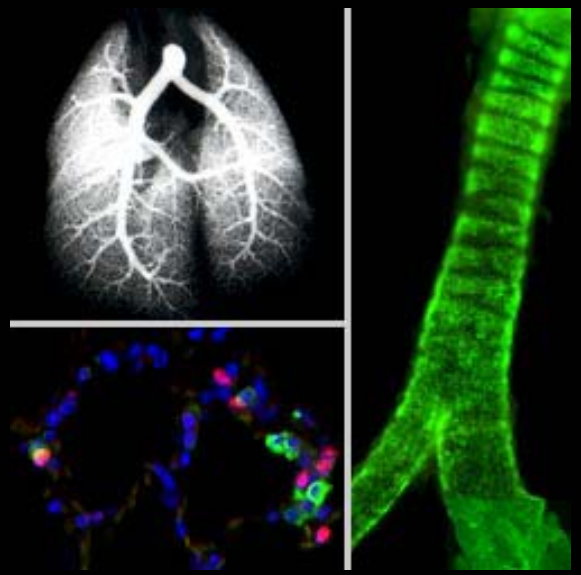
The Critical Neonate with PPHN



SickKids

Patrick McNamara

Associate Professor of Pediatrics, University of Toronto

Staff Neonatologist, Hospital for Sick Children, Toronto

Outline

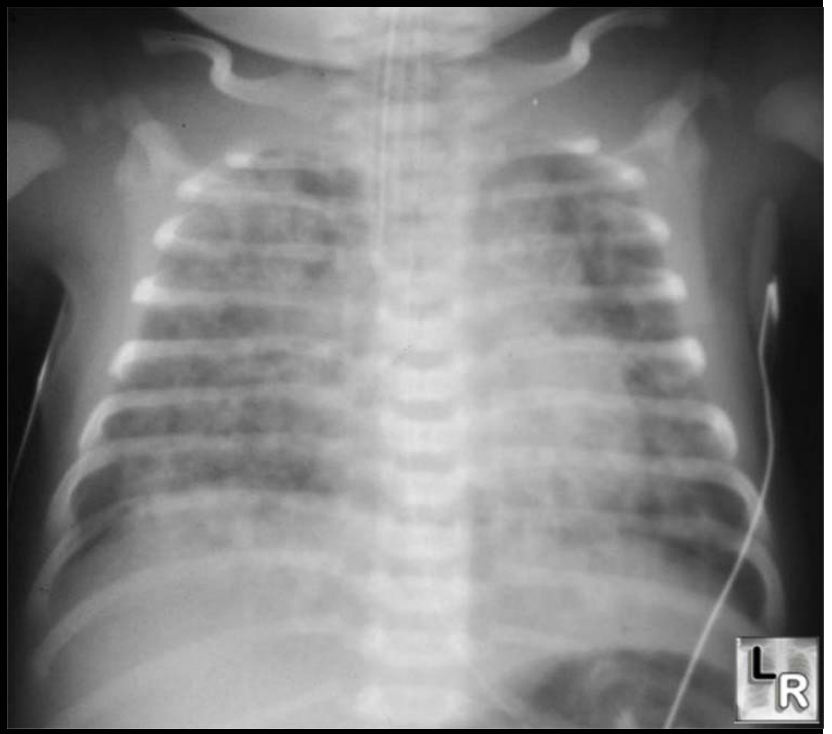
- Pathophysiology
- Approach to therapeutic intervention
- Approach to pulmonary vasodilators
- Approach to cardiovascular support

Persistent Pulmonary Hypertension Syndrome

- 1: 500 - 1500 live births
- 1 - 4 % of Level 3 NICU admissions
- Variable mortality (20%)
- High morbidity: Cognitive delay (30%), hearing loss (19%) neurodevelopmental impairment (48%)

Scenario……

- Term infant, SVD, Thin MSL, Vigorous at birth, APGAR 8, 9
- At 1 hr nurse noted baby to be dusky, with rapid breathing



SpO_2 55% in room air	Temp 36.6 C
HR 146/min	CRT 5-6 sec
Faint murmur	MBP = 36 mmHg
Mod retractions	RR 60/min

SpO2 69% / 50% in FiO_2 100

Intubated [CMV 24/6, 50/m, Ti 0.35s]
FiO_2 100%, SpO_2 85 / 69%

Art Gas: 7.01/79/35/16/-12

The Challenges

- Defining the nature of the disease
- Distinguishing PPHN of respiratory vs. non-respiratory origin
- Quantifying the magnitude of the oxygenation failure
- Quantifying the magnitude and nature of any hemodynamic disturbance

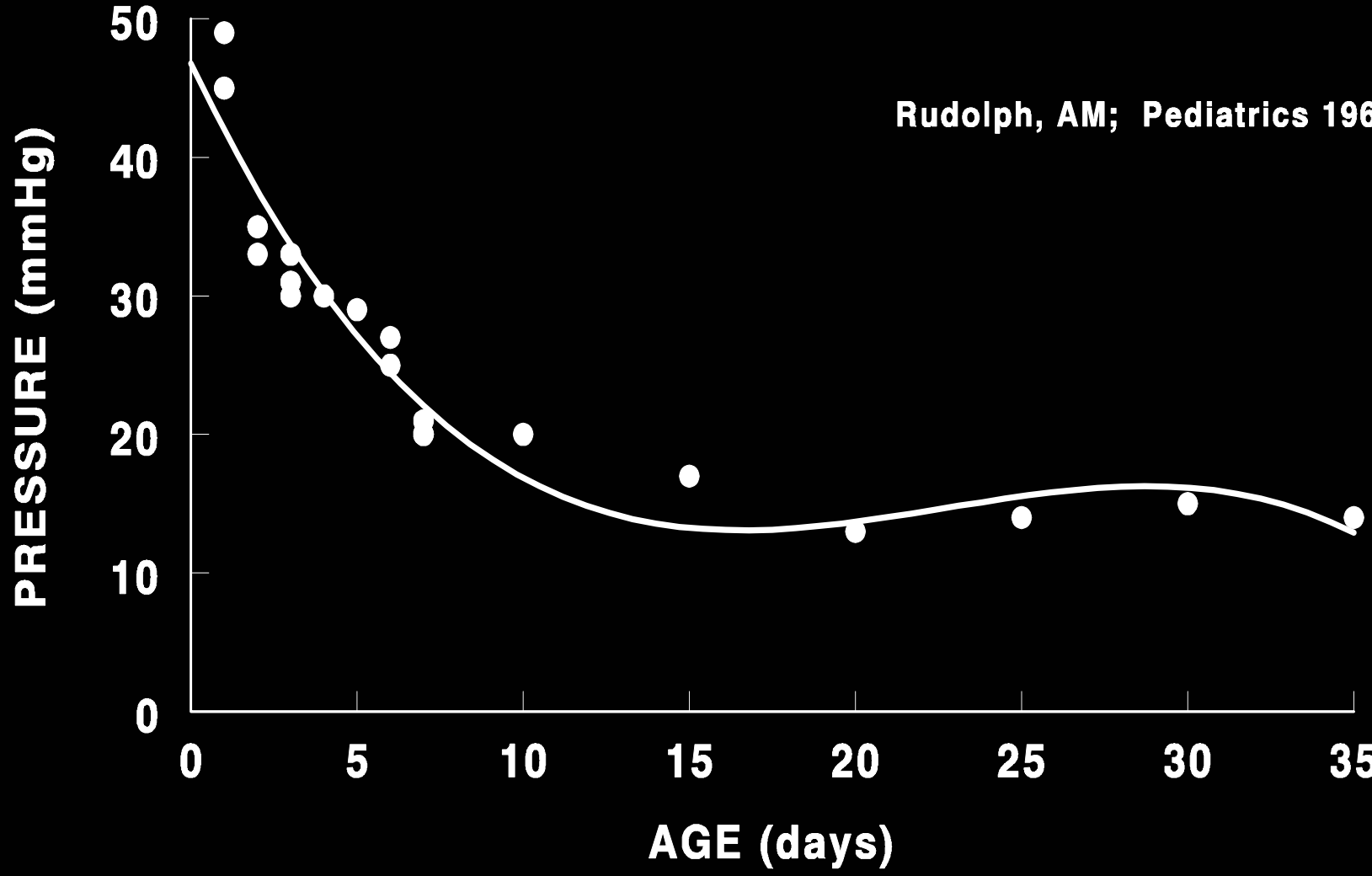
Pulmonary Hypertension

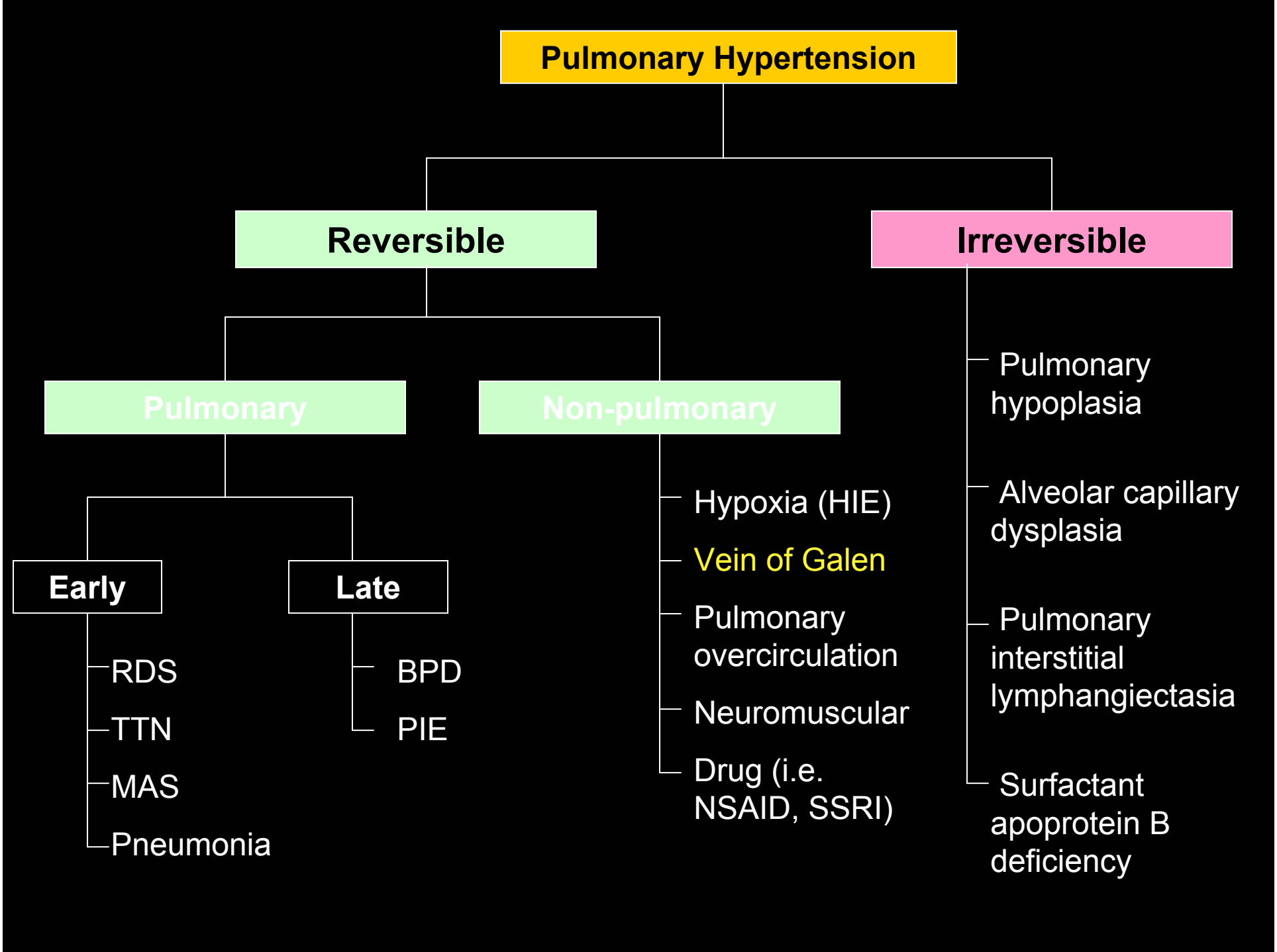
Failure of normal postnatal adaptation with **persistent high PVR** leading to

right ventricular failure and pulmonary:systemic channel shunting

Problem with RV Afterload

CANINE RIGHT VENTRICULAR PRESSURE




Pulmonary Hypertension
Reversible
Irreversible
Pulmonary
Non-pulmonary
Early
Late
RDS
TTN
MAS
Pneumonia
BPD
PIE
Hypoxia (HIE)
Vein of Galen
Pulmonary overcirculation
Neuromuscular
Drug (i.e. NSAID, SSRI)
Pulmonary hypoplasia
Alveolar capillary dysplasia
Pulmonary interstitial lymphangiectasia
Surfactant apoprotein B deficiency

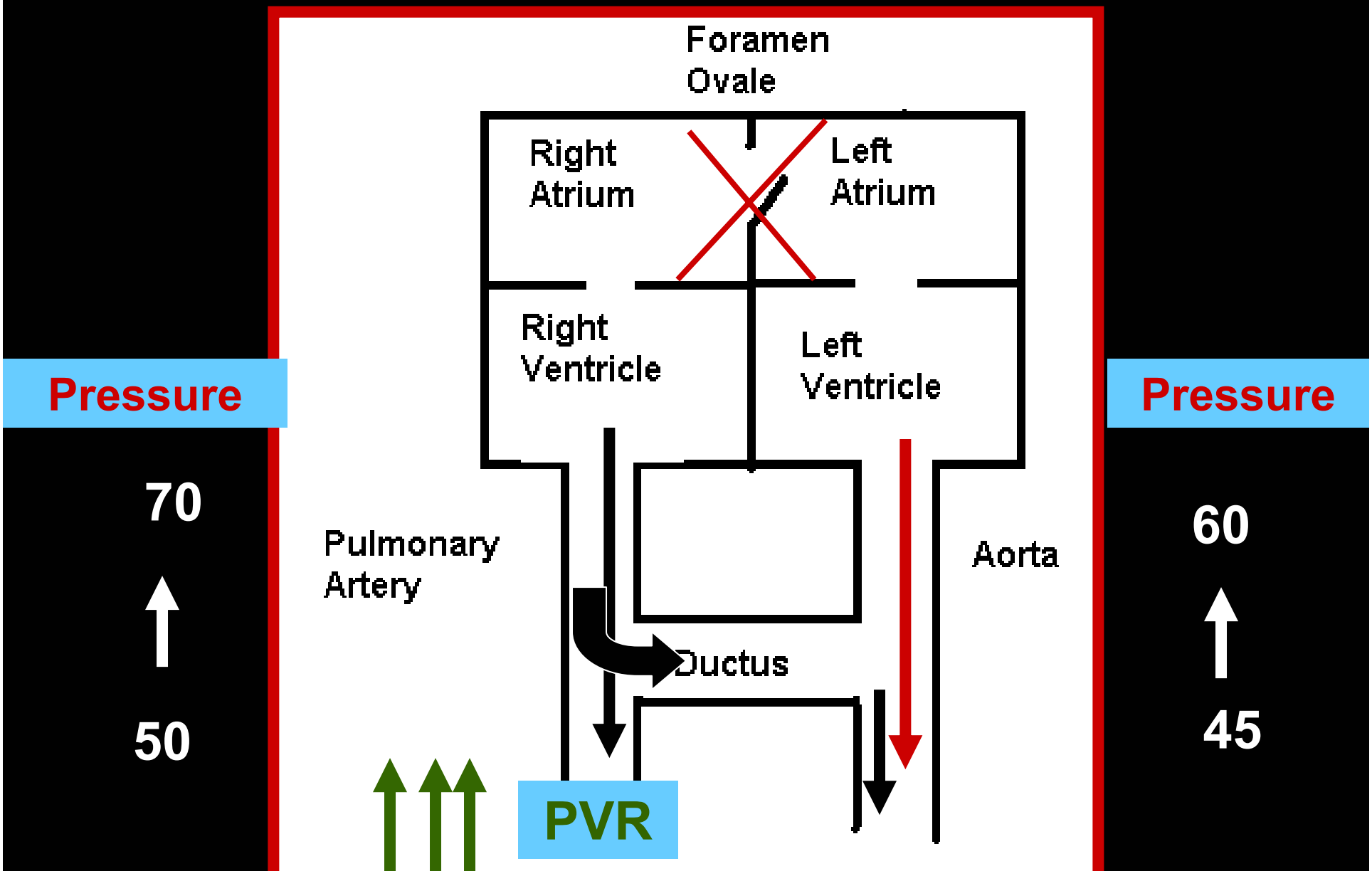
Cardiovascular approach…….

An increase in Blood Pressure improves oxygenation

Approach:

- Fluid bolus
- Inotropic support (e.g. dopamine) to increase or maintain a “high blood pressure

High PVR – Ductus Shunt



CLINICAL ASSESSMENT ALONE DOES NOT ALLOW ACCURATE EVALUATION OF THE NATURE OF THE CARDIOVASCULAR COMPROMISE

Cardiovascular considerations

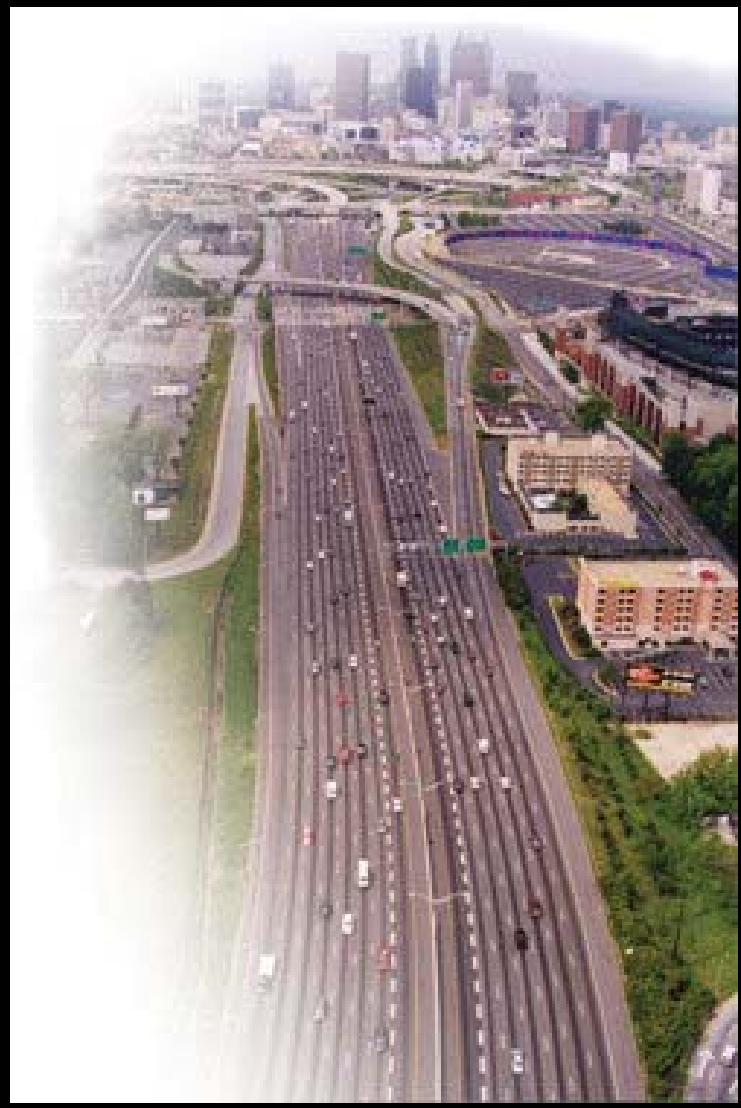
- Suprasystemic PPHN more likely if non-respiratory (85% vs 26%) origin
- PDA present in only 53% of cases with respiratory origin and highly restrictive in many cases of non-respiratory origin
- Dysfunctional right ventricle and low cardiac output commonly present

Skinner 1996 Arch Dis Child, Evans 1995 Arch Dis Child

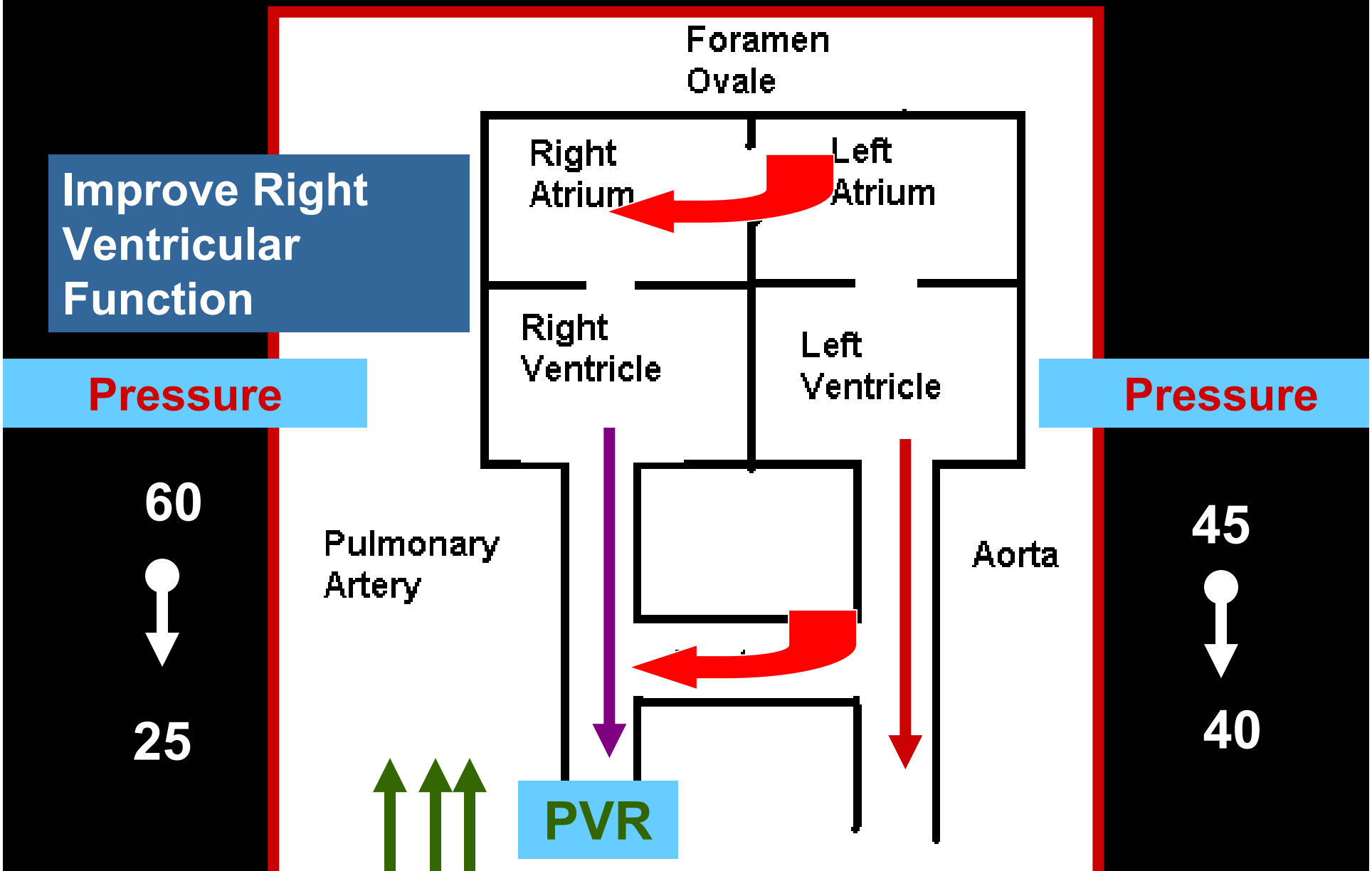
Physiologic Approach

Treat the problem not the consequences

- **Optimize lung recruitment**
- **Effective pulmonary vasodilation**
- **Achieve normal cardiac output and blood pressure**



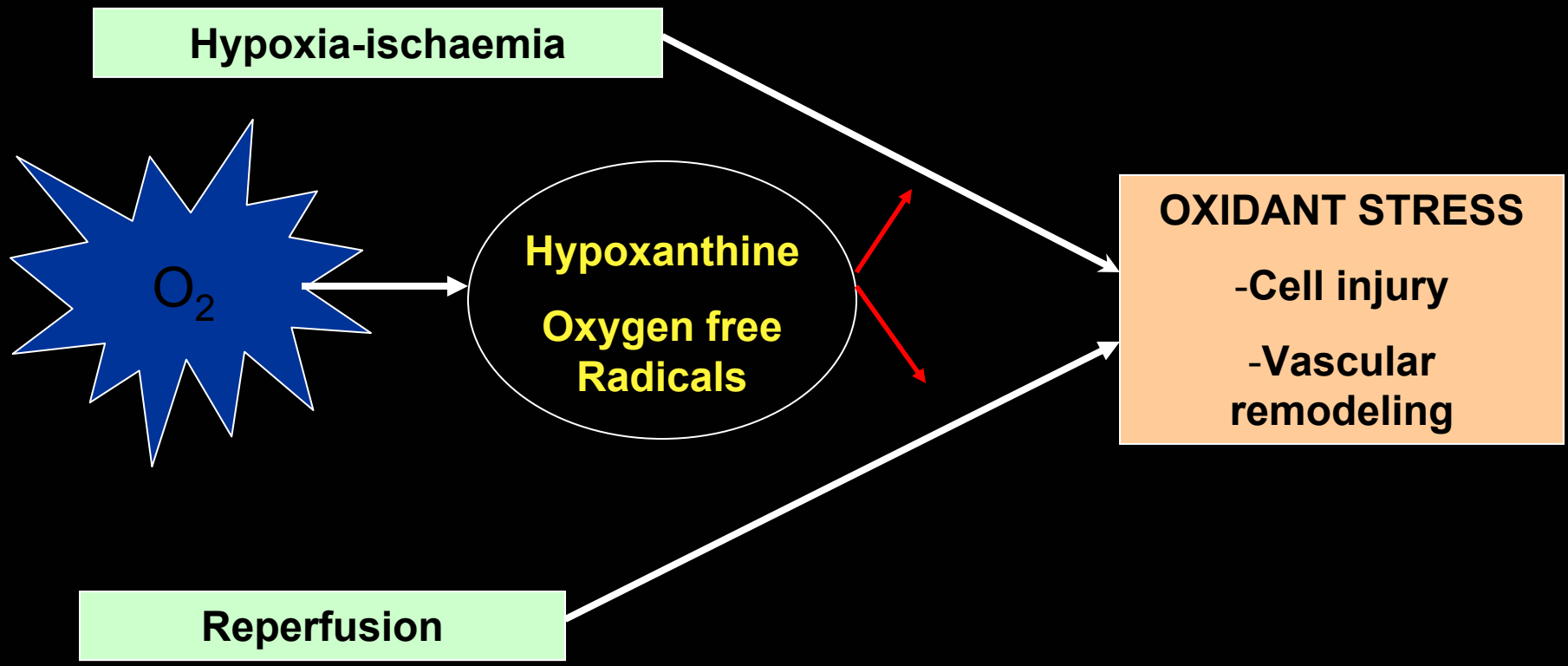
Desireable Effects



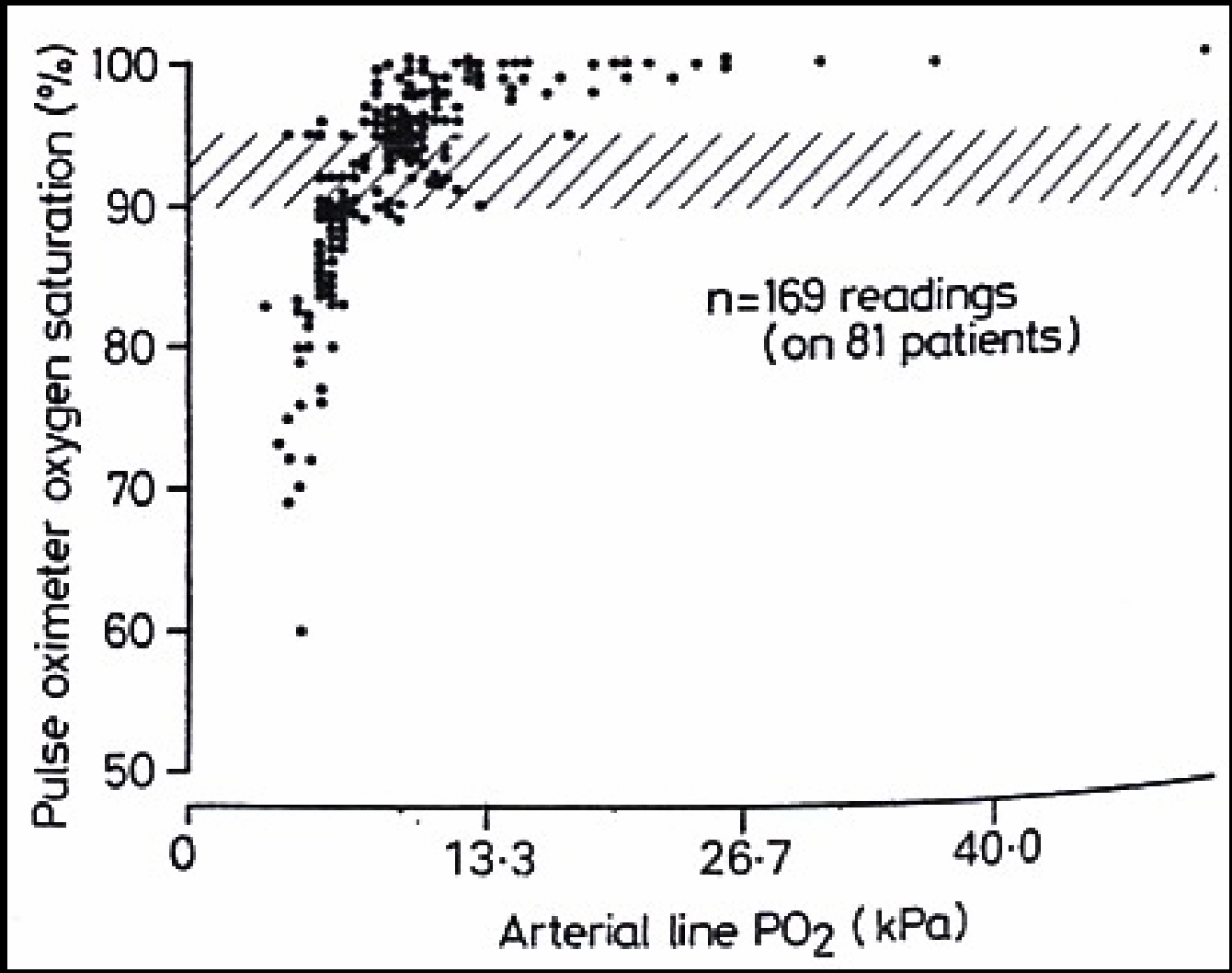
I. How much oxygen ?

- Pulmonary vasodilator
- paO_2 target range?
  > 95% vs 90-85%
- Merits of post-ductal SpO_2 monitoring?
- Acute vs convalescent SpO_2 / paO_2

Oxygen Paradox

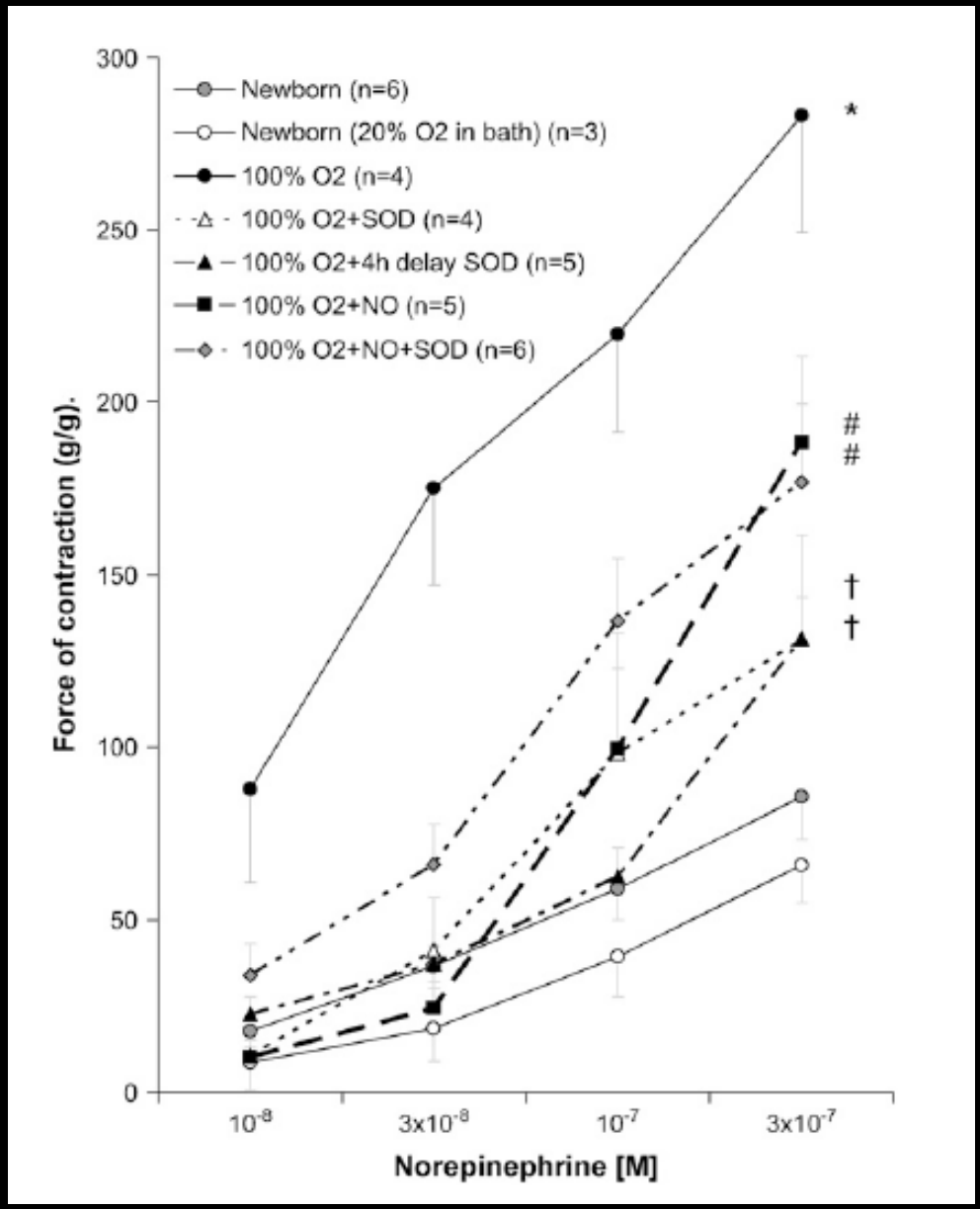


Oxygen Saturations & PaO_2



Southall 1987 Arch Dis Child

Hyperoxia and Vascular Response



Lakshminrushima 2006 Am J Resp Crit Care Med

pO2 and PVR

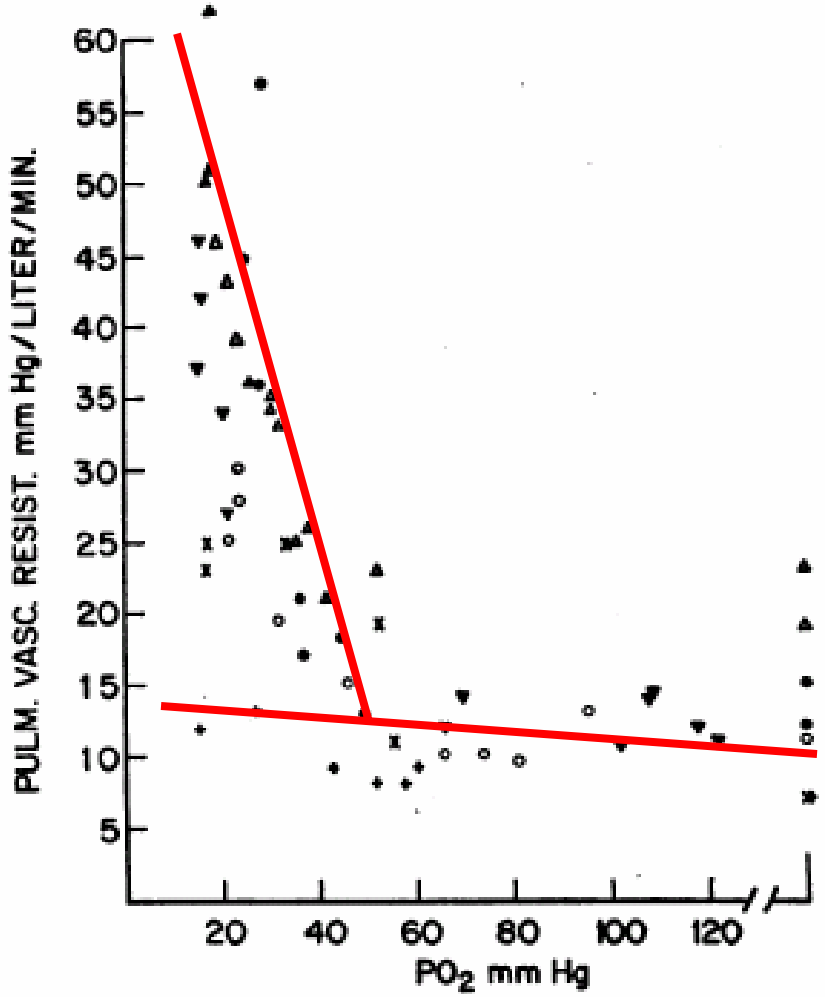


FIG. 6. RELATIONSHIP BETWEEN CALCULATED PULMONARY VASCULAR RESISTANCE AND ARTERIAL P_{O_2} IN SIX CALVES IN TABLE II. Each calf is represented by a different symbol.

Rudolph 1966

Oxygen Saturation Targets…

- Target pre-ductal SpO_2 [88-94%] and paO_2 [50-80 mmHg]
- No evidence to support SpO_2 > 95% or paO2 > 80 mmHg
- Cautious approach to pre-post ductal gradient *(?? > 75% acceptable if lactate, pH, urinary output normal)*

II. Respiratory Support - Case

- Preterm infant at 32 weeks, hx of PROM

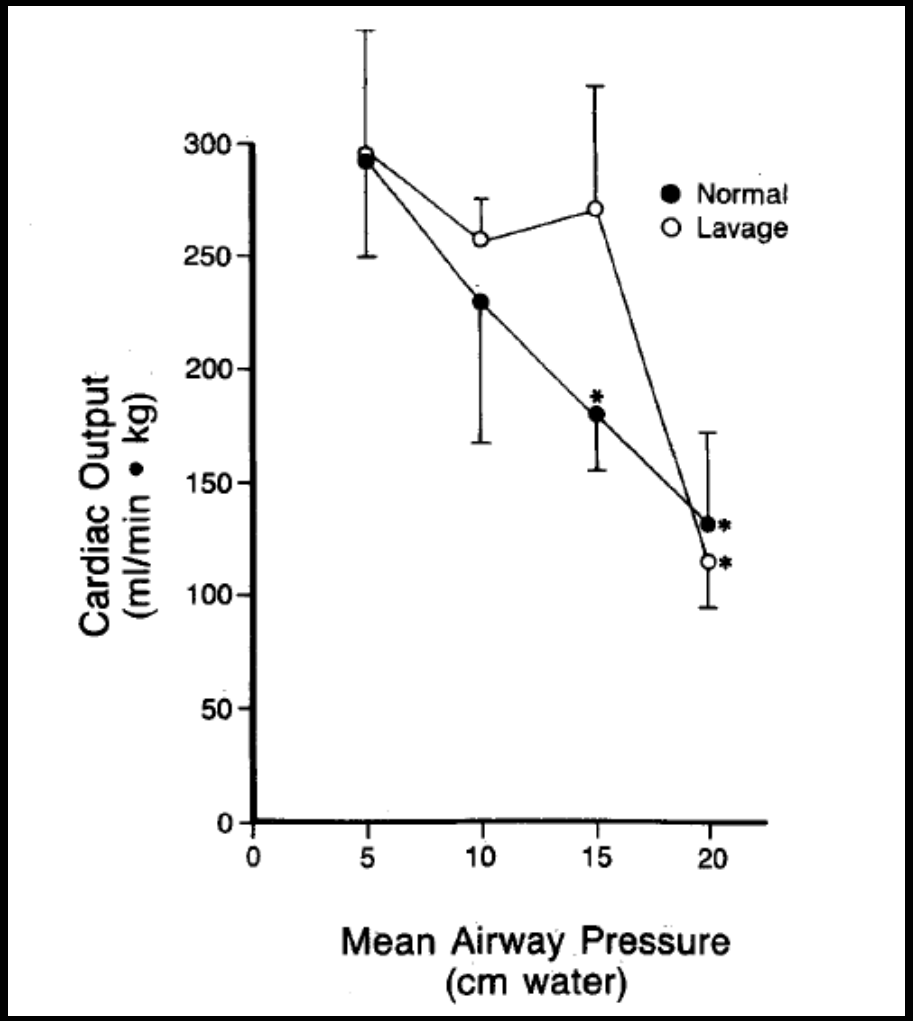
- Severe Oxygenation failure (OI 35) – received iNO (no improvement)
- Initiated on HFOV (MAP 18 on CMV) – increased to 30 cmH2O

- Progressive hemodynamic instability – treated with volume, dobutamine and dopamine
- Chest radiograph – normal lung volume

Targeted Neonatal echo

- Heart severely volume depleted [unable to see the atria clearly and both ventricles]
- ↓ pulmonary venous flow, transmitral flow and cardiac output
- After transitioning to CMV and administering a fluid bolus filling improved and overall cardiac output improved.
- Treated with milrinone / vasopressin - stabilized
- ICU support withdrawn: Pulmonary hypoplasia

Mean Airway Pressure & Blood flow



Mirro 1987 J Pediatr

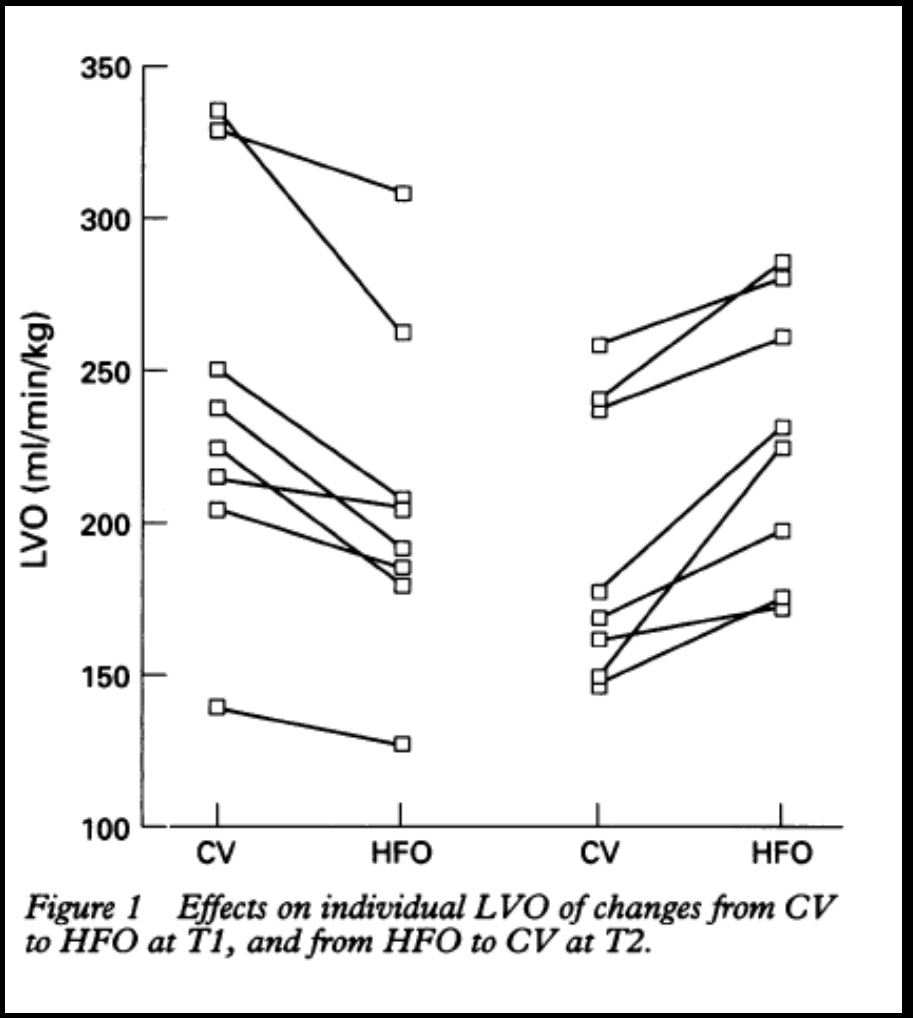
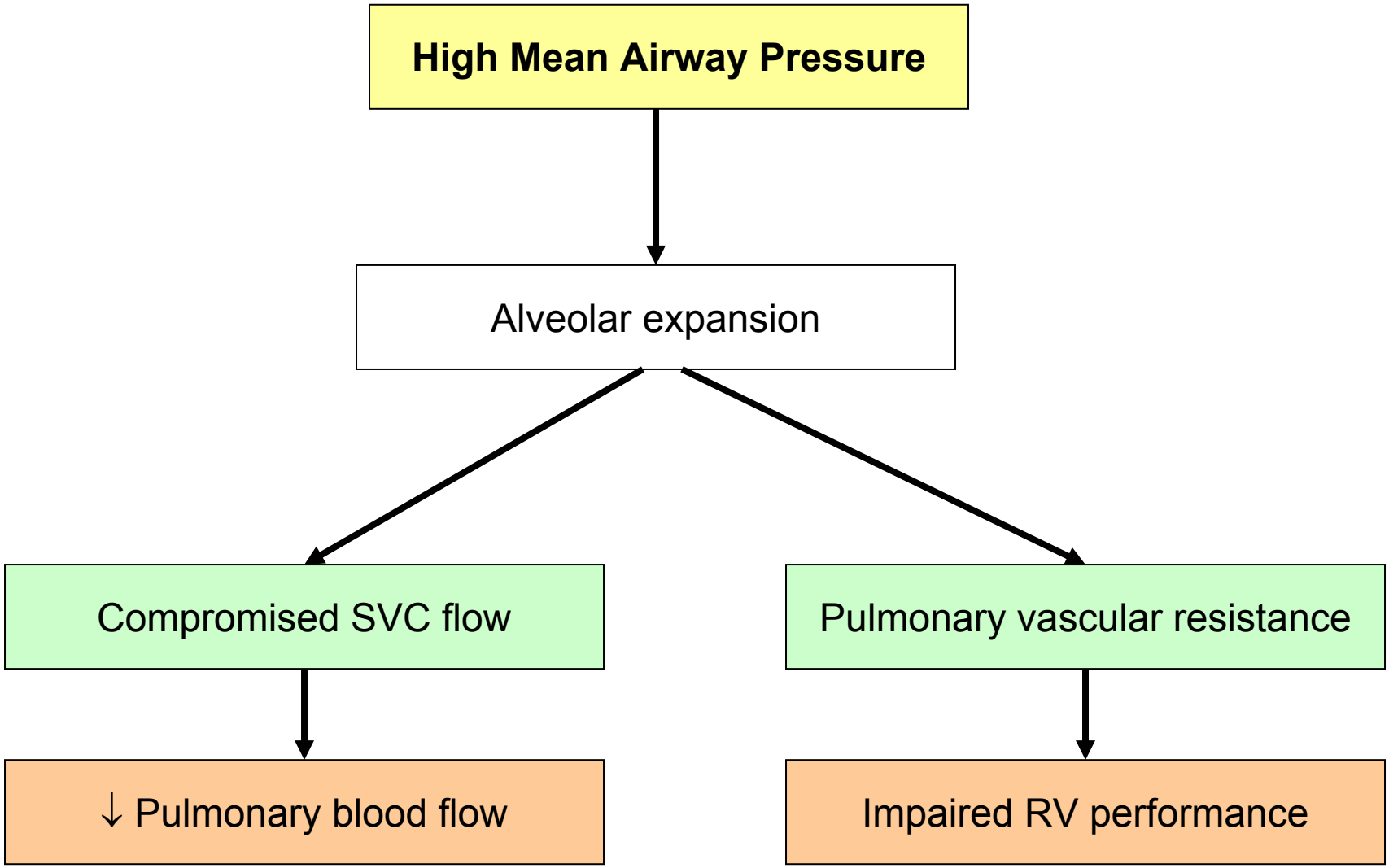


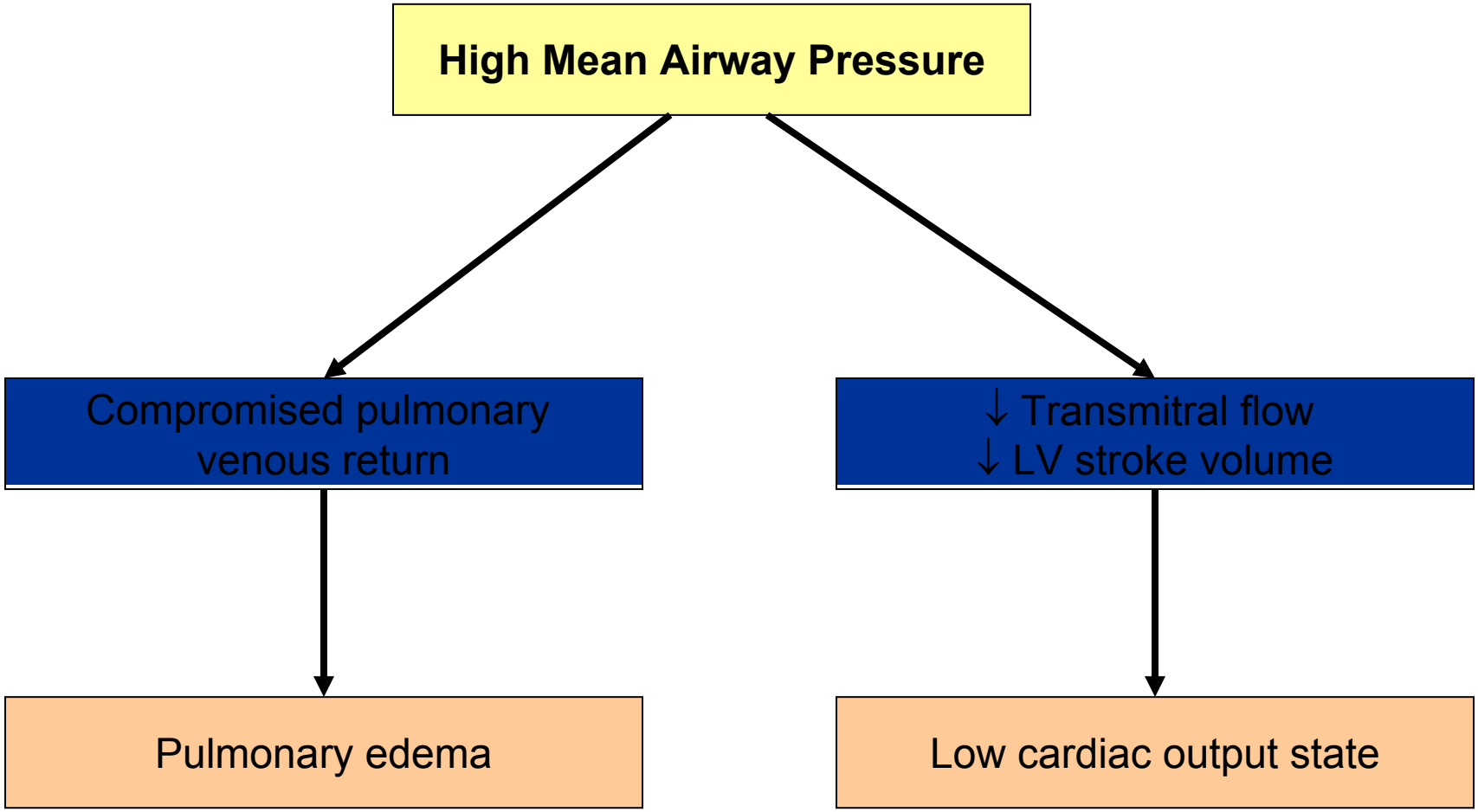
Figure 1 Effects on individual LVO of changes from CV to HFO at T1, and from HFO to CV at T2.

Laubscher 1996 Arch Dis Child

Right Heart Compromise



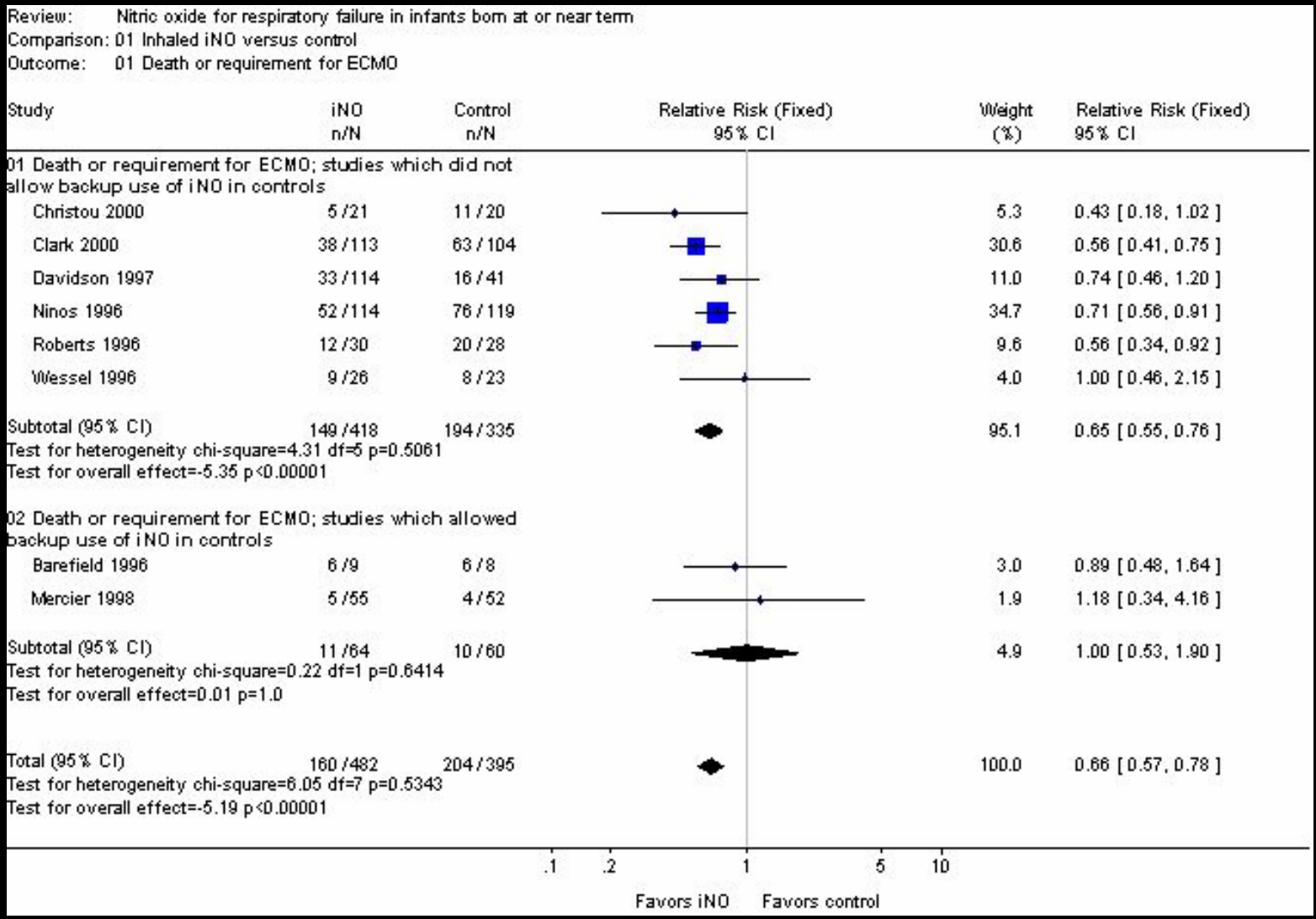
Left Heart Compromise



Approach to Pulmonary Vasodilators

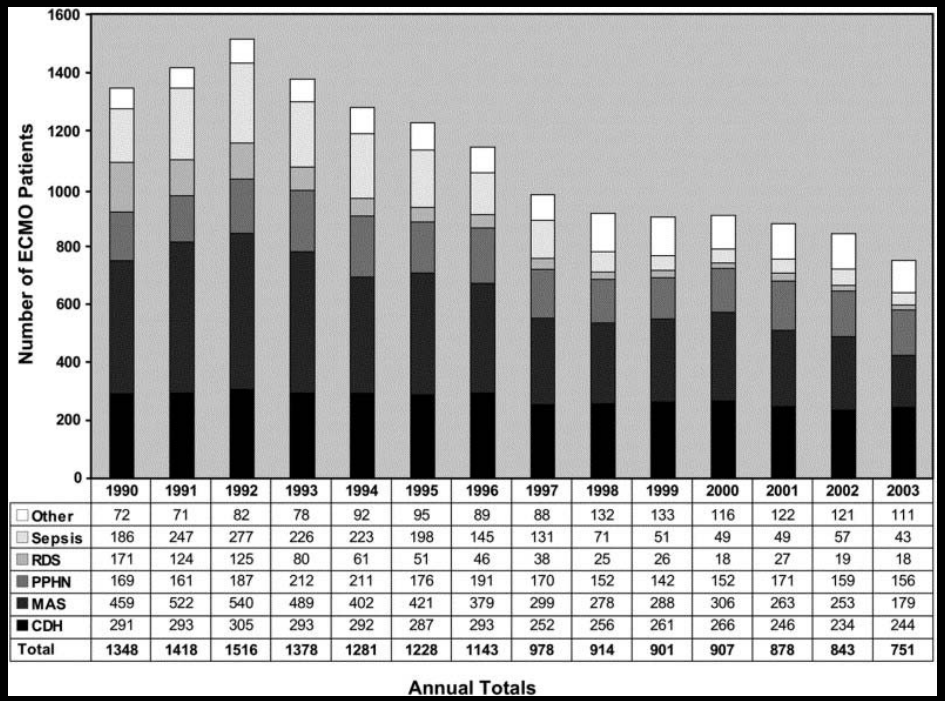
- **Selective**
  - Inhaled Nitric oxide
- **Non-selective**
  - Sildenafil
  - Prostacyclin
- **Non-specific**
  - Milrinone
  - Vasopressin

iNO and Death/ECMO……



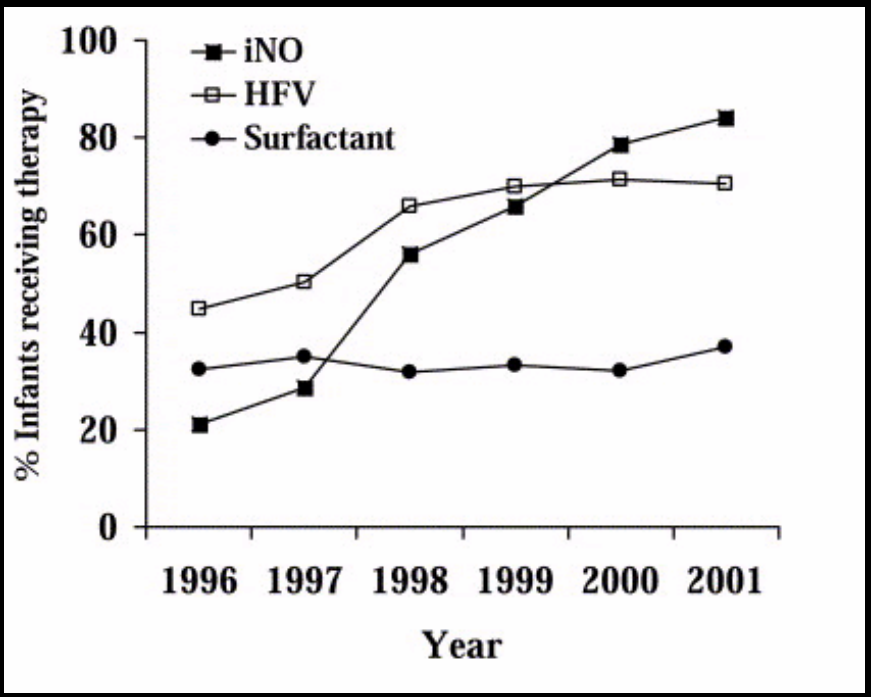
Barrington, & Finer 2008

ECMO rates



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Other	72	71	82	78	92	95	89	88	132	133	116	122	121	111
Sepsis	186	247	277	226	223	198	145	131	71	51	49	49	57	43
RDS	171	124	125	80	61	51	46	38	25	26	18	27	19	18
PPHN	169	161	187	212	211	176	191	170	152	142	152	171	159	156
MAS	459	522	540	489	402	421	379	299	278	288	306	263	253	179
CDH	291	293	305	293	292	287	293	252	256	261	266	246	234	244
Total	**1348**	**1418**	**1516**	**1378**	**1281**	**1228**	**1143**	**978**	**914**	**901**	**907**	**878**	**843**	**751**

Annual Totals



1992-2001: ↓ ECMO rates 40%

Hintz 2004 Pediatrics, ECLSO registry 2004

8. If yes at which of the following OI would you start iNO treatment?

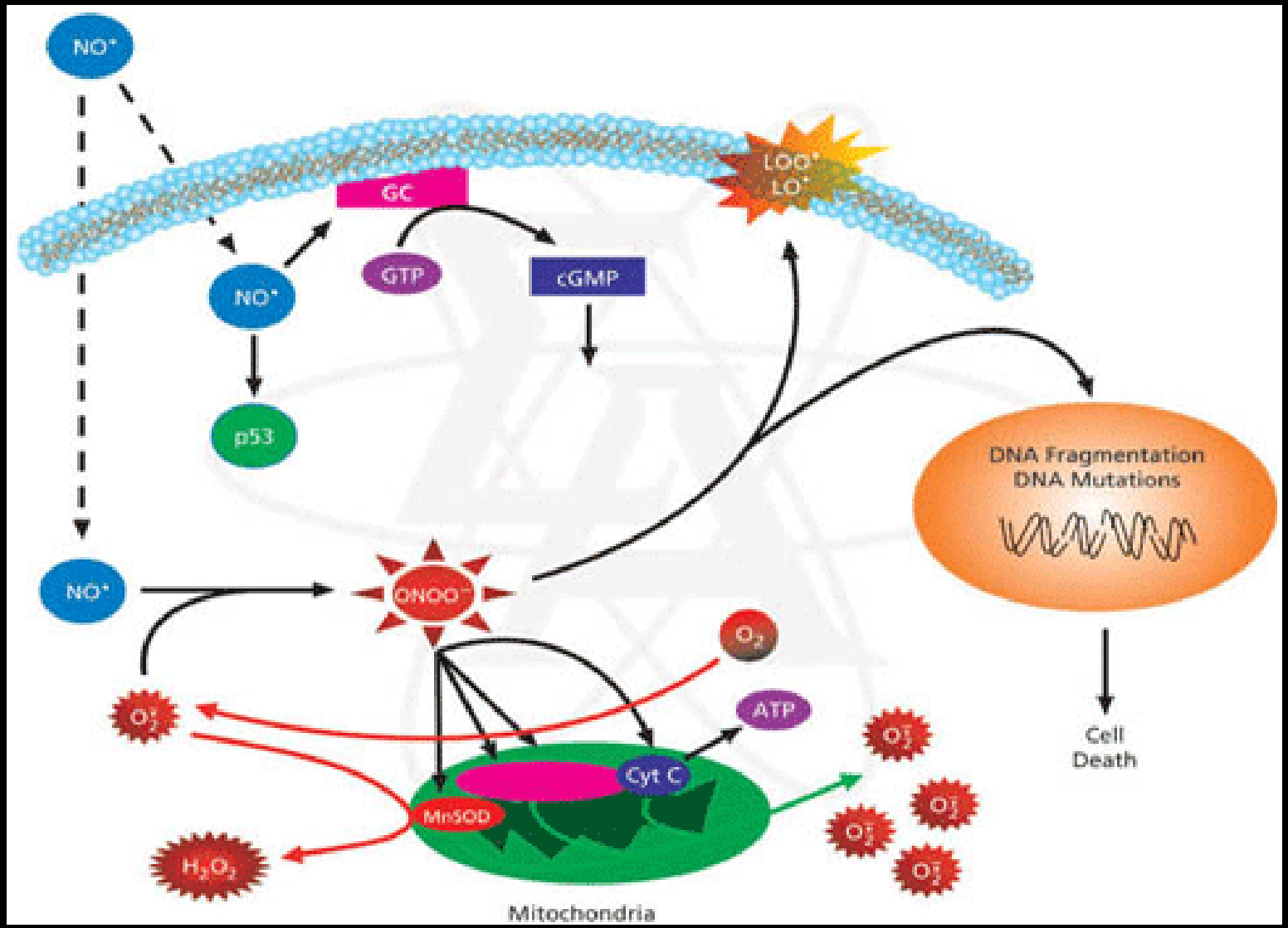
SURVEY CANADA / AUSTRALASIA

	Response Percent	Response Count
5-9	0.0%	0
10-14	10.4%	10
15-19	17.7%	17
20-24	9.4%	9
≥25	14.6%	14

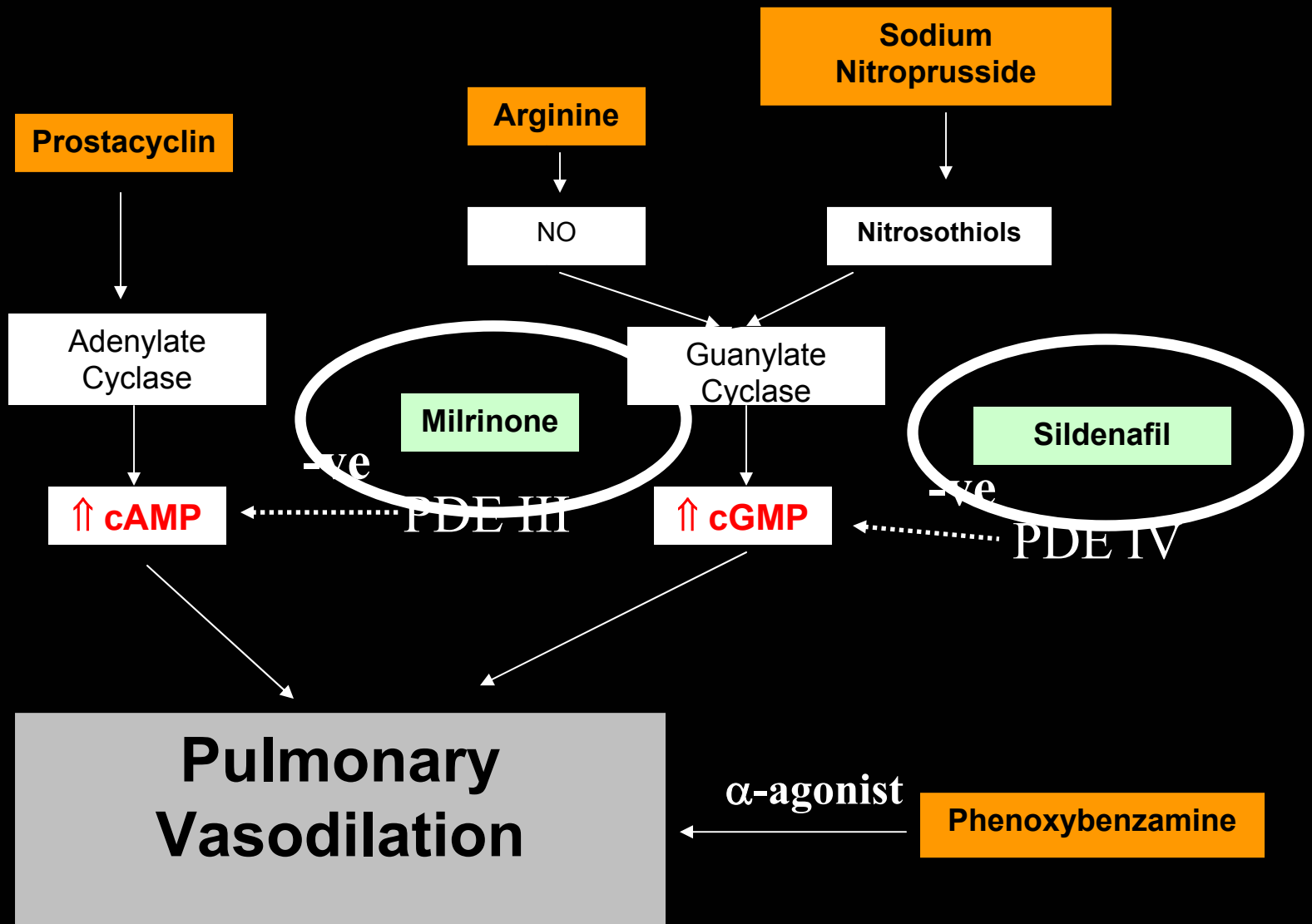
10. According to your guideline, the starting dose of inhaled NO is

	Response Percent	Response Count
5ppm	16.0%	17
10ppm	18.9%	20
15ppm	1.9%	2
20ppm	**50.9%**	54
>20ppm	0.0%	0
Not applicable	12.3%	13

NO and Oxygen –potential for harm

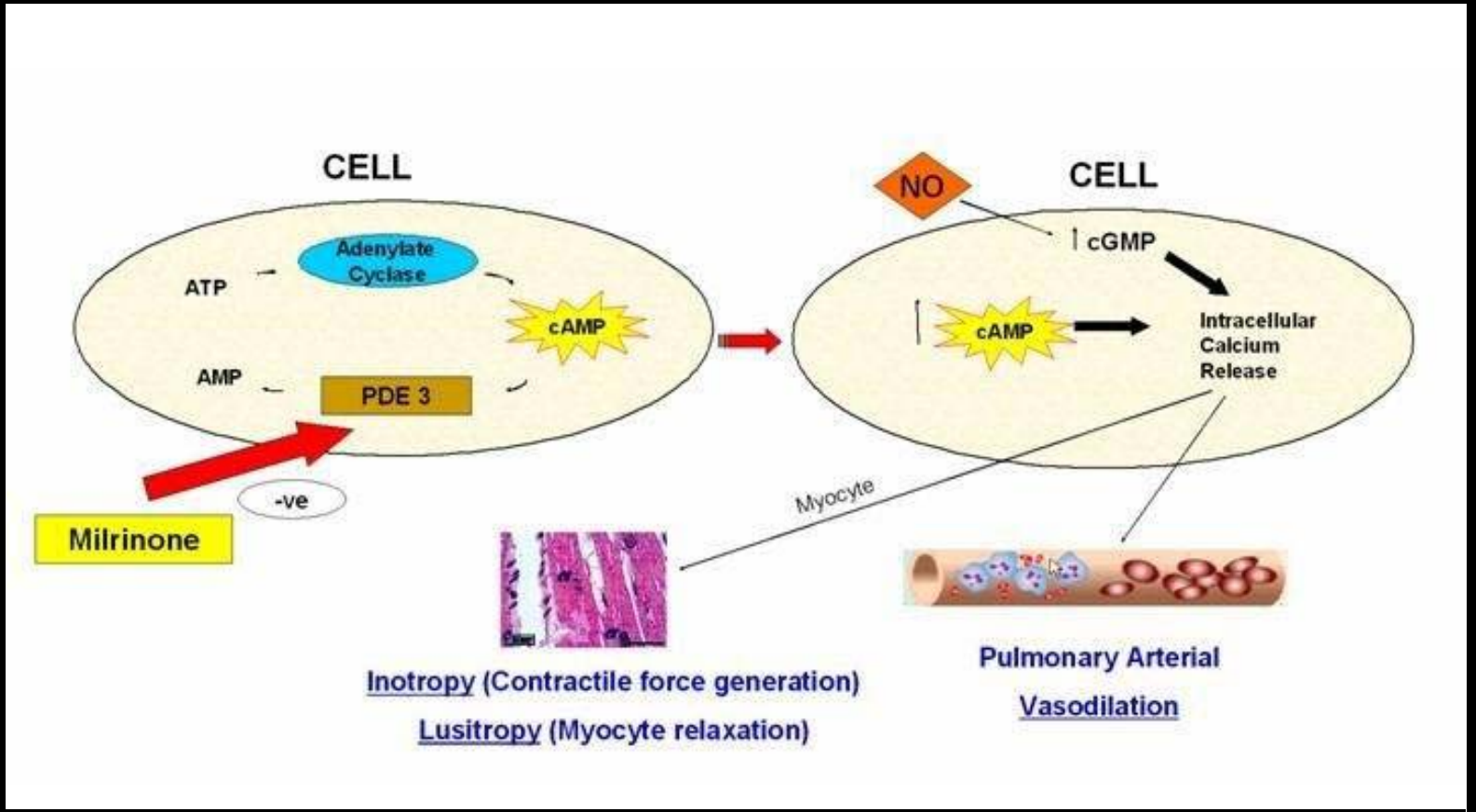


Controlling Vascular Resistance



Milrinone

(Phosphodiesterase III inhibitor)

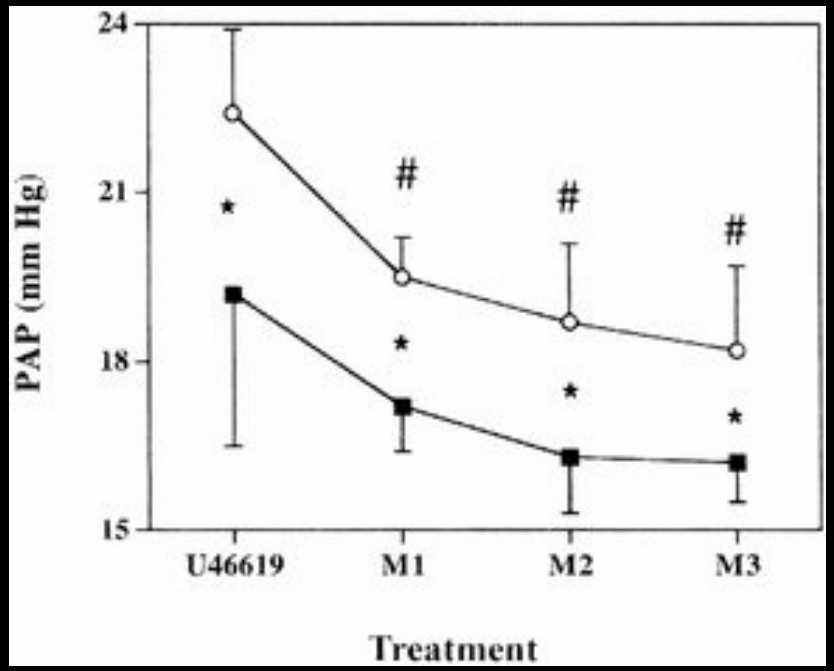


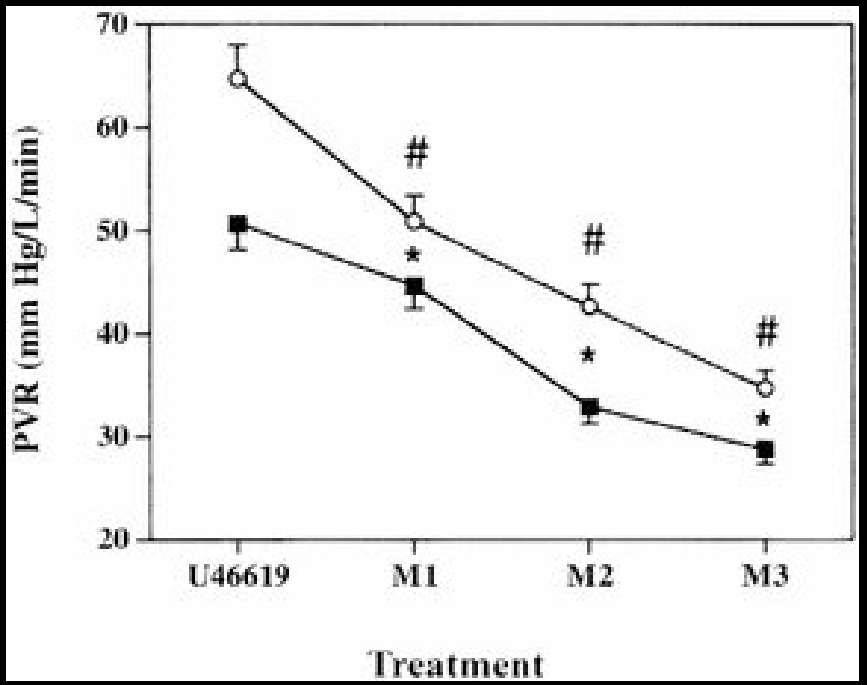
Potential synergism with iNO by increasing bioavailability of cAMP & cGMP *(central role in signal transduction and pulmonary vasodilation)*

Milrinone & PPHN

U44619 (Thromboxane Analogue) Model

N =6





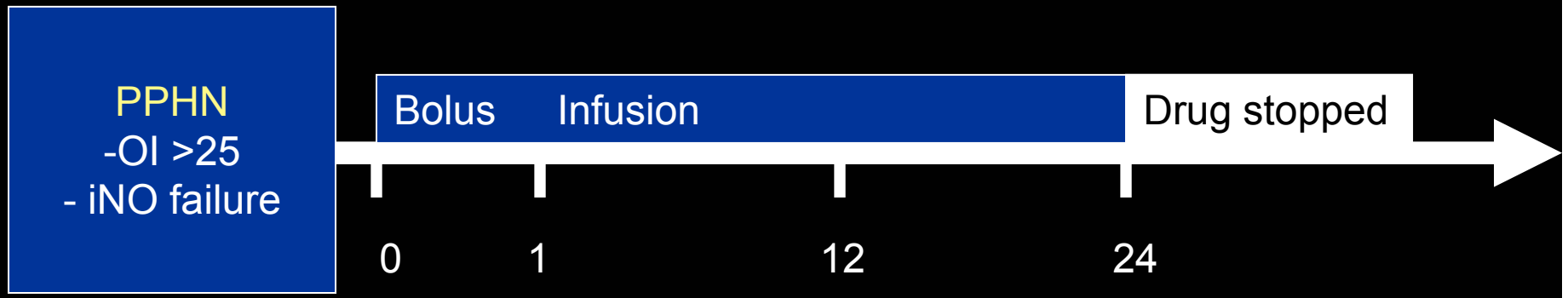
Deb 2000 Crit Care Med

Milrinone led to improvement in OI in iNO refractory PPHN (OI > 25)

McNamara et al 2006 J Critical Care

Milrinone Pharmacokinetics

Eligible neonates received an iv loading dose of milrinone (50μg/kg) over 60 minutes followed by maintenance infusion (0.33-0.99 μg/kg/min) for 24-72 hours

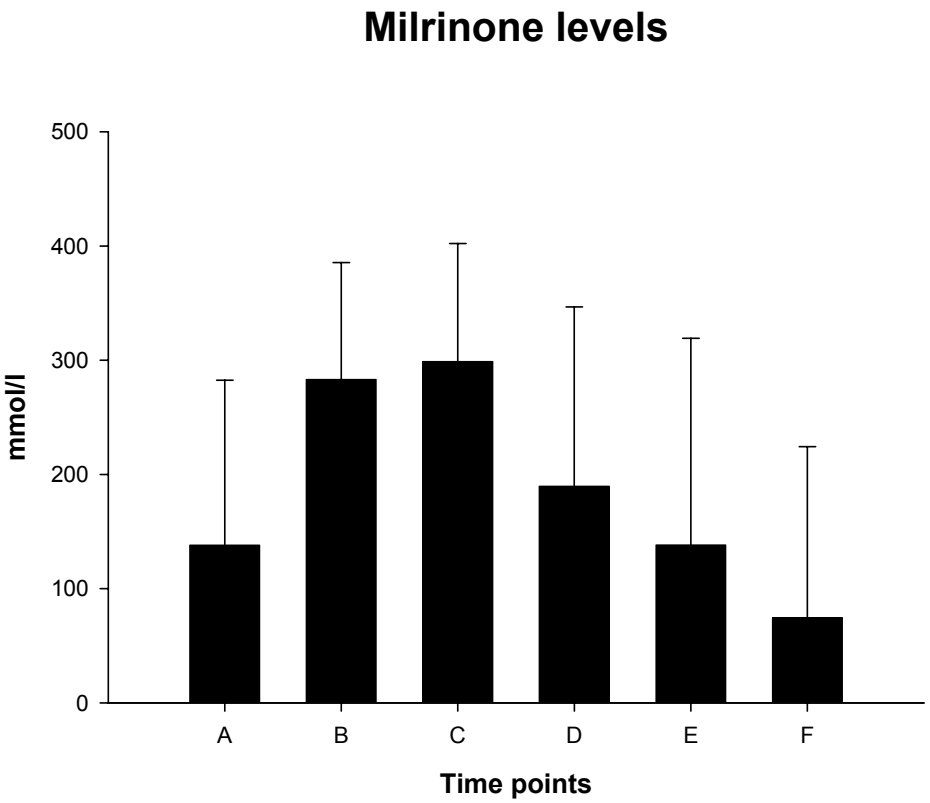


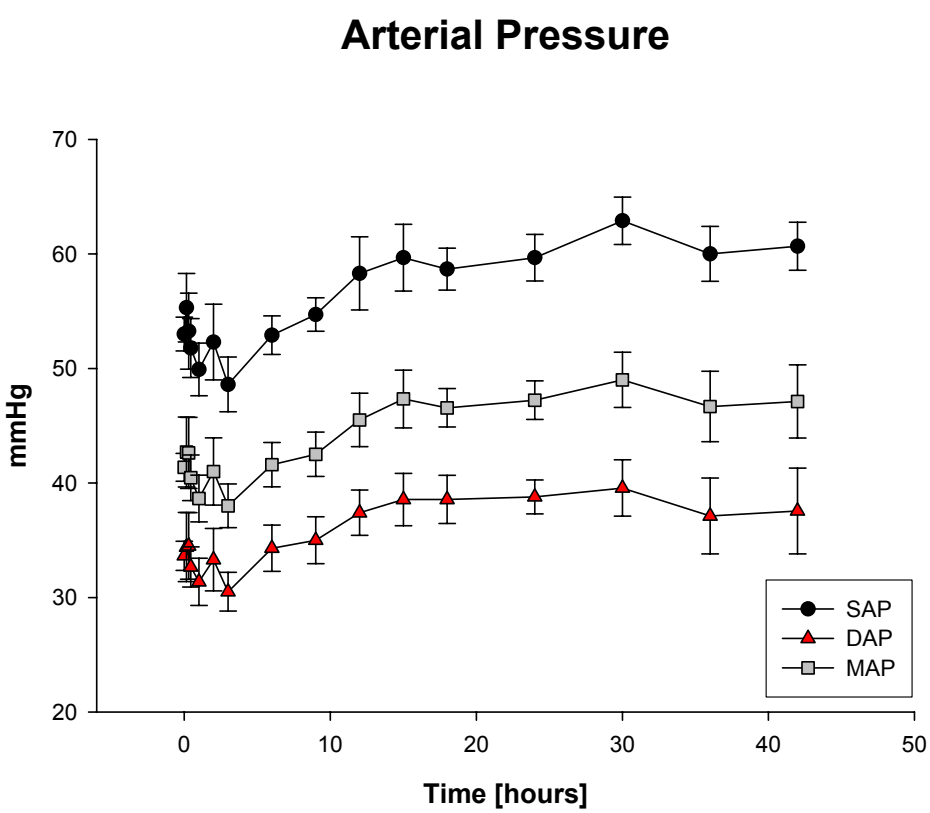
	0	1	12	24, 30, 36
Clinical	+	+	+	+
Echo	+	+	+	-
Drug levels	-	+	+	+
ABG	+	+	+	+

McNamara 2010 PAS

Milrinone Kinetics

McNamara 2010 PAS





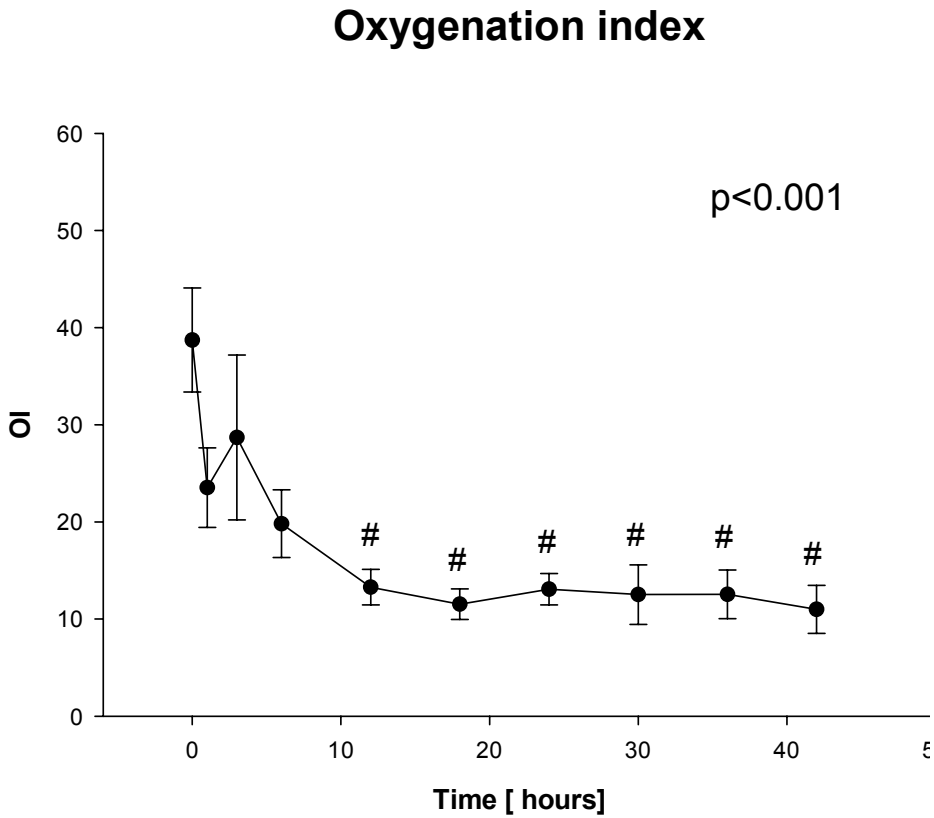
Mean half-life 4.1 (1.1) hours

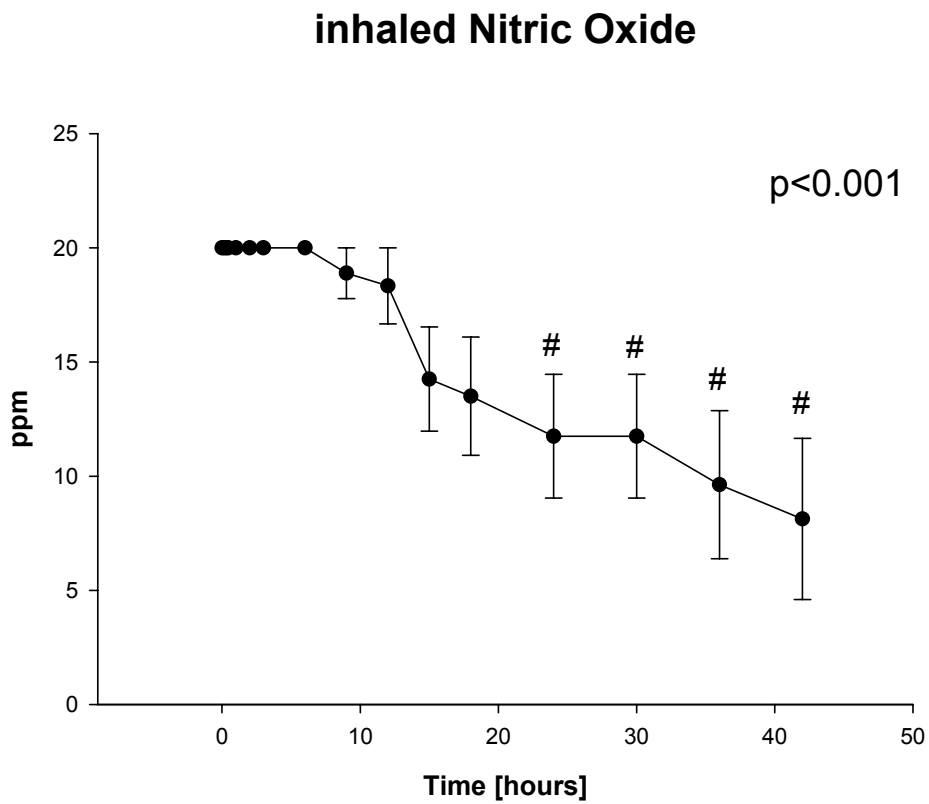
Total body clearance 0.11(0.01) L/kg/hr

Volume of distribution 0.56 (0.19) l/kg

Steady state conc. 290.9 (77.7).

Milrinone - Oxygenation

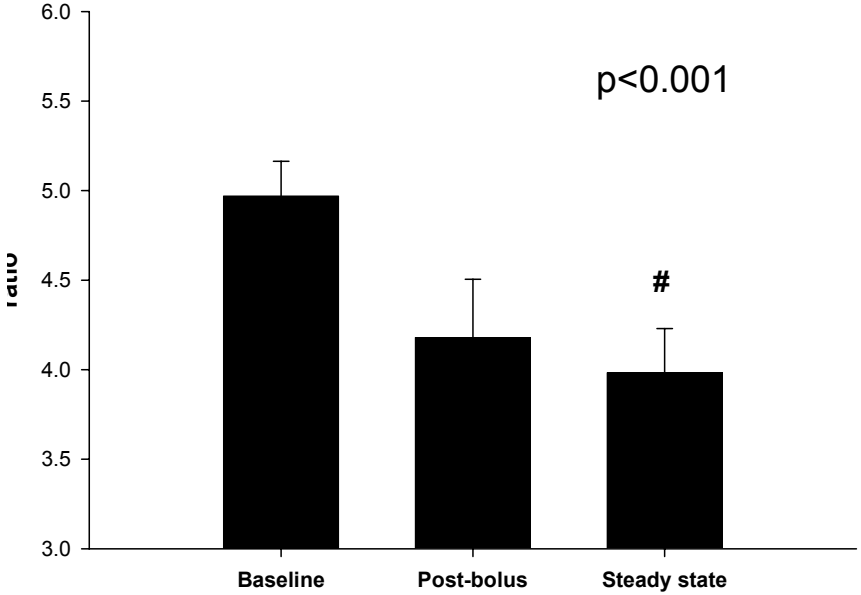




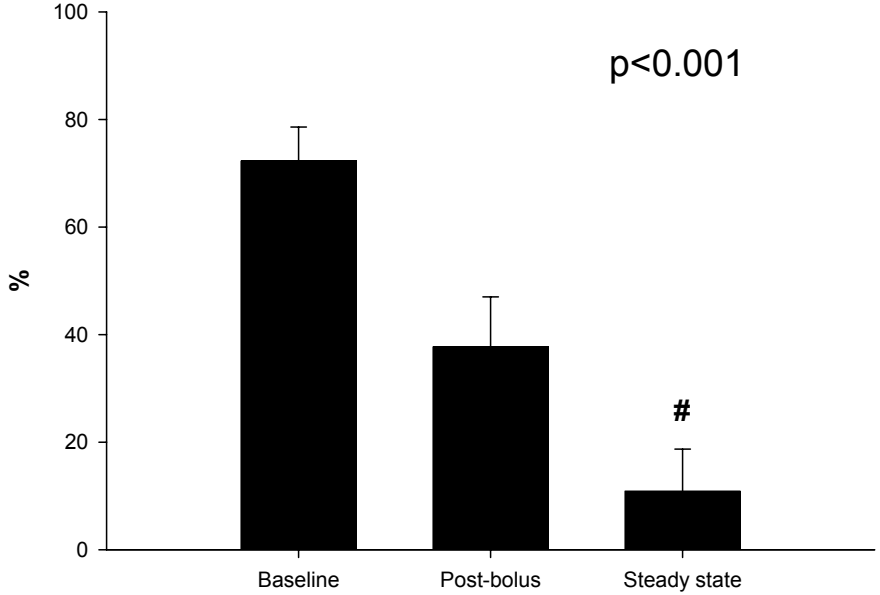
- ↓ FiO_2, MAP and ↑ pO_2
- ↓ base deficit & ↓ lactate

McNamara 2010 PAS

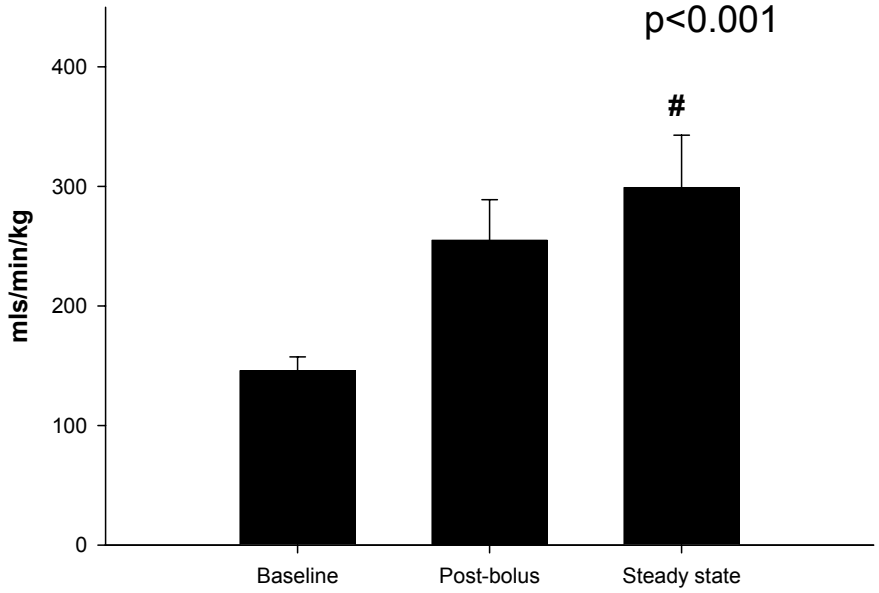
PAAT:RVET



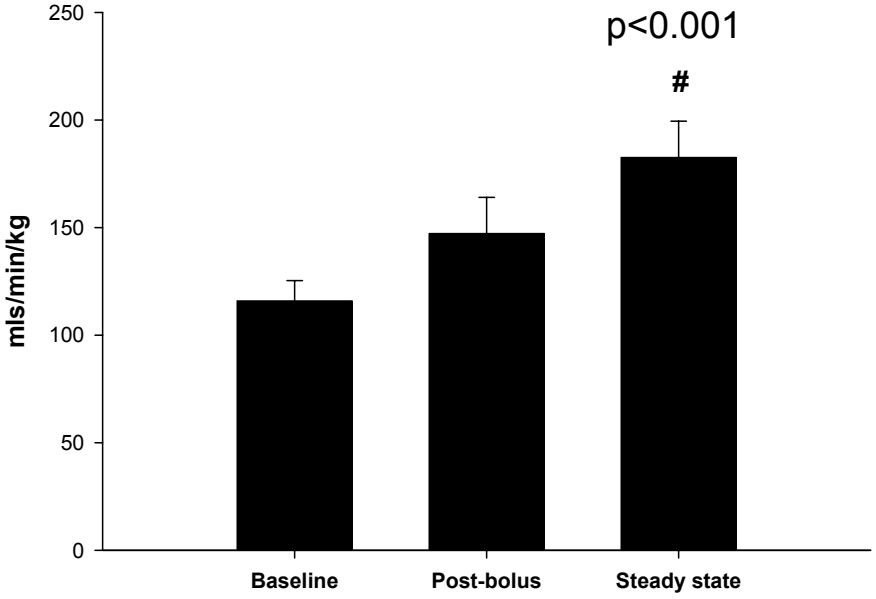
R-L Transductal flow



RVO



LVO



Summary

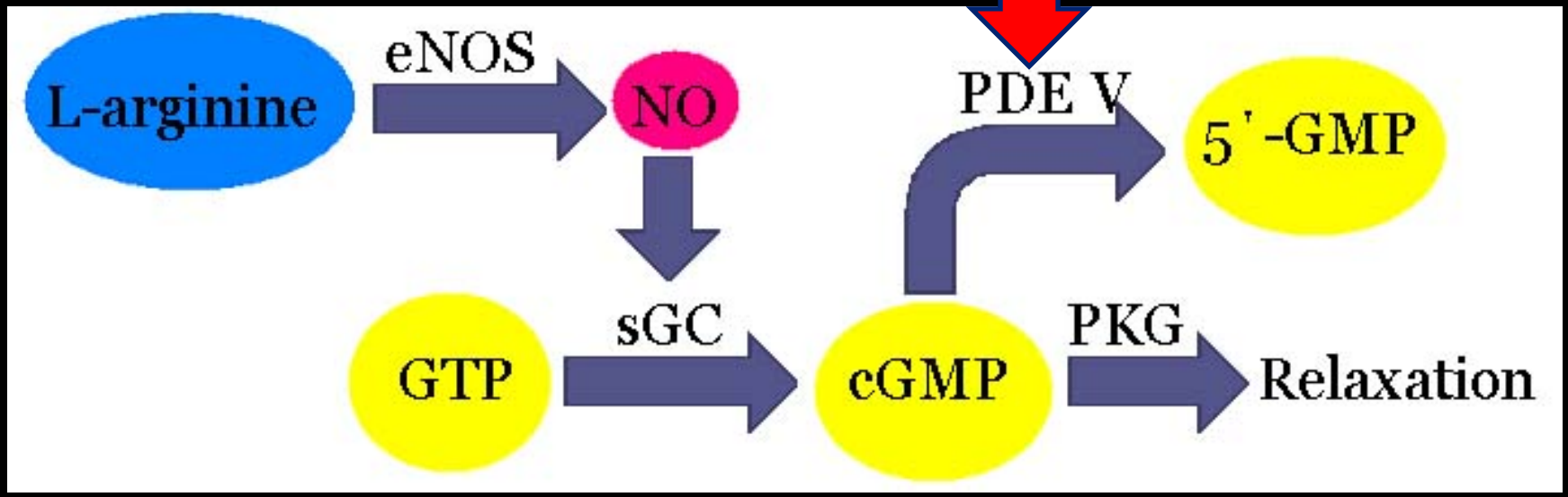
Intravenous milrinone is associated with…..

- Improvement in the efficacy of oxygenation in iNO non-responsive patients
- Reduced PVR and R-L transductal shunting
- increased right and left ventricular output

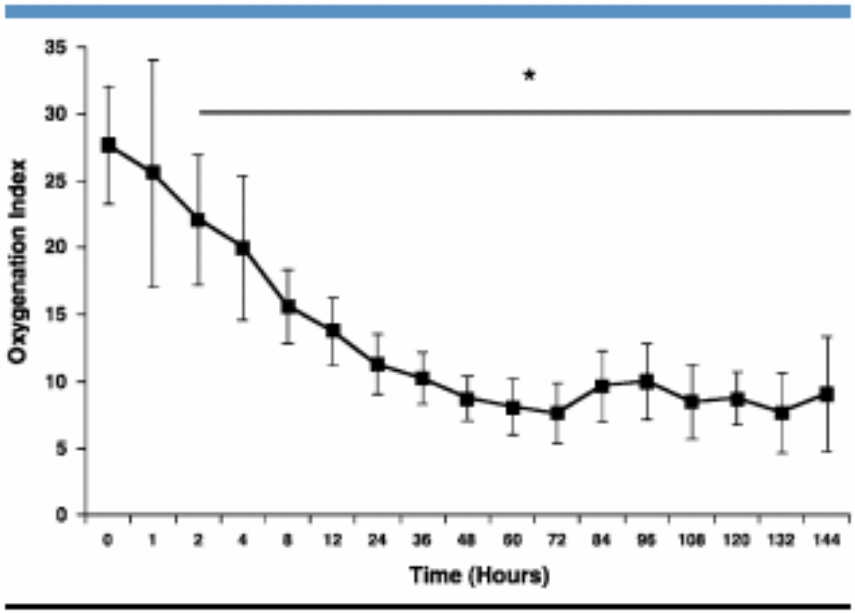
McNamara 2010 PAS

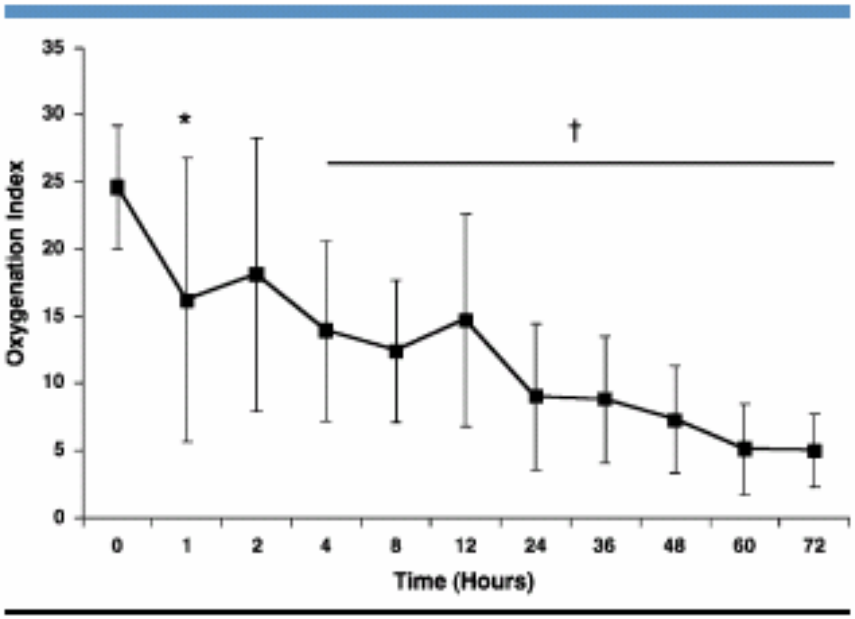
SILDENAFIL

cGMP PATHWAY MODULATION



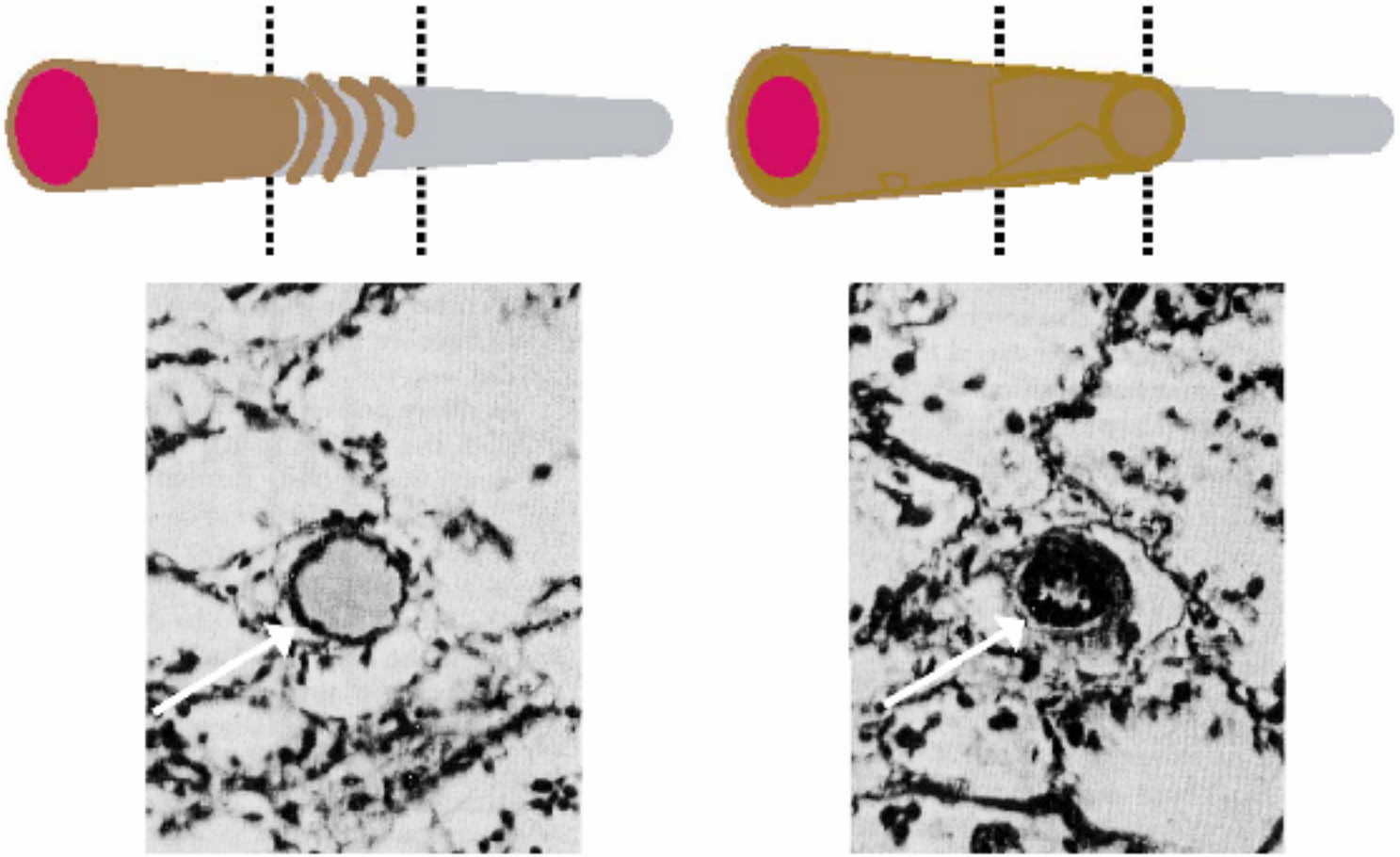
Intravenous Sildenafil



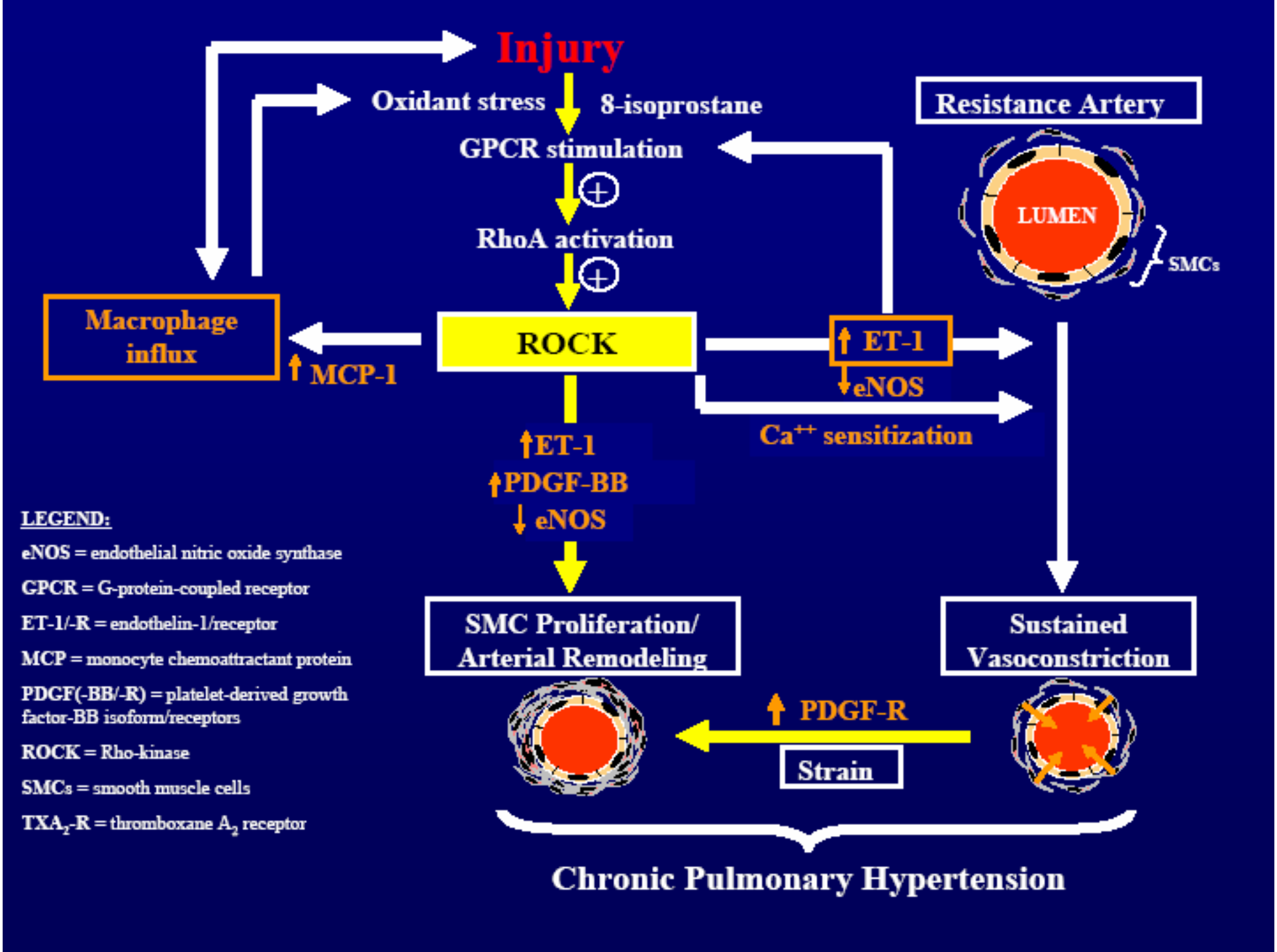


Steinhorn 2009 J Pediatr

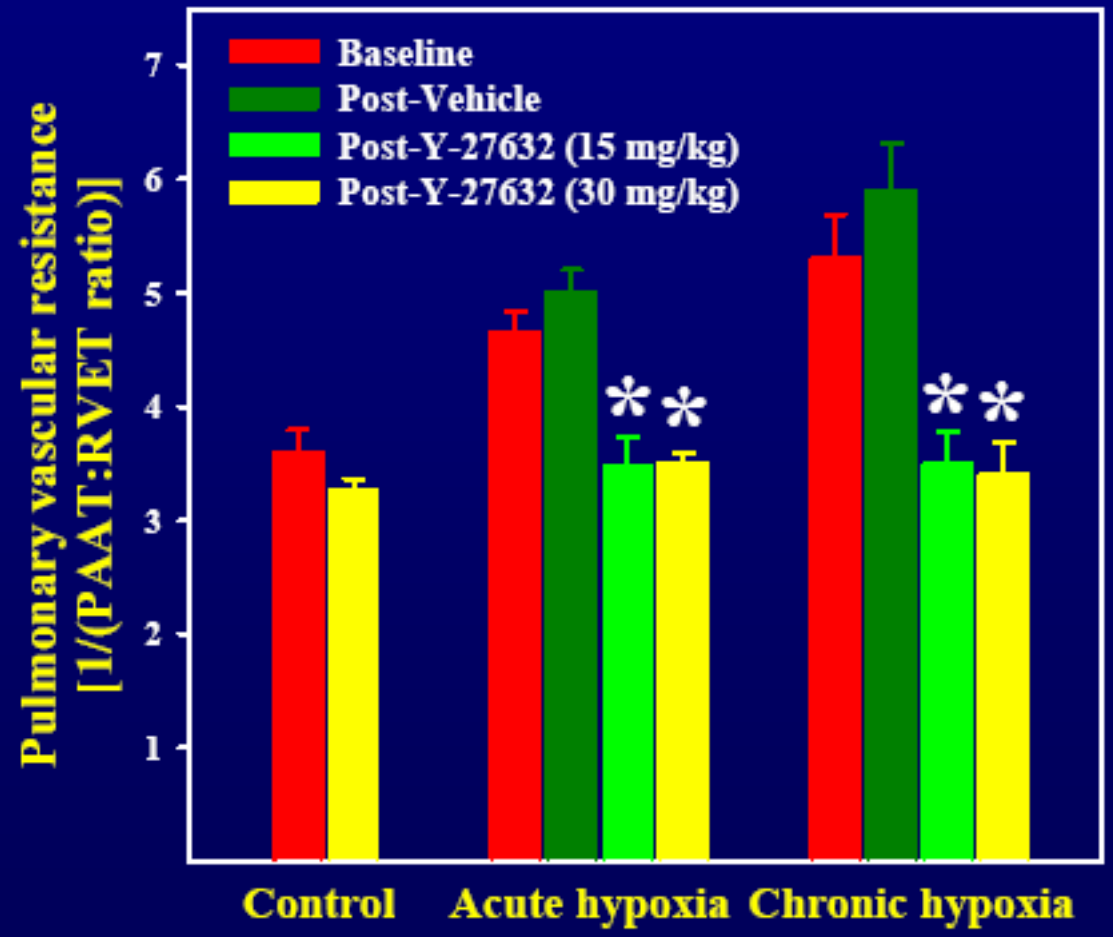
Vascular Remodeling: Distal Extension of Smooth Muscle



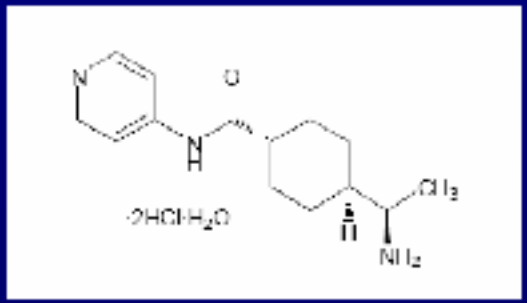
Histology from: Geggel RL *Clinics in Perinatology* 1984; 11(3):536


Injury
Oxidant stress
8-isoprostane
GPCR stimulation
RhoA activation
Resistance Artery
LUMEN
SMCs
Macrophage influx
MCP-1
ROCK
ET-1
eNOS
Ca++ sensitization
ET-1
PDGF-BB
eNOS
SMC Proliferation/ Arterial Remodeling
Sustained Vasoconstriction
PDGF-R
Strain
Chronic Pulmonary Hypertension
LEGEND:
eNOS = endothelial nitric oxide synthase
GPCR = G-protein-coupled receptor
ET-1/-R = endothelin-1/receptor
MCP = monocyte chemoattractant protein
PDGF(-BB/-R) = platelet-derived growth factor-BB isoform/receptors
ROCK = Rho-kinase
SMCs = smooth muscle cells
TXA2-R = thromboxane A2 receptor

ROCK Inhibitors: Pulmonary Hemodynamics



Y-27632



McNamara PJ and Murthy P et al. *AJP:Lung Cell Mol Physiol* 2007

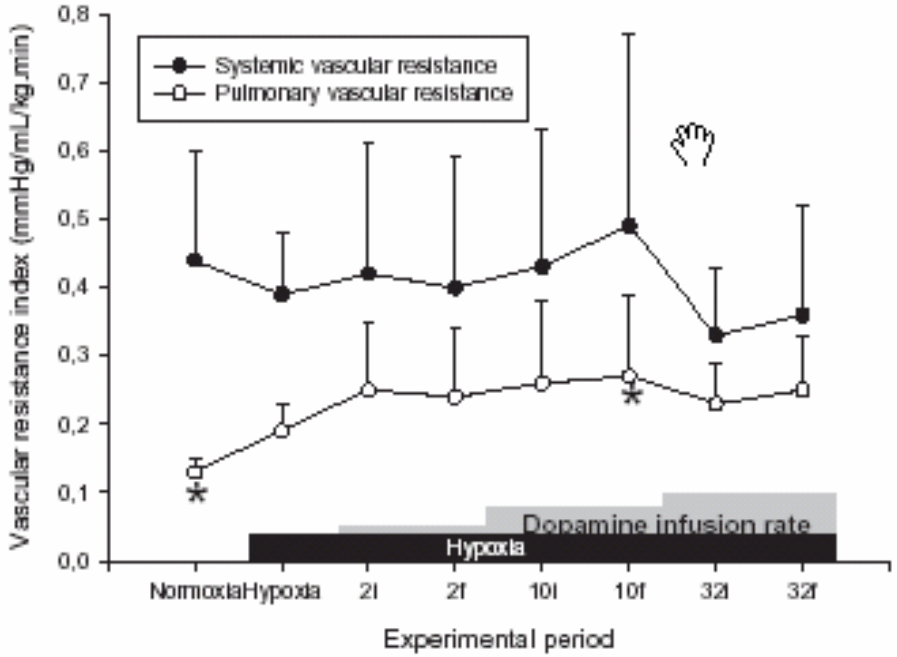
Cardiotropic Drugs in PPHN?

Physiologic Considerations:

- Impaired RV contractility and ↓ pulmonary blood flow
- Pressure loaded RV
- Compromised left heart preload and low cardiac output
- Hypercontractile LV

Dopamine and PVR

Figure 2



Effects of hypoxia and dopamine infusion on systemic and pulmonary vascular resistance indices. i, initial (3 min average at 30 min of infusion at that dose); f, final (3 min average at 60 min of infusion). *$P < 0.05$ compared with effects of hypoxia.

Cheung & Barrington 2001 CCM

Effect on Systemic perfusion

	Dobutamine	Dopamine	*P* value
Number	16	11	
Infusion rate			
10 µg/kg/min	5	7	
20 µg/kg/min	11	4	
Gestation (wk)	26.3 (2.1)	25.8 (1.1)	.4
Birth weight (g)	1014 (348)	900 (171)	.3
MAP (cm H_2O)	6.5 (1.5)	8.2 (2.3)	.03
HR (bpm)	160 (12)	145 (12)	.004
Mean BP (n = 24)	39.8 (4.9)	35.4 (4.9)	.04
RVO (mL/kg/min)	294.5 (81.3)	169.2 (51.9)	<.001
SVC flow (mL/kg/min)	85.6 (24.7)	68.0 (30.2)	.1

Mean ± SD.

Included if SVC flow < 40 mls kg^{-1}

Osborn 2002 J Pediatr

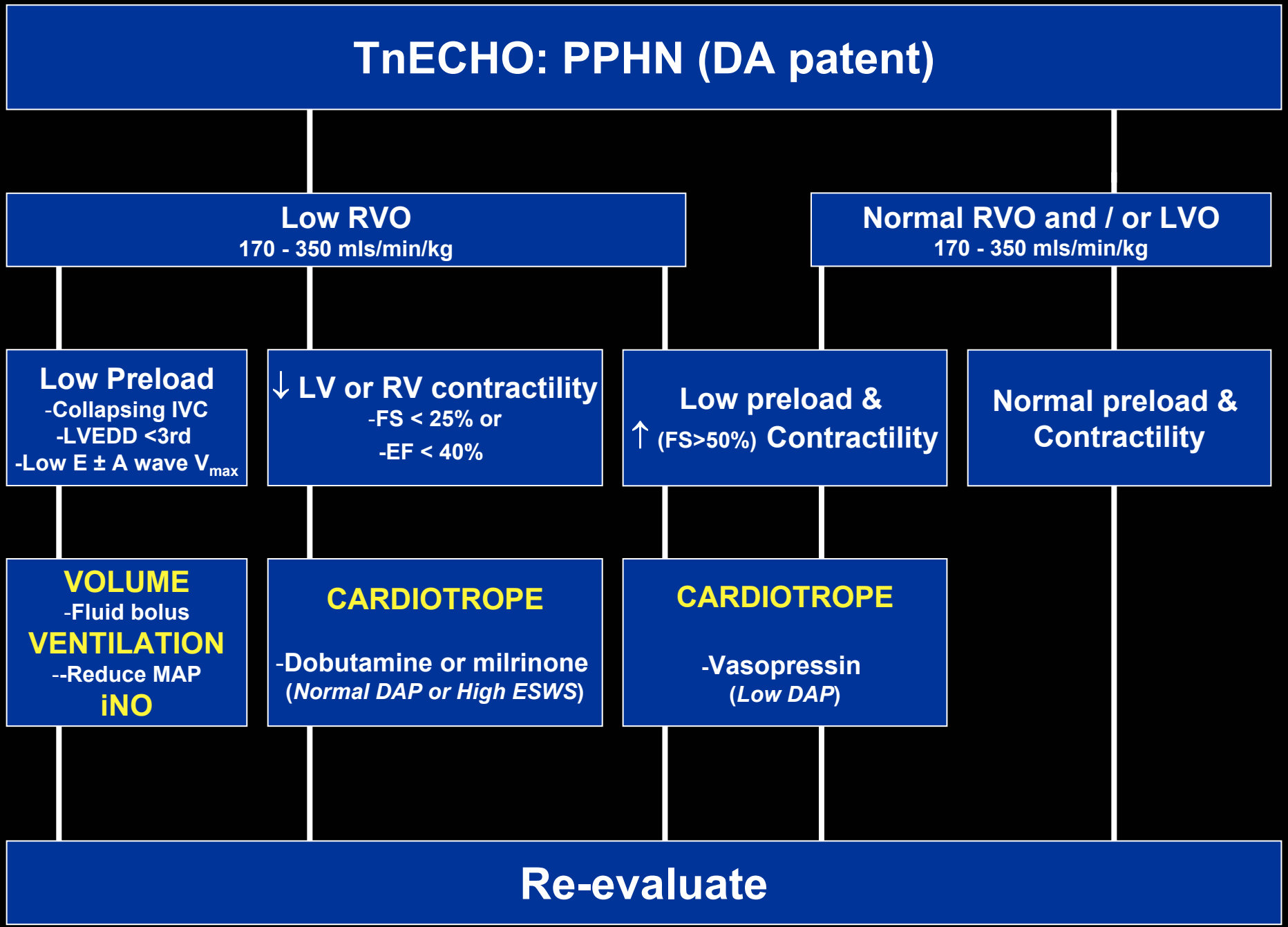
Goal is maintenance of effective tissue perfusion

- Target normal systolic and diastolic blood pressures
- Ensure adequate cardiac output state (urinary output, pH, lactate)

Dobutamine is preferable for neonates with <u>hypotension</u> and signs of a <u>low cardiac output</u> (RV or LV) state

Use of Targeted Neonatal Echo

- Quantification of magnitude of pulmonary hypertension
  - Tricuspid regurgitant jet, dunctal shunt direction, septal wall motion, PAAT:RVET ratio
- Evaluation of RV performance
  - RV contractility
  - RV output
- Evaluation of LV performance
  - LV diastolic performance
  - LV contractility
  - LV output


TnECHO: PPHN (DA patent)
Low RVO
170 - 350 mls/min/kg
Normal RVO and / or LVO
170 - 350 mls/min/kg
Low Preload
-Collapsing IVC
-LVEDD <3rd
-Low E ± A wave V_{max}
↓ LV or RV contractility
-FS < 25% or
-EF < 40%
Low preload &
↑ (FS>50%) Contractility
Normal preload &
Contractility
VOLUME
-Fluid bolus
VENTILATION
--Reduce MAP
iNO
CARDIOTROPE
-Dobutamine or milrinone
(Normal DAP or High ESWS)
CARDIOTROPE
-Vasopressin
(Low DAP)
Re-evaluate

Exceptions

- Infant with **Septal or biventricular hypertrophy**
  - Volume resuscitation
  - Avoid cardiotropic agents
  - Consider vasopressin or esmolol
- Infant with **abnormal cardiac anatomy** or ductus closed and **impaired RV performance**
  - Intravenous Prostaglandin
  - Timely cardiac consultation
- Infant with impaired myocardial performance and pericardial or pleural **effusion**
  - Timely intervention [pericardiocentesis or thoracocentesis]

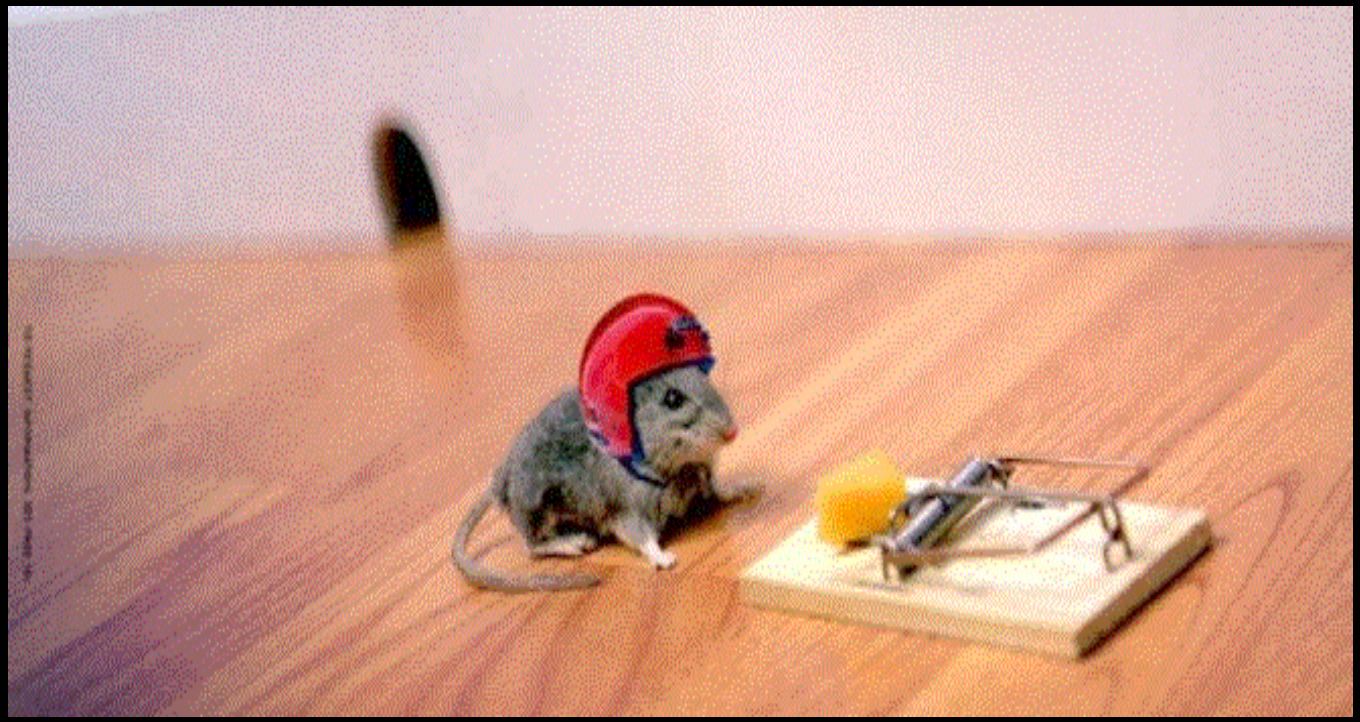
Summary I

- PPHN is about elevated PVR and impaired myocardial performance
- Consider impact of oxygen and mechanical ventilation
- Consider tolerating postductal SpO_2 > 75%
- iNO is an effective pulmonary vasodilator but issues related to toxicity, lack of response and cost are concerning

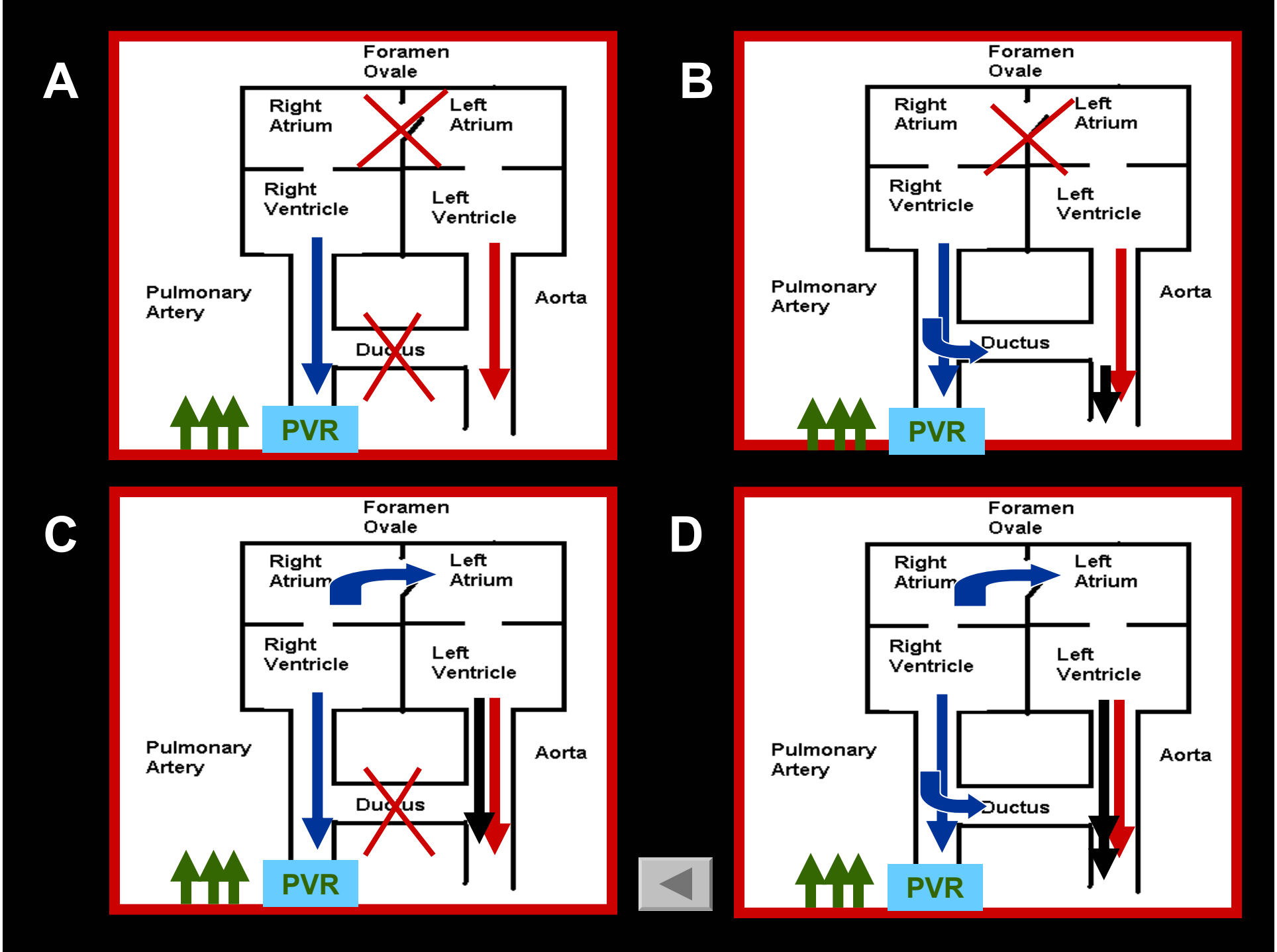
Summary II

- Evidence for Adjunctive therapy (milrinone / sildenafil) promising
- fECHO evaluation essential in determining the nature of the hemodynamic instability
- Consider cardiotropic support to optimize cardiac output (but not to induce systemic hypertension or raise postductal SpO_2)
- Avoid vasoconstricting agents that increased RV (pulmonary) afterload

QUESTIONS




BMO
BMO Bank of Montreal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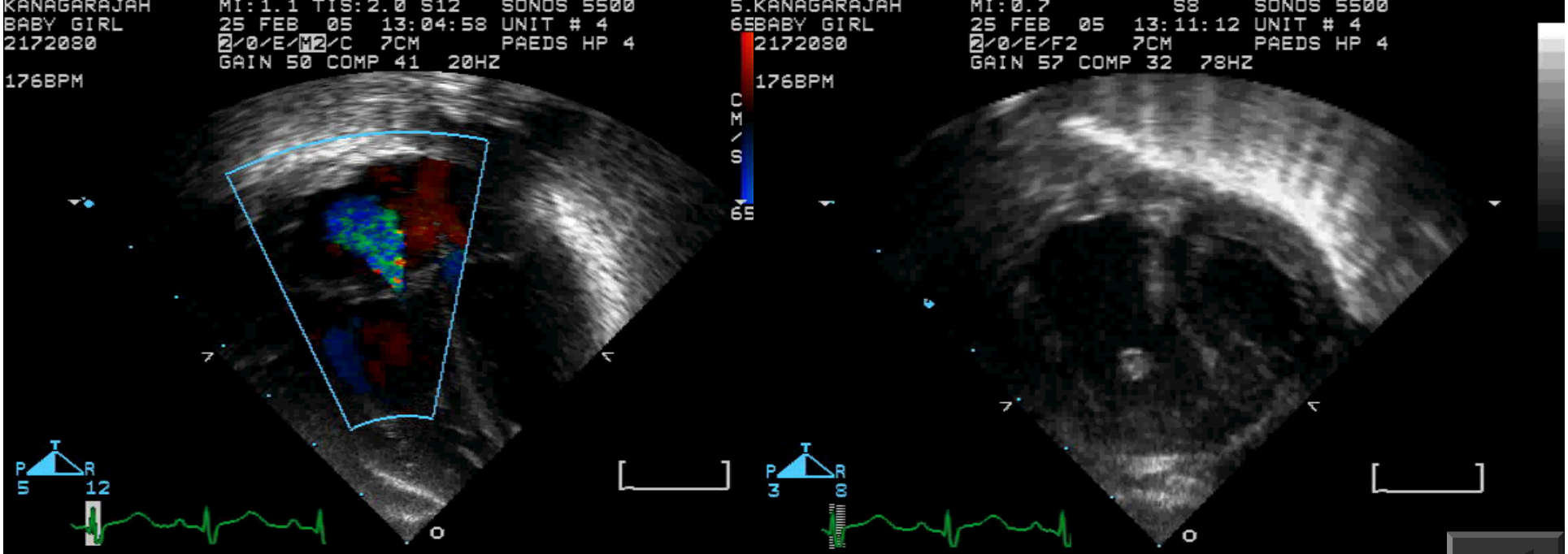
Foramen Ovale
Right Atrium
Left Atrium
Right Ventricle
Left Ventricle
Pulmonary Artery
Aorta
Ductus
PVR
B
Foramen Ovale
Right Atrium
Left Atrium
Right Ventricle
Left Ventricle
Pulmonary Artery
Aorta
Ductus
PVR
C
Foramen Ovale
Right Atrium
Left Atrium
Right Ventricle
Left Ventricle
Pulmonary Artery
Aorta
Ductus
PVR
D
Foramen Ovale
Right Atrium
Left Atrium
Right Ventricle
Left Ventricle
Pulmonary Artery
Aorta
Ductus
PVR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GAIN 50 COMP 41 20HZ
176BPM
C M/S
65
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BABY GIRL
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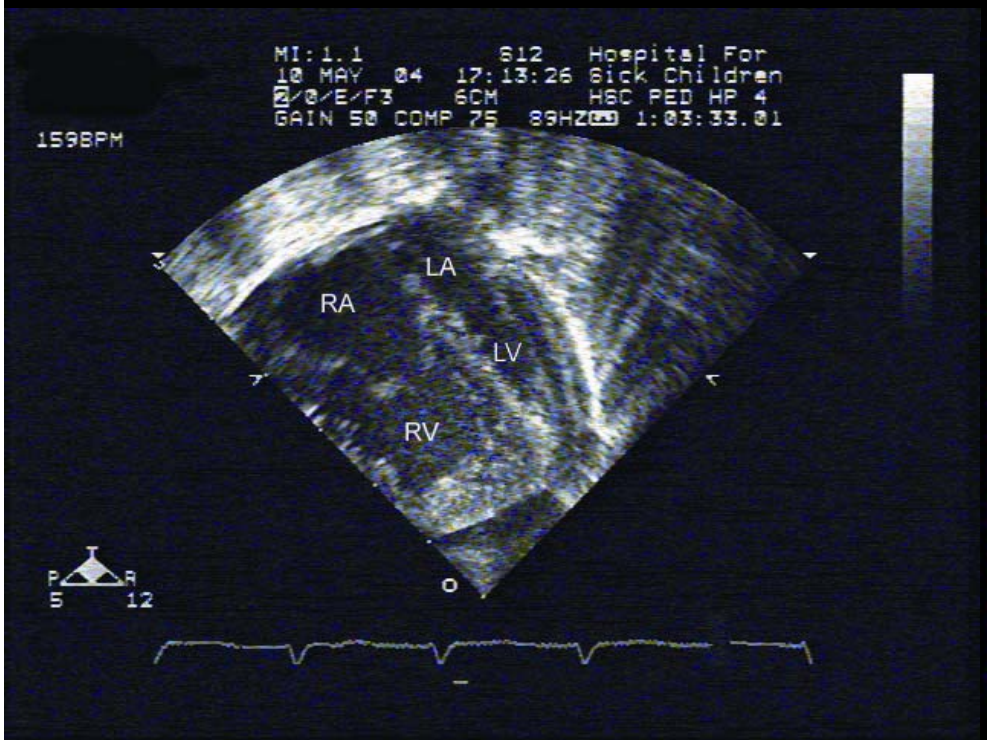
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10 MAY 04 17:13:26 Sick Children
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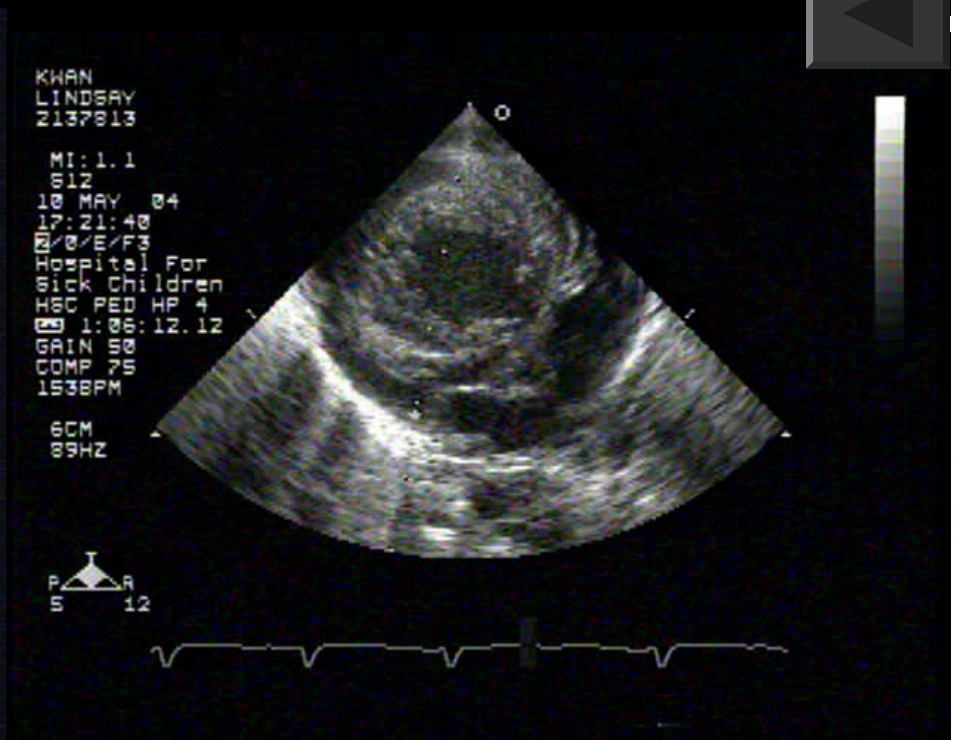
159BPM
LA
RA
LV
RV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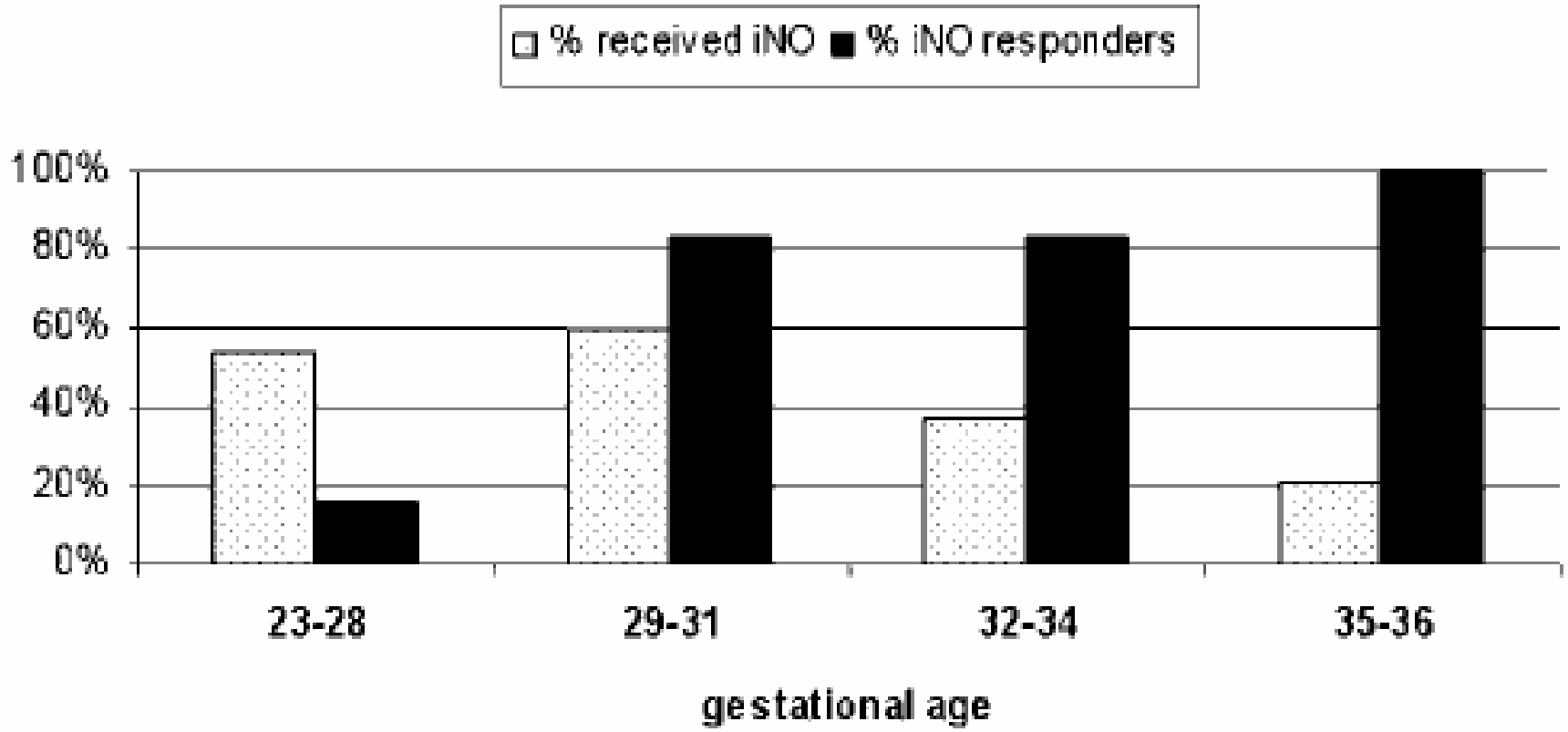
Hospital For
Sick Children
H&C PED HP 4
1:06:12.12
GAIN 50
COMP 75
153BPM
6CM
89HZ

Response is Developmentally Regulated

Responder = paO2 > 30 mmHg



Immaturity of iNO signaling or vascular smooth muscle

Kumar 2007 J Perinat

Author	Population	Dose	Time	Intermed. outcomes	CLD	CNS
Kinsella 1999 (n=80)	<34 wks a : A < 0.22	5 ppm	D 0-7	↑ a:A ratio	↔	↔
Schrieber 2003 (n=207)	<34 wks < 3 d	10 ppm 5 ppm	D 1 D 1-7	N/A	↓	↓ severe IVH/PVL
Van Meurs 2005 (n=420)	< 34 wks OI > 10	5-10 ppm	D 0-3	N/A	↔ >1kg: ↓	↔ < 1kg:↑
Hascoet 2005 (n=415)	<34 wks a : A < 0.22	5 ppm	clin	a:A response 45%	↔	↔
Mestan 2005	<34 wks < 3 d	10 ppm 5 ppm	D 1 D 1-7	N/A	↓	↓ delay & disability
Ballard 2006 (n=582)	< 32 wks < 1250 g	20 ppm→ 10, 5, 2	D7-21	↓ O_2 duration Early disch.	↓	↔
Kinsella 2006 (n= 793)	< 34 wks < 48 hrs old 500-1250g	5ppm	D1-21	N/A	↔	↓ 750-999g

iNO & Preterm Lung Disease

- Prevent airway and vascular muscularanization

Bland 2005 Am J Resp Crit Care Med

- Anti-oxidant

Cotton 2006 Ped Res

- Anti-inflammatory (inhibits neutrophil chemotaxis)

Terada 1996 J Appl Phys

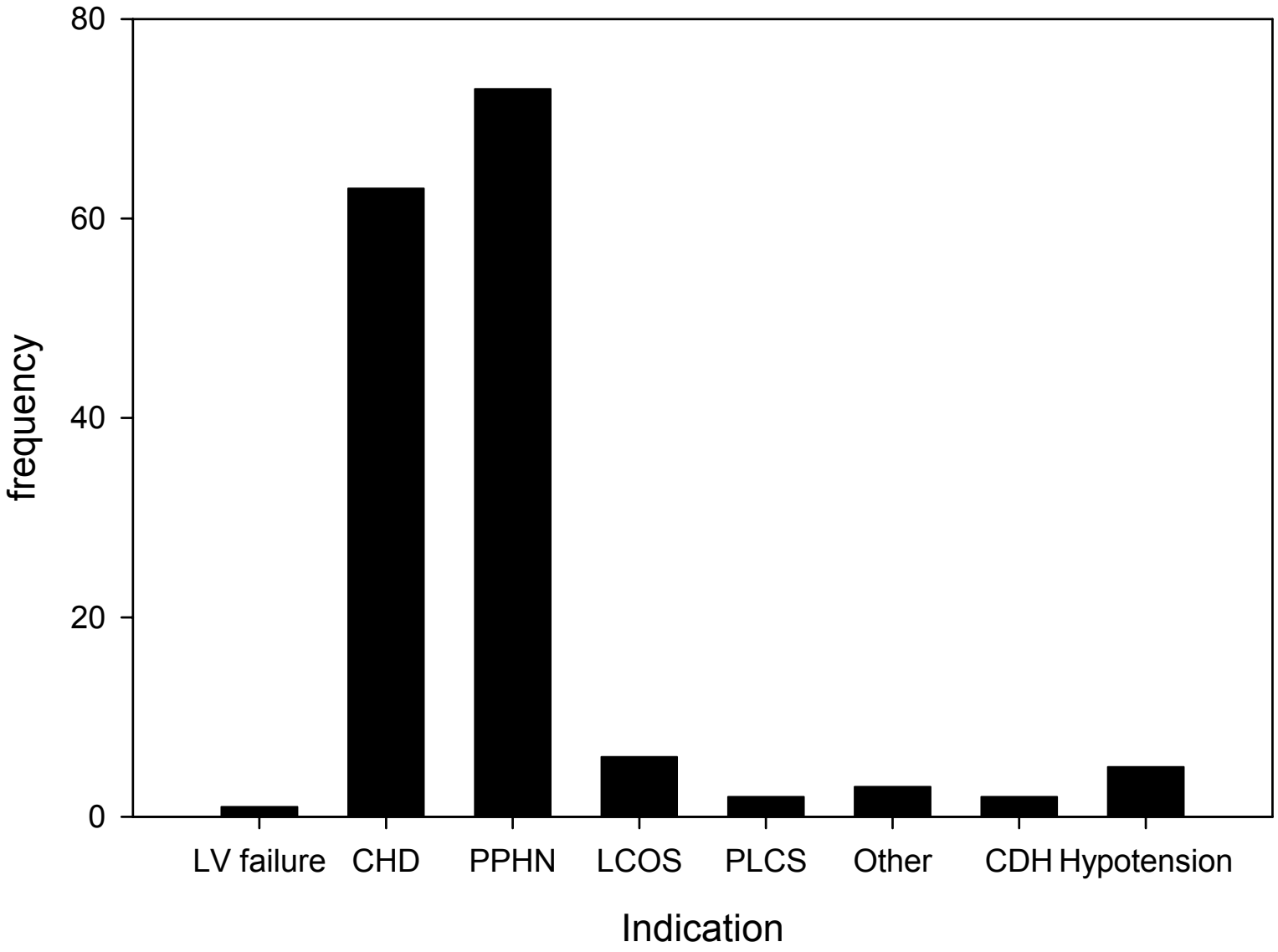
- Surfactant protection

Ballard 2006 Ped Res

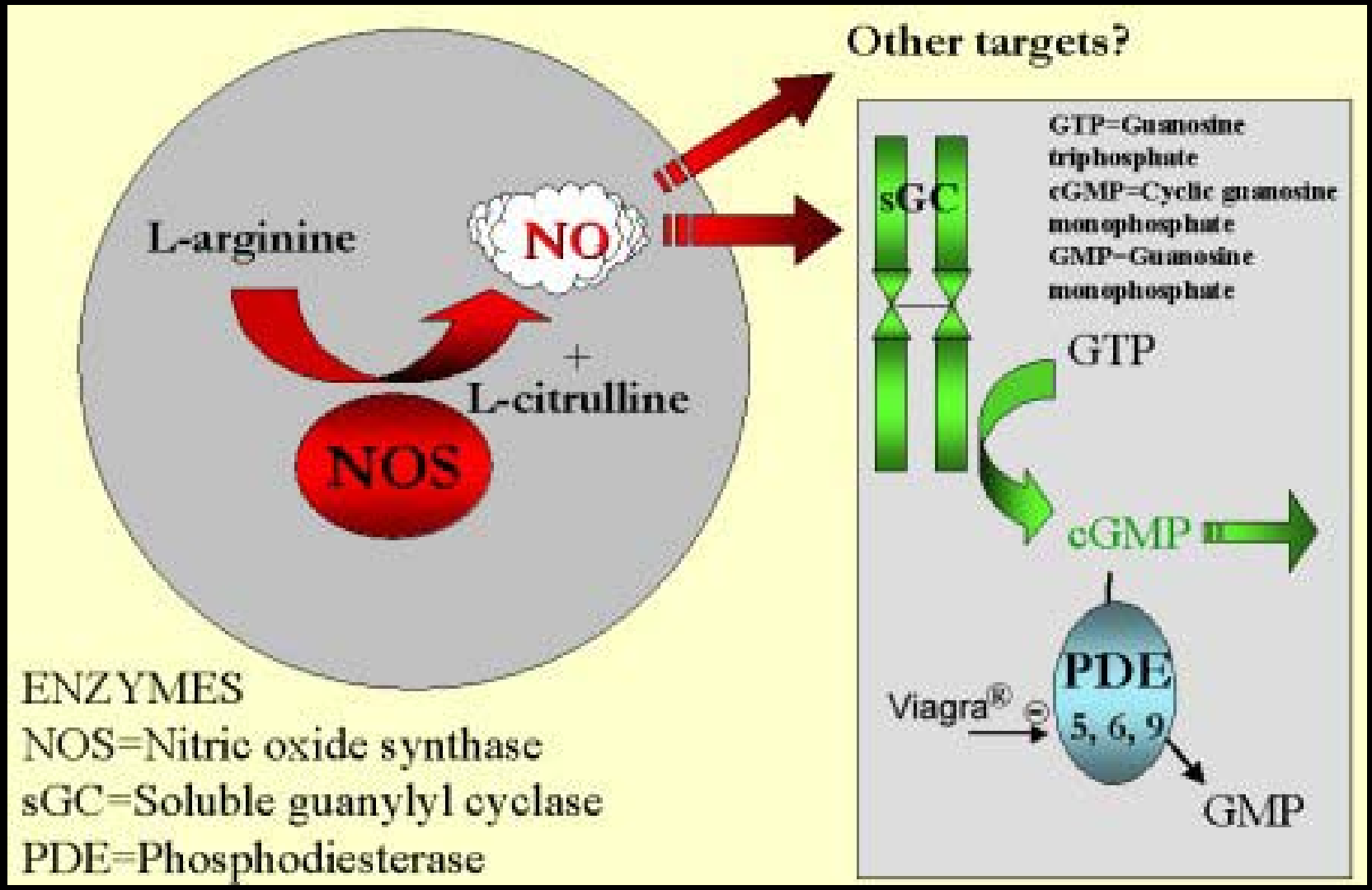
- Angiogenesis
- Alveolarization

McCurnin 2005 Am J Phys Lung Cell Mol Phys

Therapeutic use of Milrinone [All]



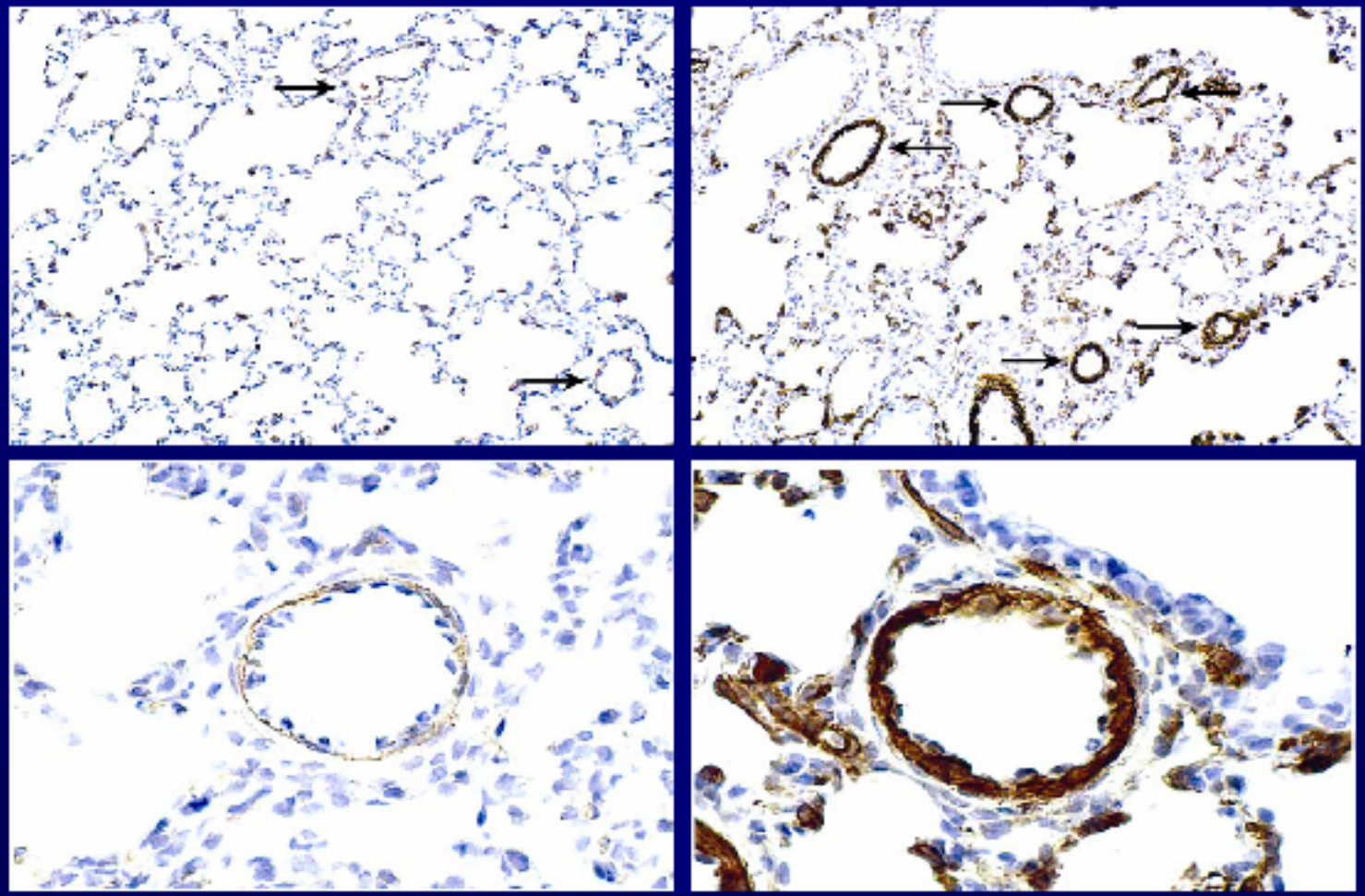
Sildenafil-mechanism of action



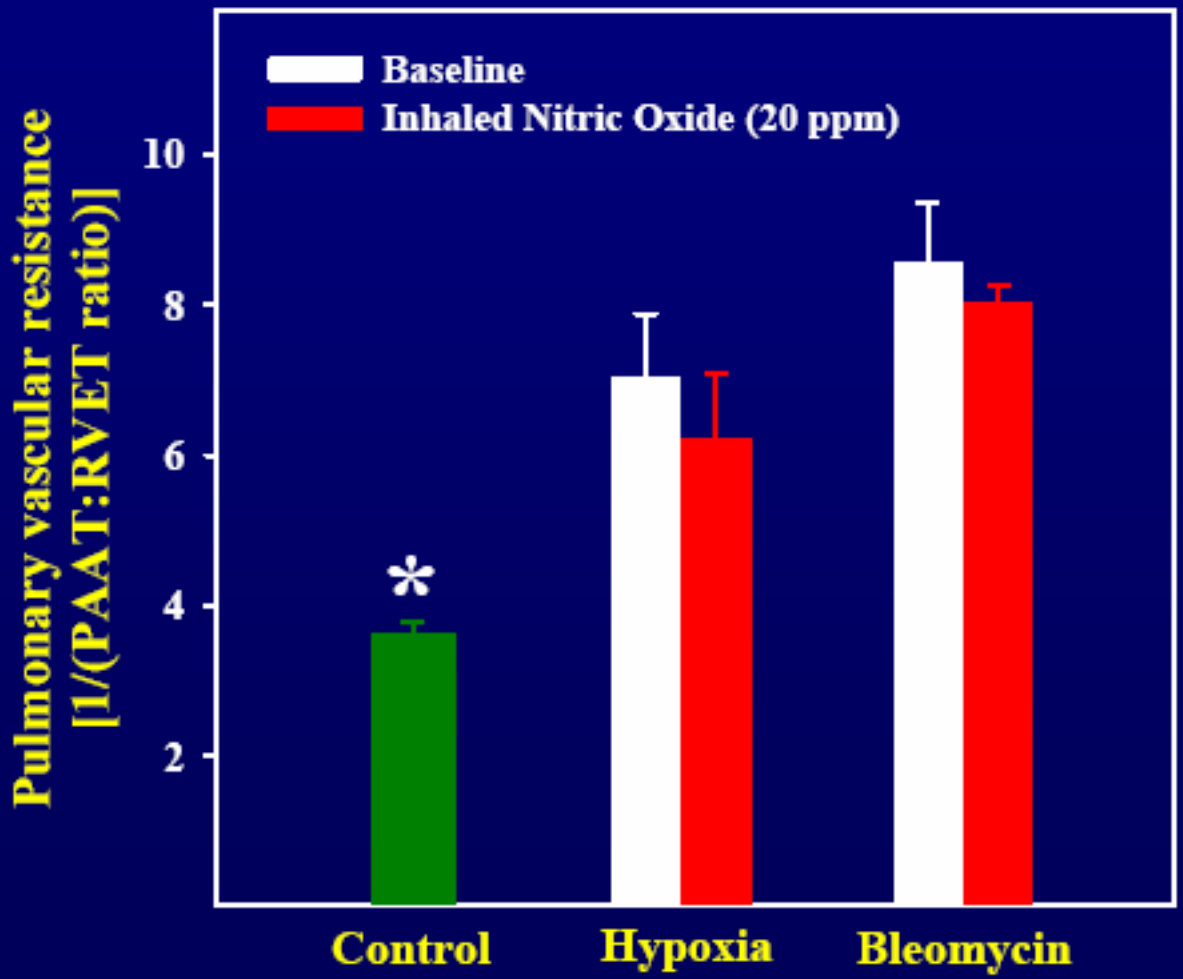
Vascular Remodeling: Chronic Hypoxia Model

Normoxia

Chronic Hypoxia



Chronic Pulmonary Hypertension: Therapeutic Implications



McNamara PJ and Murthy P et al. *AJP:Lung Cell Mol Physiol* 2007