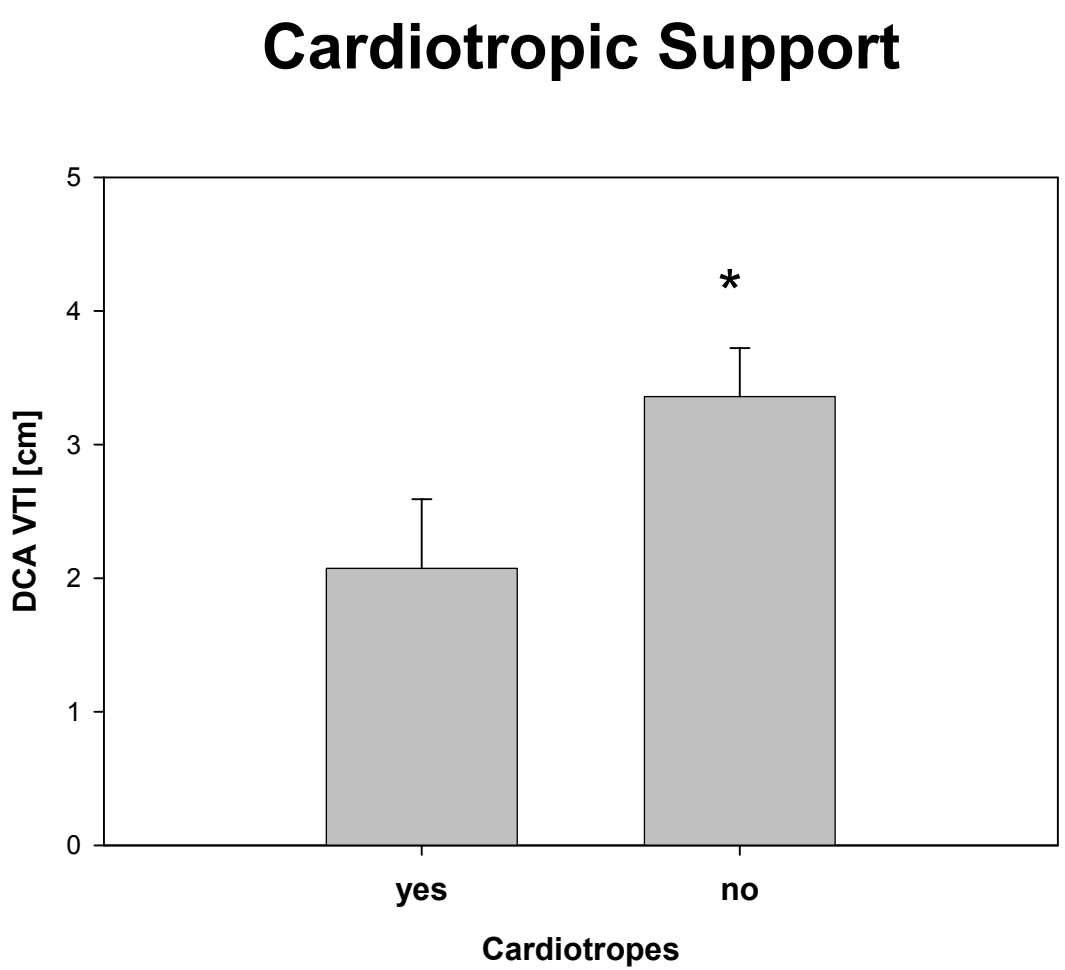
Table 2. Postoperative Parameters in the Two Groups

	< 21 Days (range 5–20 days) (n = 30)	> 21 Days (range 21–74 days) (n = 28)	
Mean arterial pressure (mm Hg), H6	38 (37–70)	42 (29–67)	NS
Mean arterial pressure (mm Hg), H24	42 (30–81)	46 (29–65)	NS
Heart rate (bpm)	145 (117–175)	149 (90–189)	NS
Inotrope requirement	19 (63%)	16 (57%)	NS
F_iO_2 at H24	21 (21–60)	28 (21–65)	$p < 0.05$
Extubation (day from surgery)	3 (1–26)	4.5 (1–64)	NS
Extubation (day from birth)	10 (10–41)	35 (24–86)	$p < 0.001$
Oxygen weaning (day from birth)	97 (12–187)	96 (57–195)	NS
Bronchopulmonary dysplasia (O_2 requirement at 36 weeks of CA)	7	6	NS
Date of full oral feeding (days of life)	37.5 (4–84)	57 (25–136)	$p < 0.001$
Weight at 36 weeks of CA (g)	1800 (1,250–2,750)	1607 (1,274–2,200)	$p < 0.05$

CA = conceptional age.

Jaillard 2006 Ann Thor Surg

CA Flow & Post-ligation instability

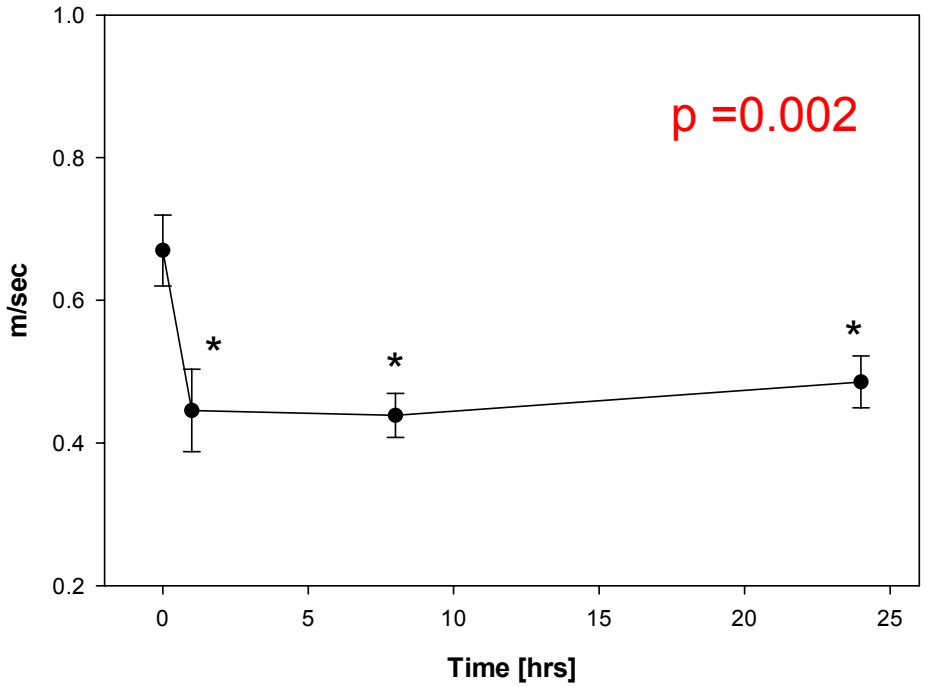


Increased risk of myocardial dysfunction may relate to chronic myocardial ischemia

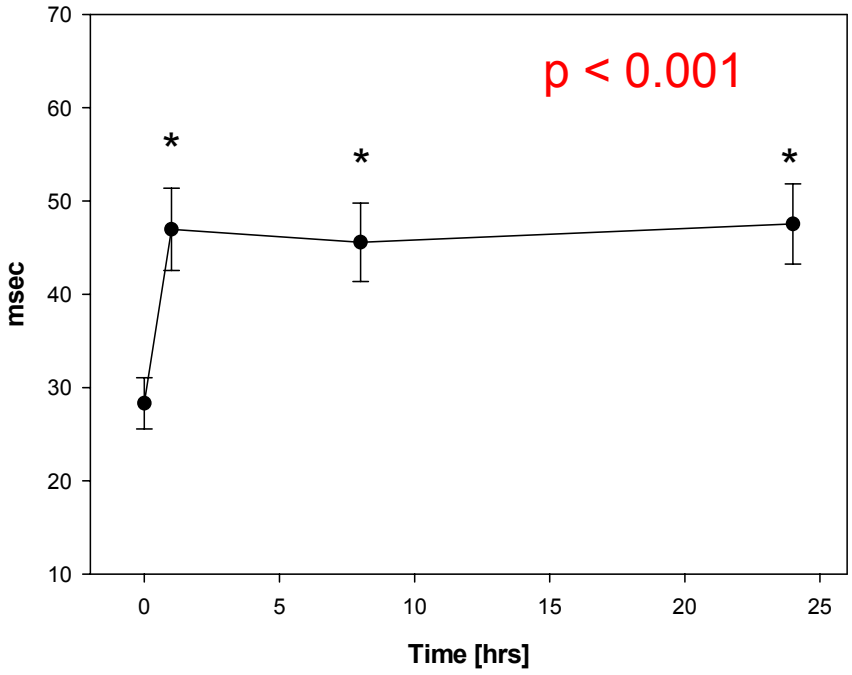
* $p<0.05$ vs no inotropes

Transmitral Doppler

E wave

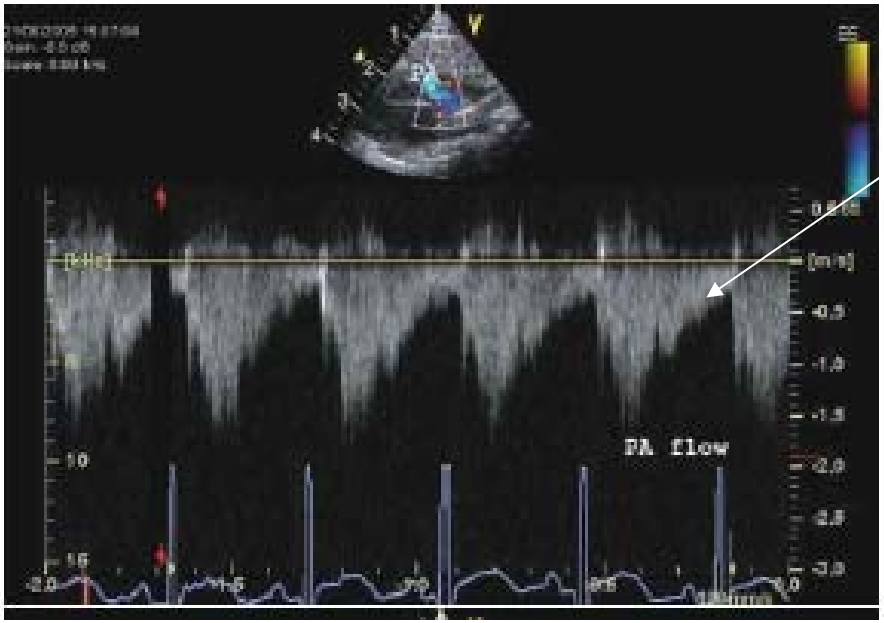


IVRT



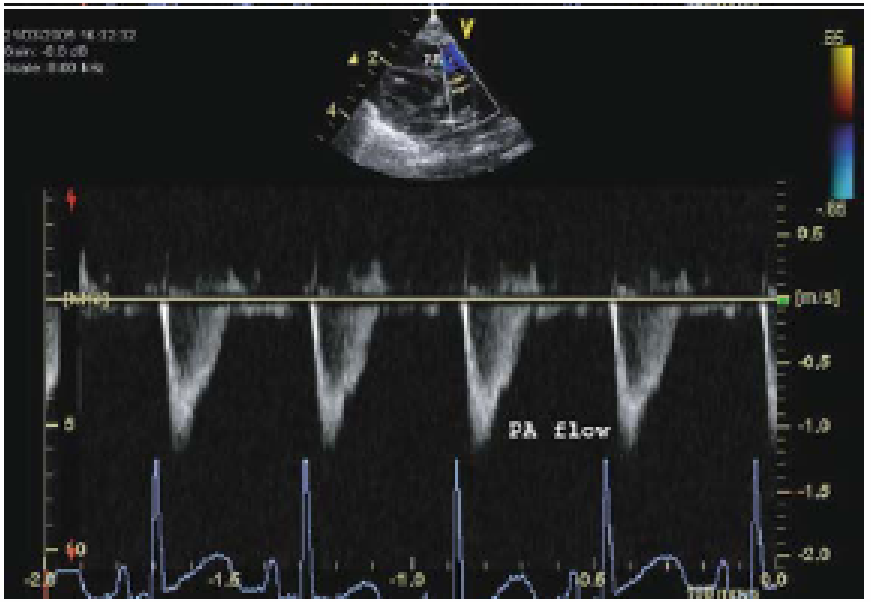
* p < 0.05 vs baseline

Pulmonary Artery Flow

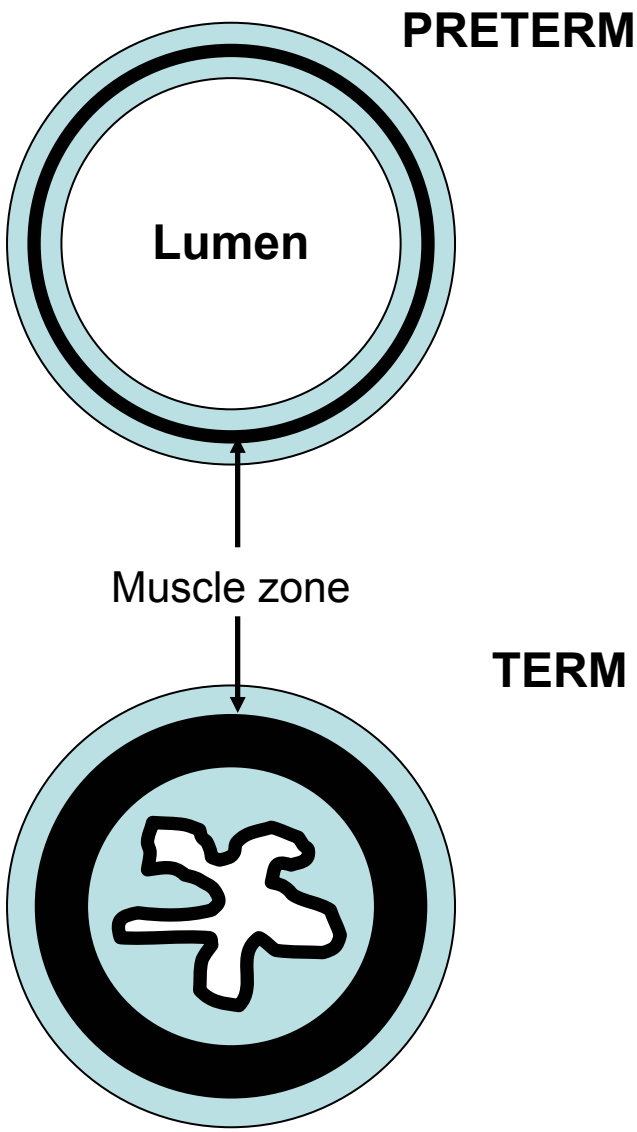


Duct open, diastolic flow

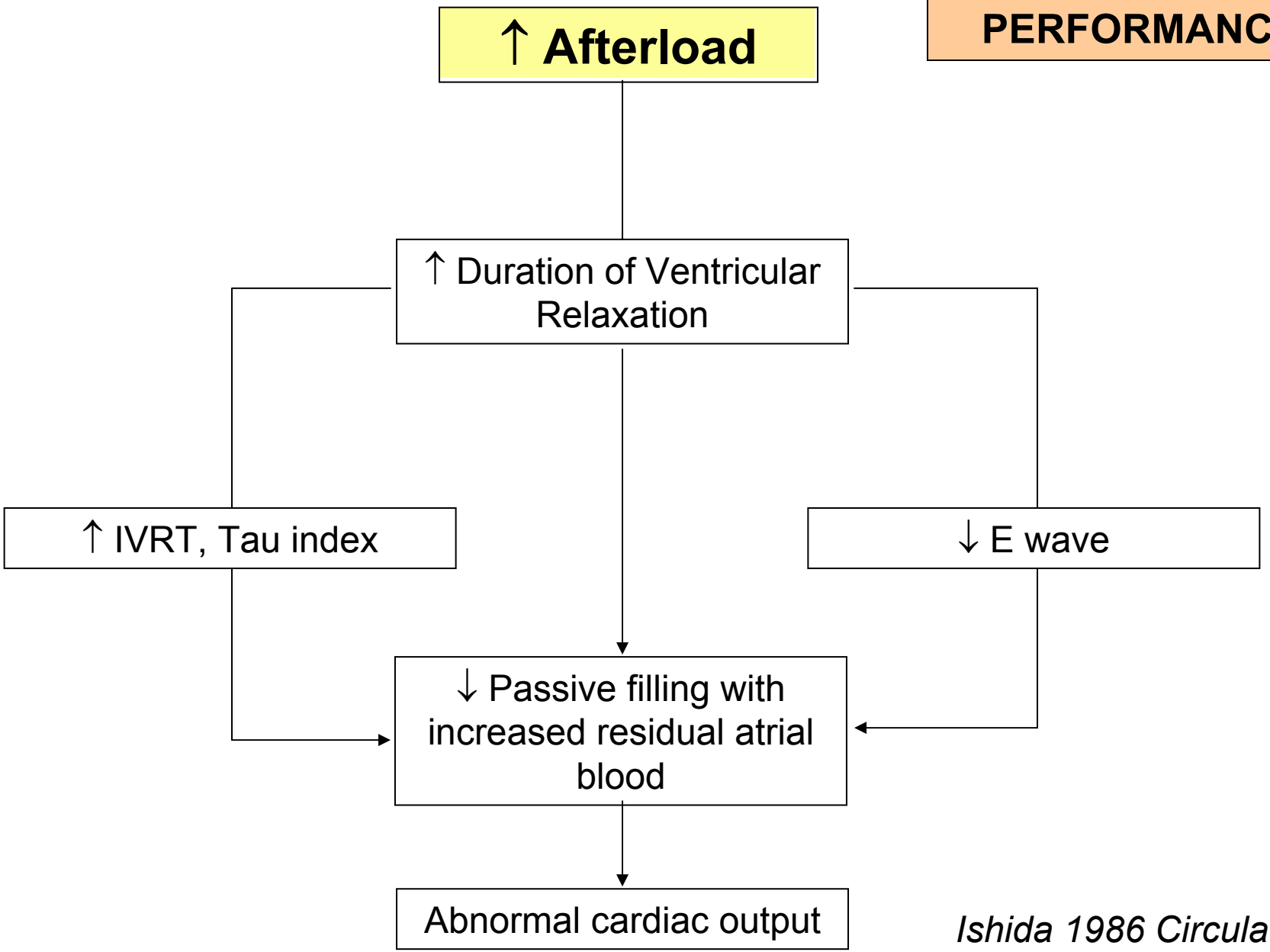
Duct closed



Ductal Closure & Immaturity



DIASTOLIC PERFORMANCE



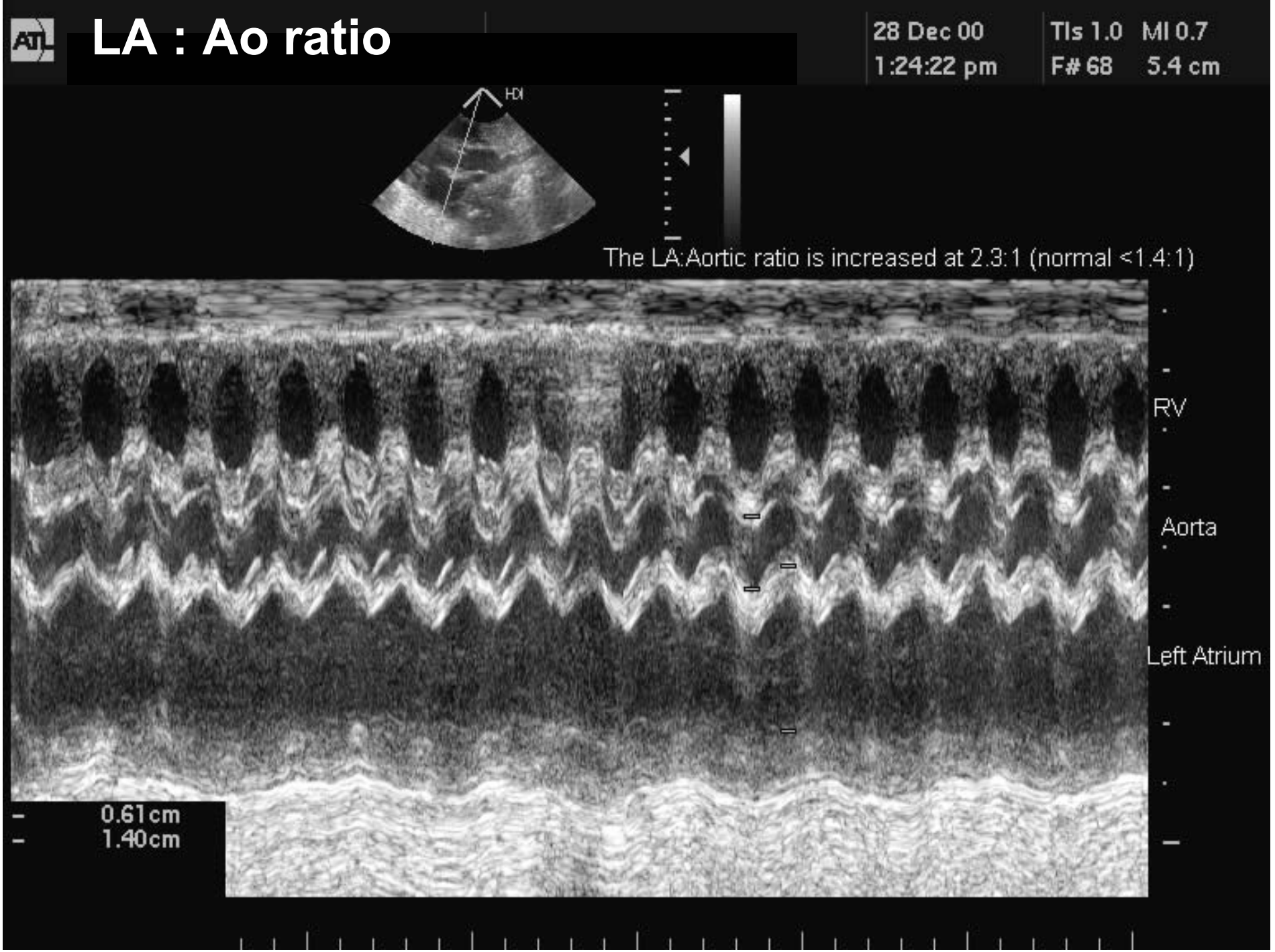
Ishida 1986 Circulation

Diastolic Performance

PDA ligation followed by:

- ↓ E wave, E:A ratio ($p<0.05$, ANOVA)
- ↑ IVRT ($p<0.05$, ANOVA)

- ↑ CA: LVO flow ($p<0.05$, ANOVA)

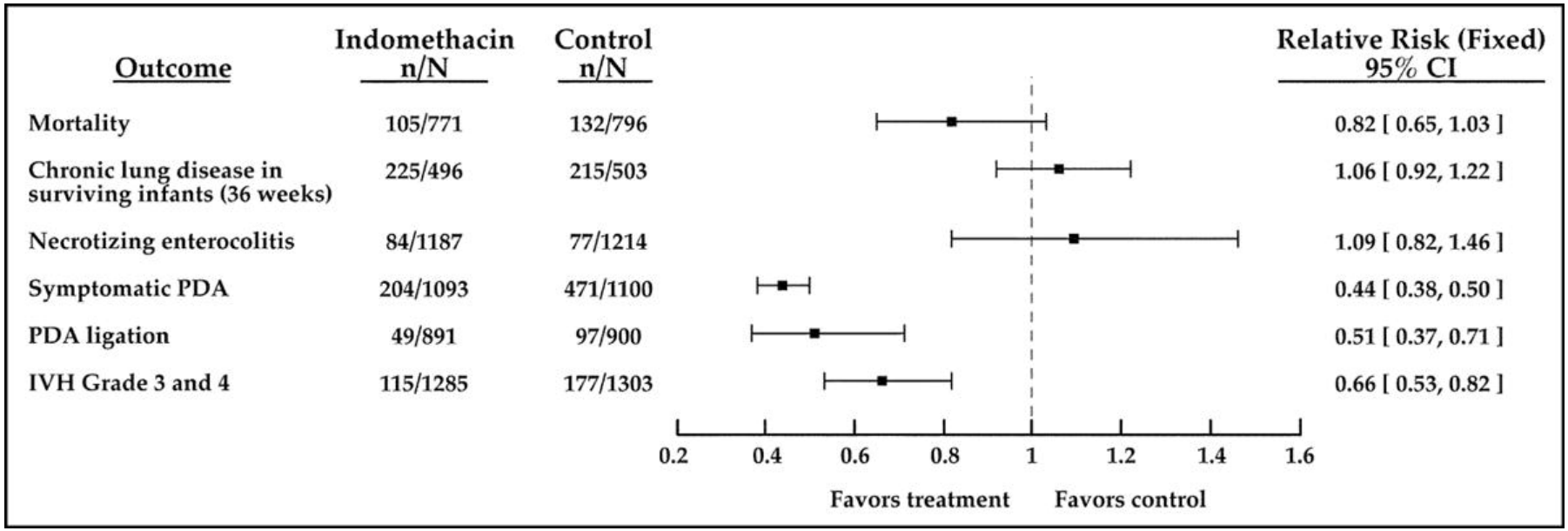

LA : Ao ratio
28 Dec 00
1:24:22 pm
TIs 1.0 MI 0.7
F# 68 5.4 cm
HDI
The LA:Aortic ratio is increased at 2.3:1 (normal <1.4:1)
RV
Aorta
Left Atrium
0.61cm
1.40cm

Implications for clinical practice

- Need for **early identification** of infants at increased risk of PLCS
  - Early fECHO (1 hour)
  - Targeted prophylaxis (LVO<200 mls/min/kg) appears promising

- **Focused** intensive care
  - ***Systolic BP*** is a better marker of early myocardial compromise & the need for cardiotropic agents
  - Avoid cardiotropic agents which increase vascular resistance (dopamine, epinephrine)

Prophylactic intervention



Fowlie 2002 Cochrane database

35% reduction in severe pulmonary hemorrhage

Alfaleh 2008 Pediatrics