An Update on PPHN and iNO in Premature Infants

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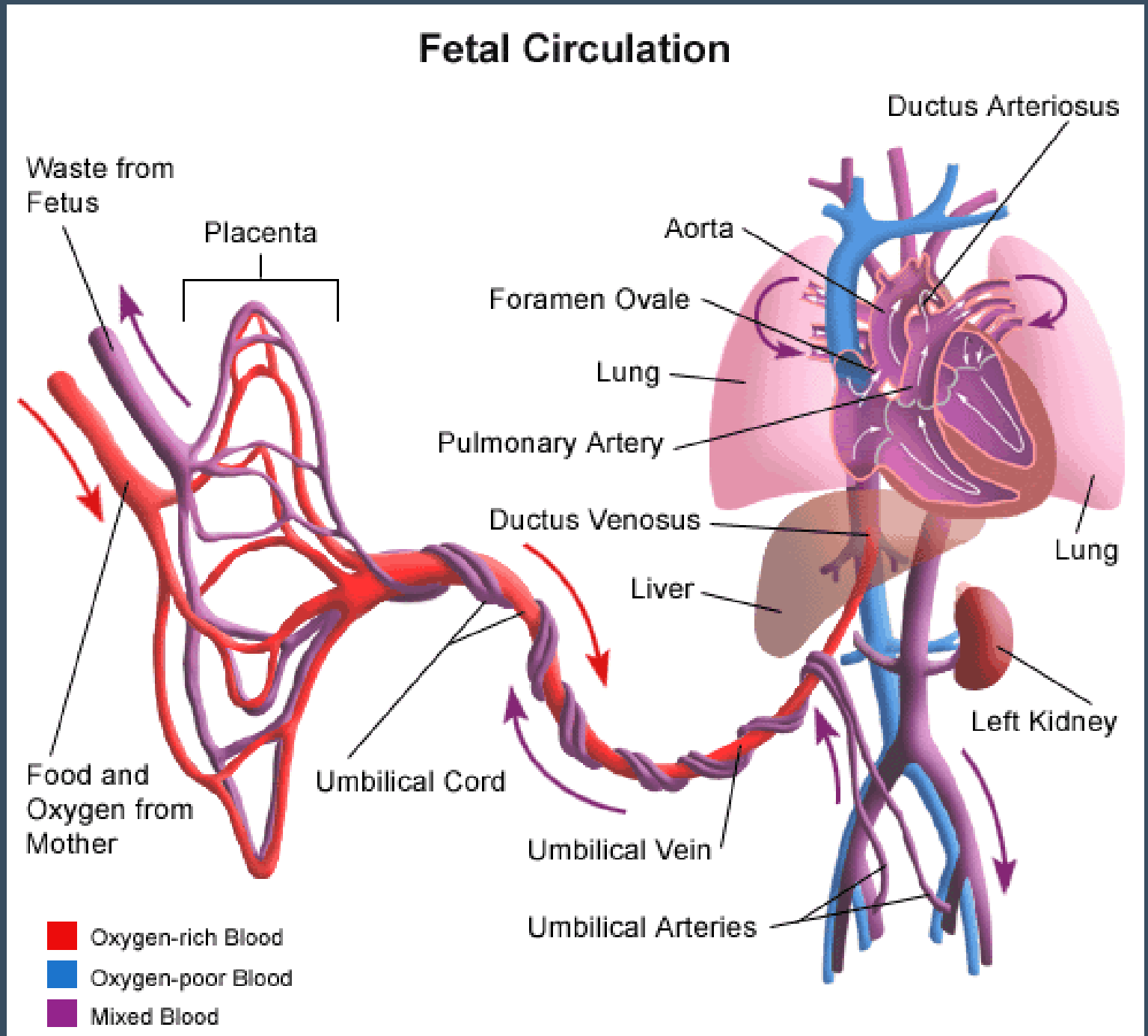
Objectives

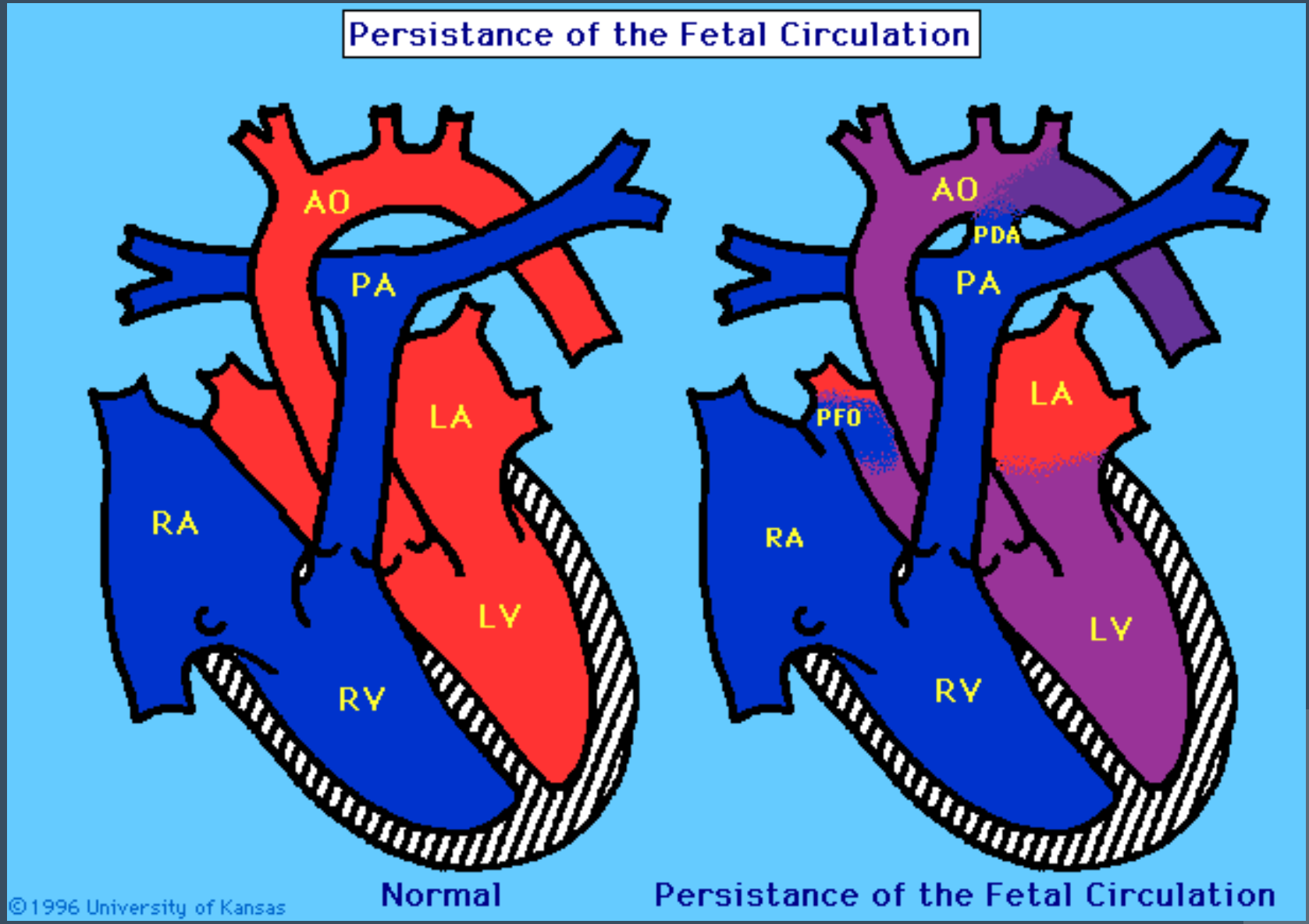
- To review the physiologic basics for diagnosis of pulmonary hypertension
- To describe ventilatory management of infants with pulmonary hypertension
- To identify available therapy for PPHN
- To visit the evidence for the use of inhaled nitric oxide in premature infants


Cleveland Clinic

Jen-Tien Wung, MD

Fetal Circulation

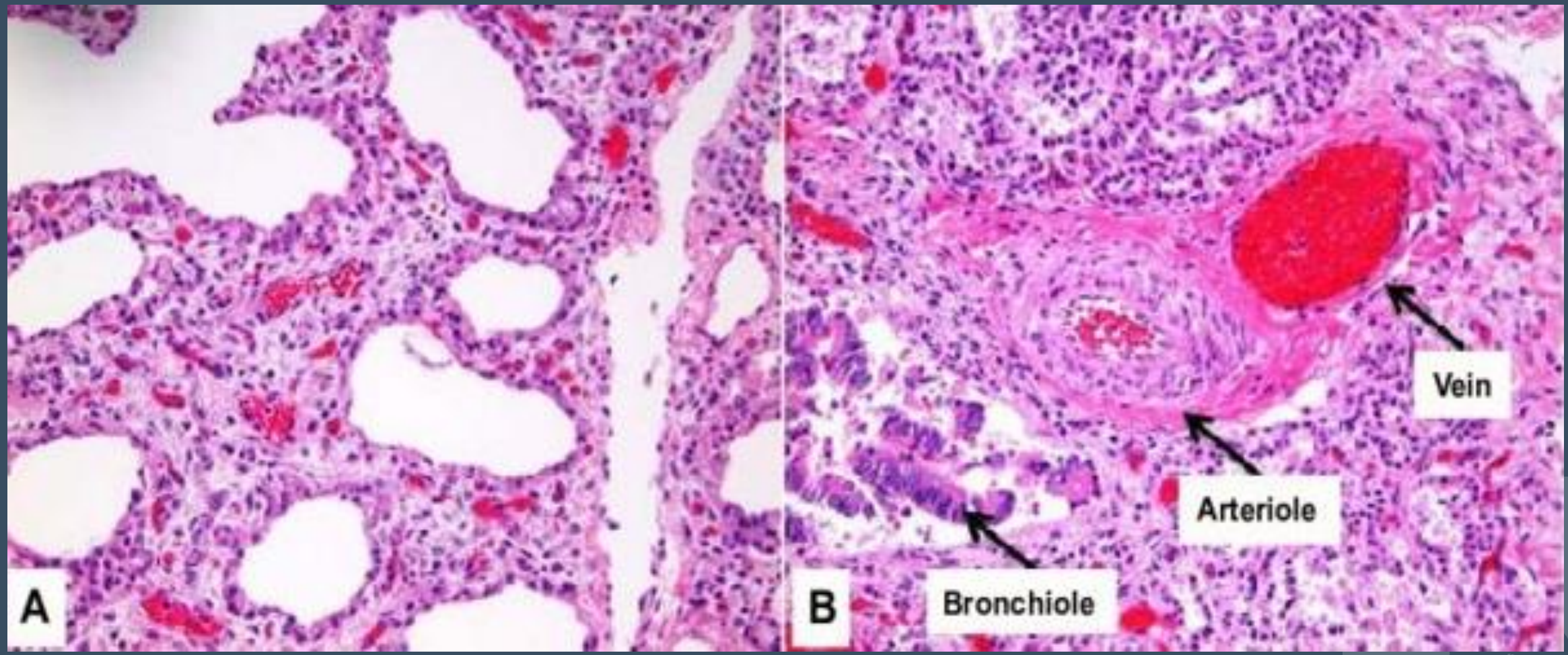



Persistance of the Fetal Circulation
AO
PA
LA
RA
LV
RV
AO
PDA
PA
LA
PFO
RA
LV
RV
©1996 University of Kansas
Normal
Persistance of the Fetal Circulation

PPHN Causes

- Prenatal constriction of the ductus arteriosus due to prenatal use of aspirin or indocin
- Meconium aspiration syndrome, asphyxia, sepsis, chronic intrauterine stress, hypoxia, CDH, lung cysts, pleural effusion, etc.
- Increase of blood viscosity as in polycythemia and IUGR
- Anomalous pulmonary venous return
- Misalignment of pulmonary vessels (alveolar capillary dysplasia, ACD)

Alveolar Capillary Dysplasia (ACD)



Diagnosis

- Chest X-ray is not helpful, except for:
  - Decreased vascularity
  - Suggestive for some underlying diseases
- Pre- and post-ductal oxygenation gradient
  - >15 points in SpO_2 is suggestive
  - Difference may not exist in severe cases
- Blood gases with PO_2 (not PCO_2) problems

Diagnosis- ECHO

- Will rule out congenital heart diseases
- Findings
  - Deviation of right atrial and/or ventricular dilatation with deviation of the septum to the left
  - Tricuspid regurgitation
  - R to L shunting at PFO and/or PDA

Clinical Severity

- **Oxygen Index (O.I.)**
- **O.I. = MAP x FiO_2/ PaO_2**

Alveolar Arterial O_2 Gradient

- Pa_{O2} : Arterial P_{O2}
- PA_{O2} “ideal alveolar P_{O2}” that is the alveolar P_{O2} when assuming there is no existing shunt
- $PA_{O2}= PI_{O2} - PA_{CO2}/R$
- $PI_{O2} =(760 -47) . FiO_2$
- (A-a) $D_{O2} = (760 -47) FiO_2 - P_{CO2}/R - Pa_{O2}$

Management

- Minimal handling (avoid excessive manipulation)
- Supportive care
  - Temperature control
  - Sugar control
  - Ensure adequate fluid intake

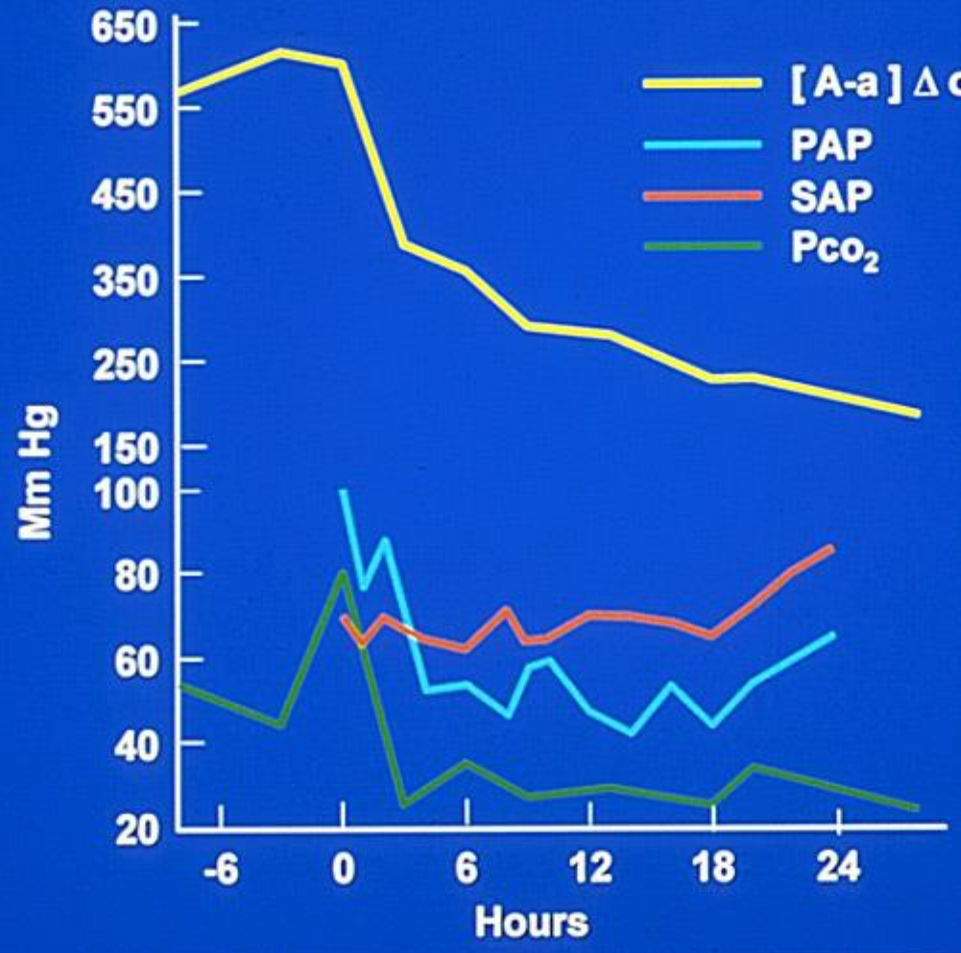
Ventilation

- Use PIP adequate for chest excursion
- Ti=0.5 sec
- IMV 40 bpm
- PEEP = 5 Cm.H_2O
- Monitor pre-ductal saturation
- Avoid hyperventilation

Alternative Ventilatory Strategies

- HFPPV (IMV=100, Ti=0.3, PEEP= 0-1)
- HFOV

Pulmonary Artery Pressure in Infants with Persistent Pulmonary Hypertension

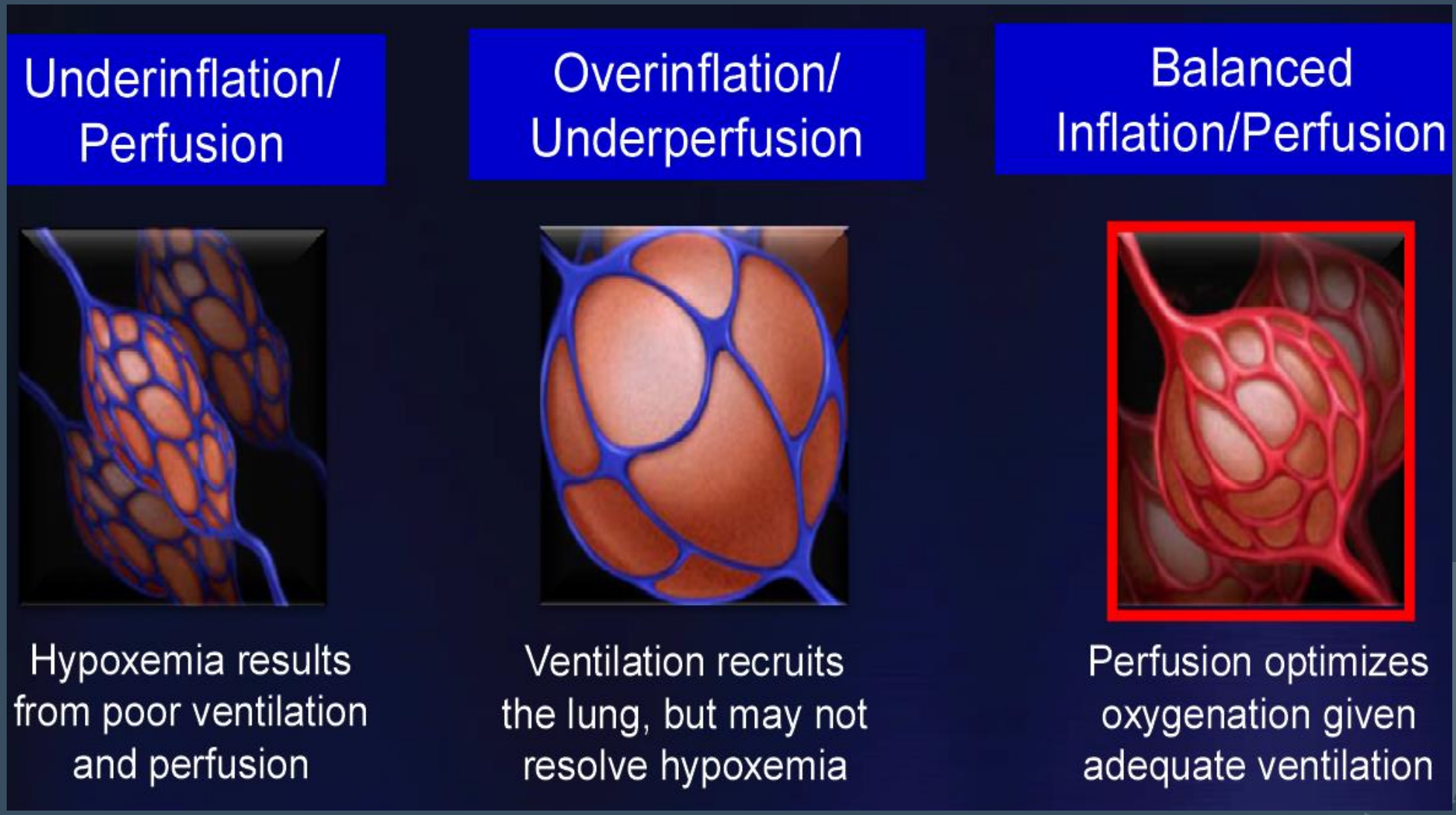


J Pediatric 93:1005, 1978

Avoid Hyperventilation

- Over-inflation of the lungs impedes venous return that decreases pulmonary blood flow and decreases oxygenation. Also, over-inflation decreases cardiac output leading to hypotension
- Over-inflation of alveoli can overstretch pulmonary vasculature decreasing its diameter and increasing PVR

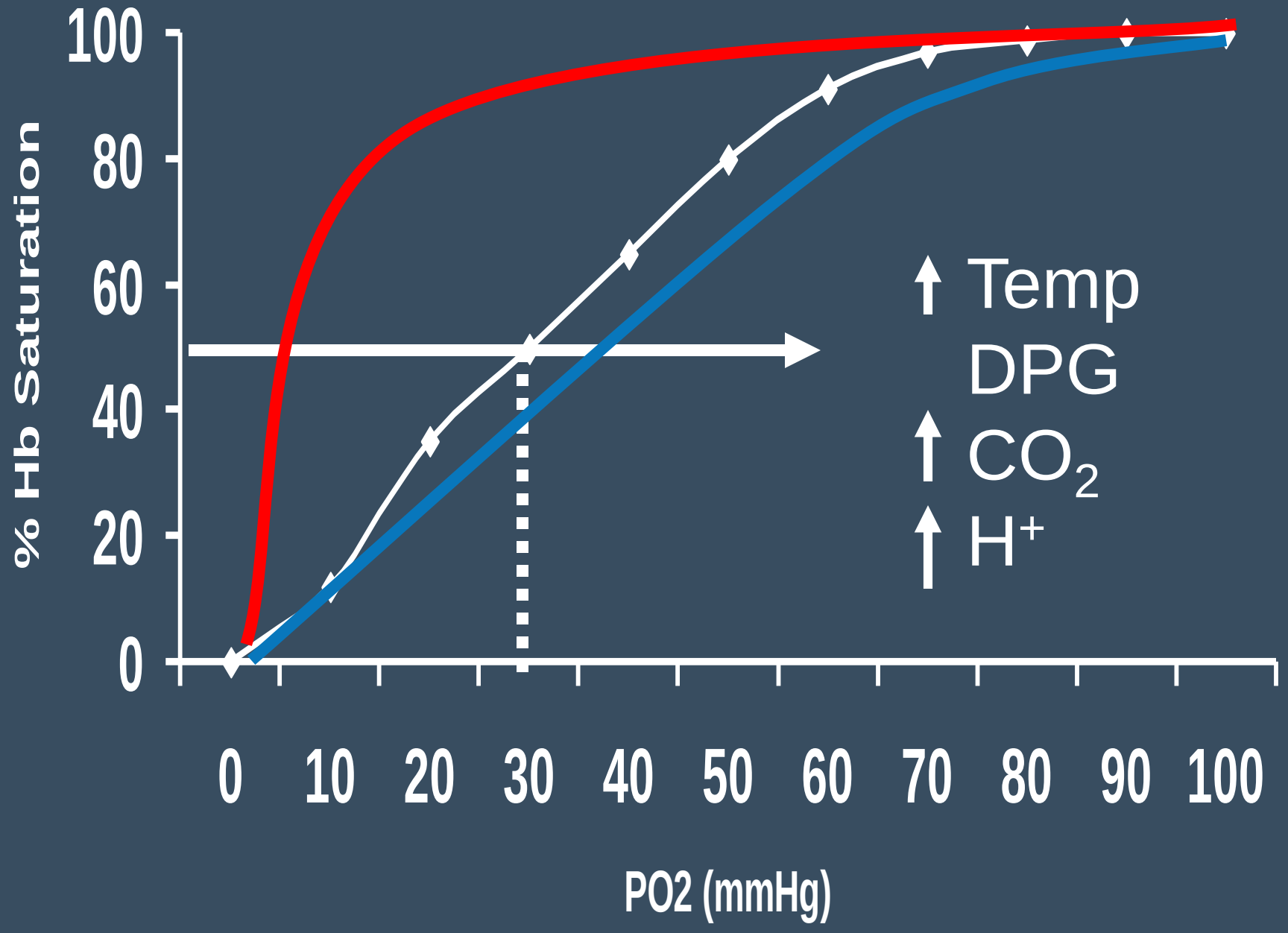
Lung Perfusion During Ventilation



Kinsella JP. Early Hum Dev 2008;84:709-716

Avoid Hyperventilation

- Alkalosis----- shifts oxygen dissociation curve to the left ---causes more tissue hypoxia
- Alkalosis-----decreases cerebral blood flow
- Alkalosis ----causes neuronal hearing loss


% Hb Saturation
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80 90 100
PO2 (mmHg)
Temp
DPG
CO_2
H^+

Inhaled NO: Pharmacology

- Nitric oxide relaxes vascular smooth muscle by binding to the heme moiety of cytosolic *guanylate cyclase (GC)*
- When GC is activated, it increases intracellular levels of cGMP, that leads to vasodilatation
- When inhaled, nitric oxide produces selective pulmonary vasodilatation

Nitric Oxide: Toxicity

- Direct toxicity
- Toxicity of its oxidative products

  $NO + O_2$ ----------→ NO_2

  $NO + O_3$ ----------→ peroxynitrite
- Methemoglobin
- Inhibition of platelet aggregation
- Negative inotropic effect

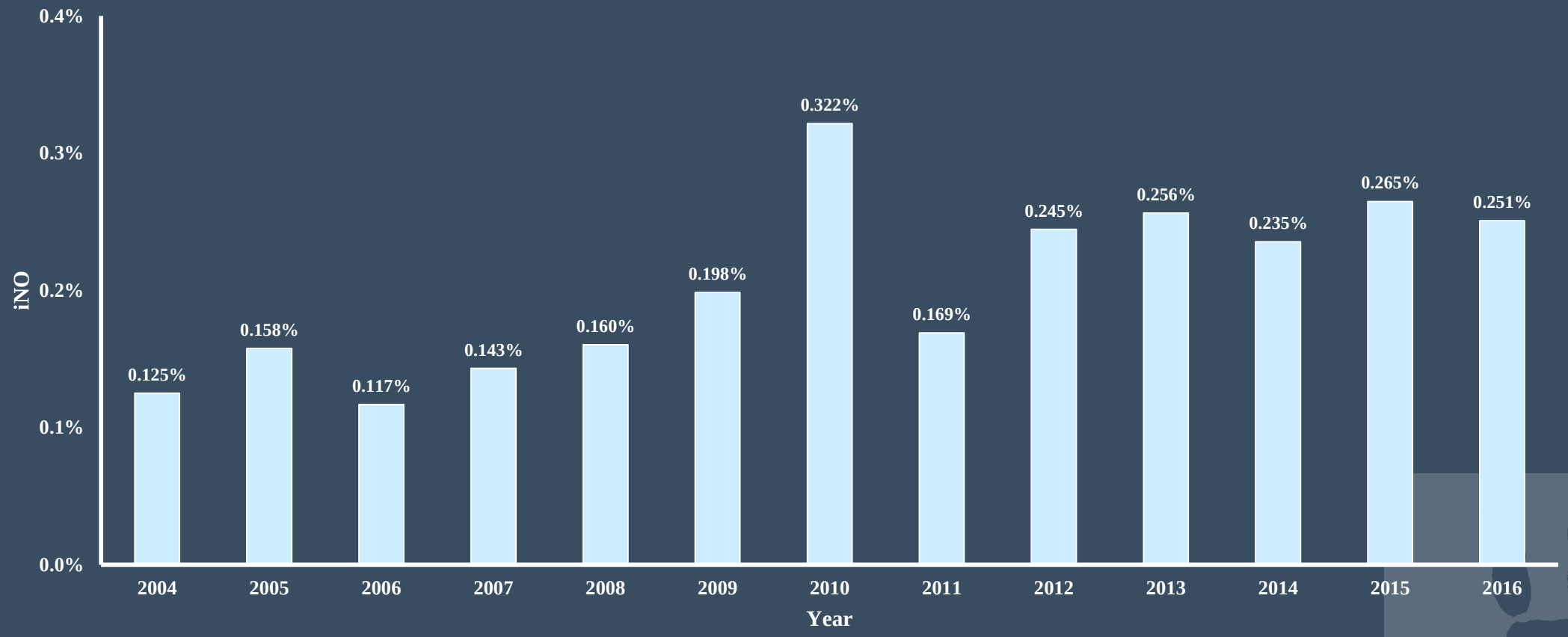
INO Elimination

- Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled
- Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration

INO Indications

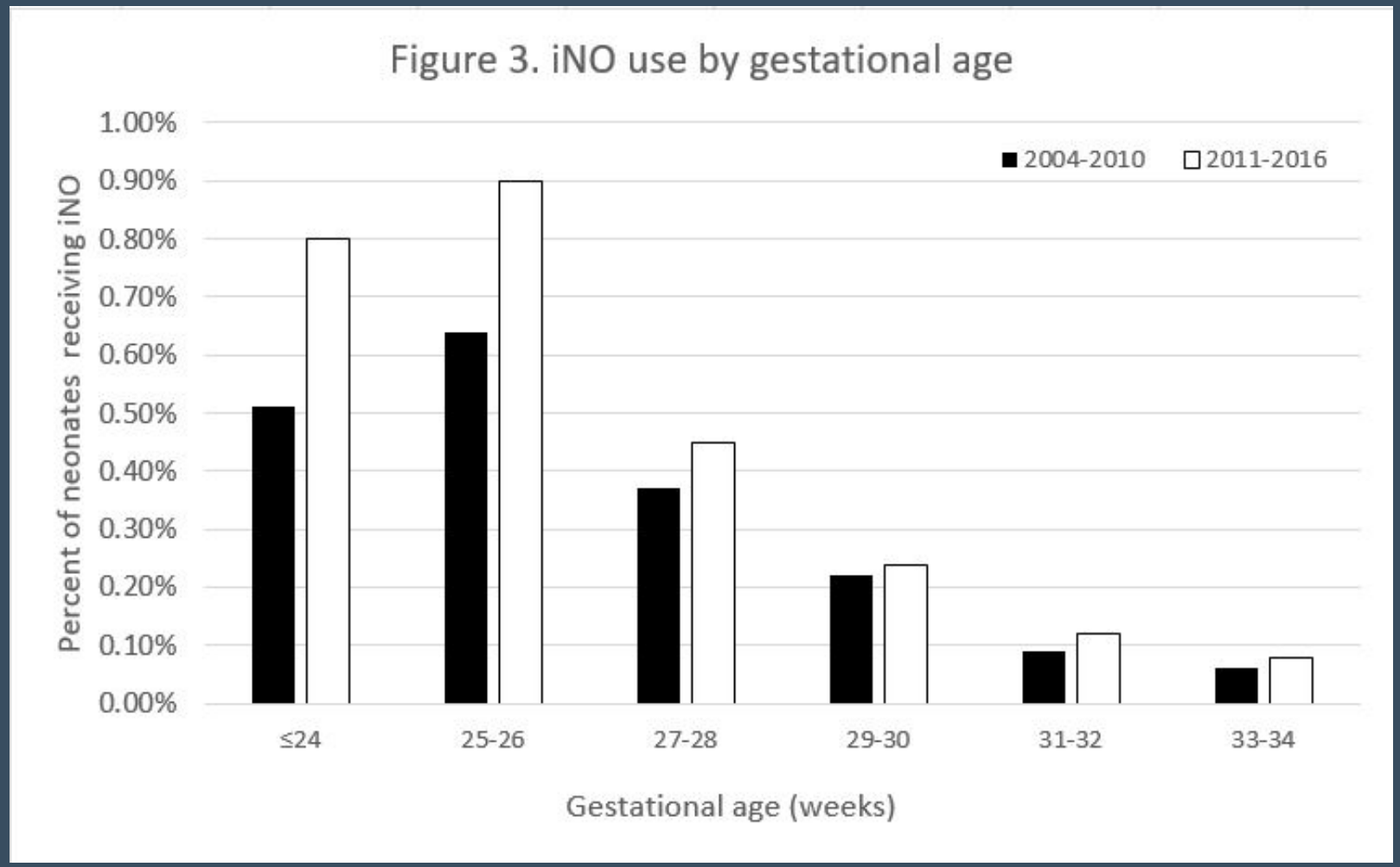
Neonates (>34 weeks gestation) with hypoxic respiratory failure associated with clinical or echocardiograph evidence of pulmonary hypertension

Trends in iNO use in Preterm Infants



Pediatr Pulmonol. 2022 Feb;57(2):427-434

Distribution of iNO by GA



Pediatr Pulmonol. 2022 Feb;57(2):427-434

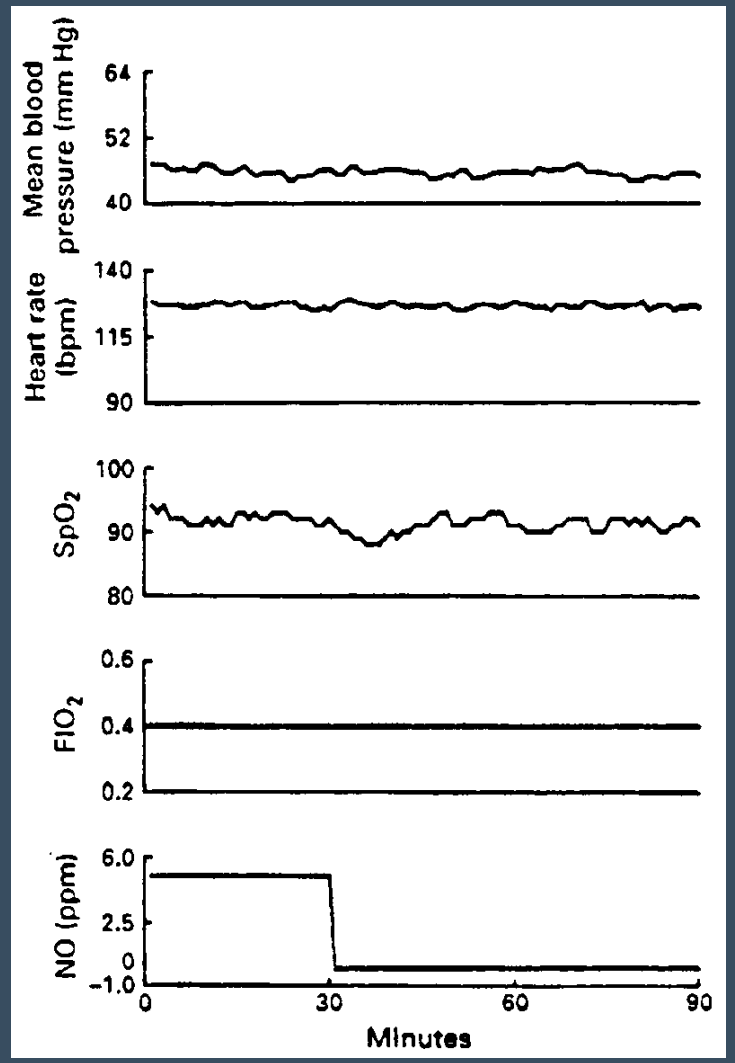
INO Contraindication

- Congenital heart disease with ductal dependent R -> L shunting
- Pulmonary venous congestion
- High baseline methemoglobin (>5%) levels

Weaning Nitric Oxide

- …sometimes is associated with a “rebound phenomenon”
- This rebound hypoxemia can be overcome by giving oxygen simultaneously during weaning

Weaning Nitric Oxide (1)

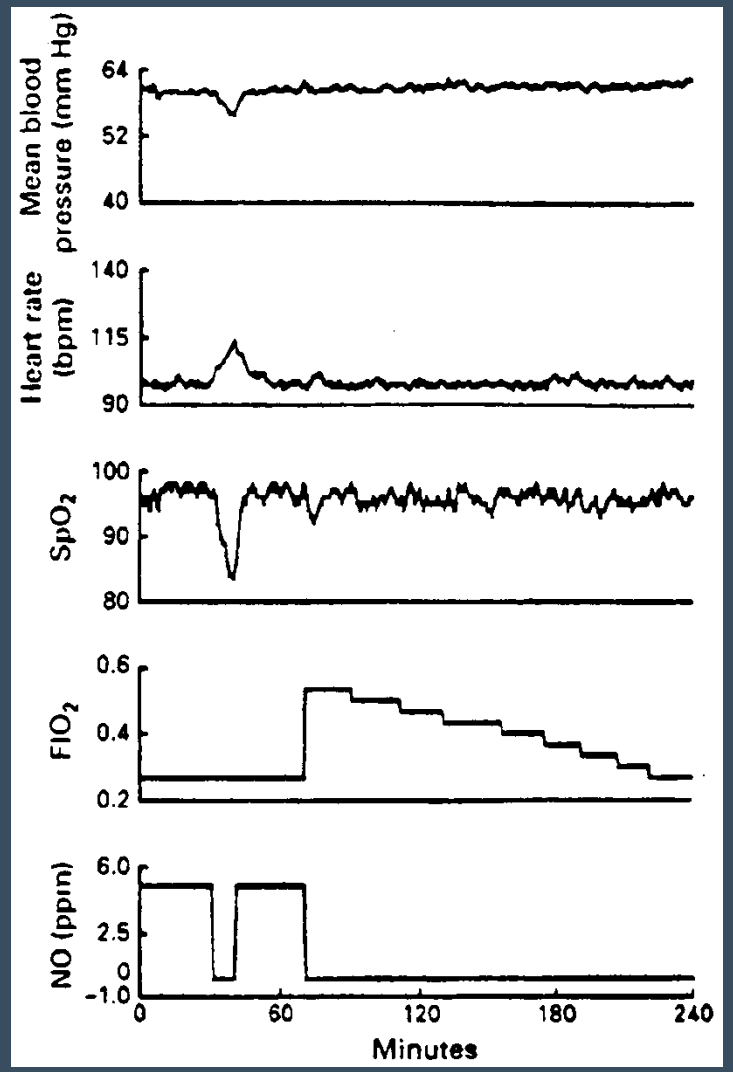


Note the stability of mean blood pressure, heart rate, and SPO2 with the same FiO2 as INO is withdrawn.

Aly H, Sahni R, Wung JT

Arch Dis Child 1997;76:

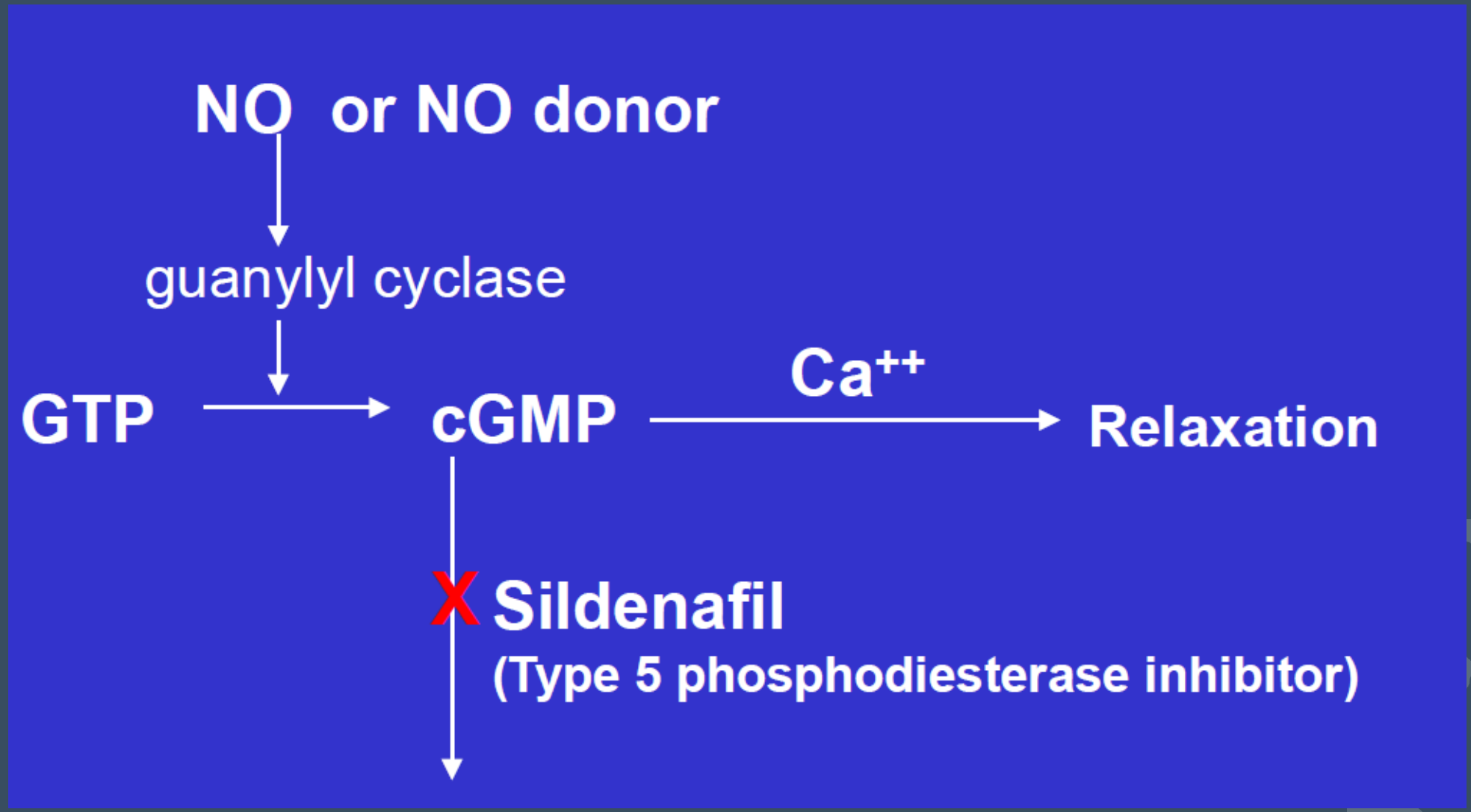
Weaning Nitric Oxide (2)



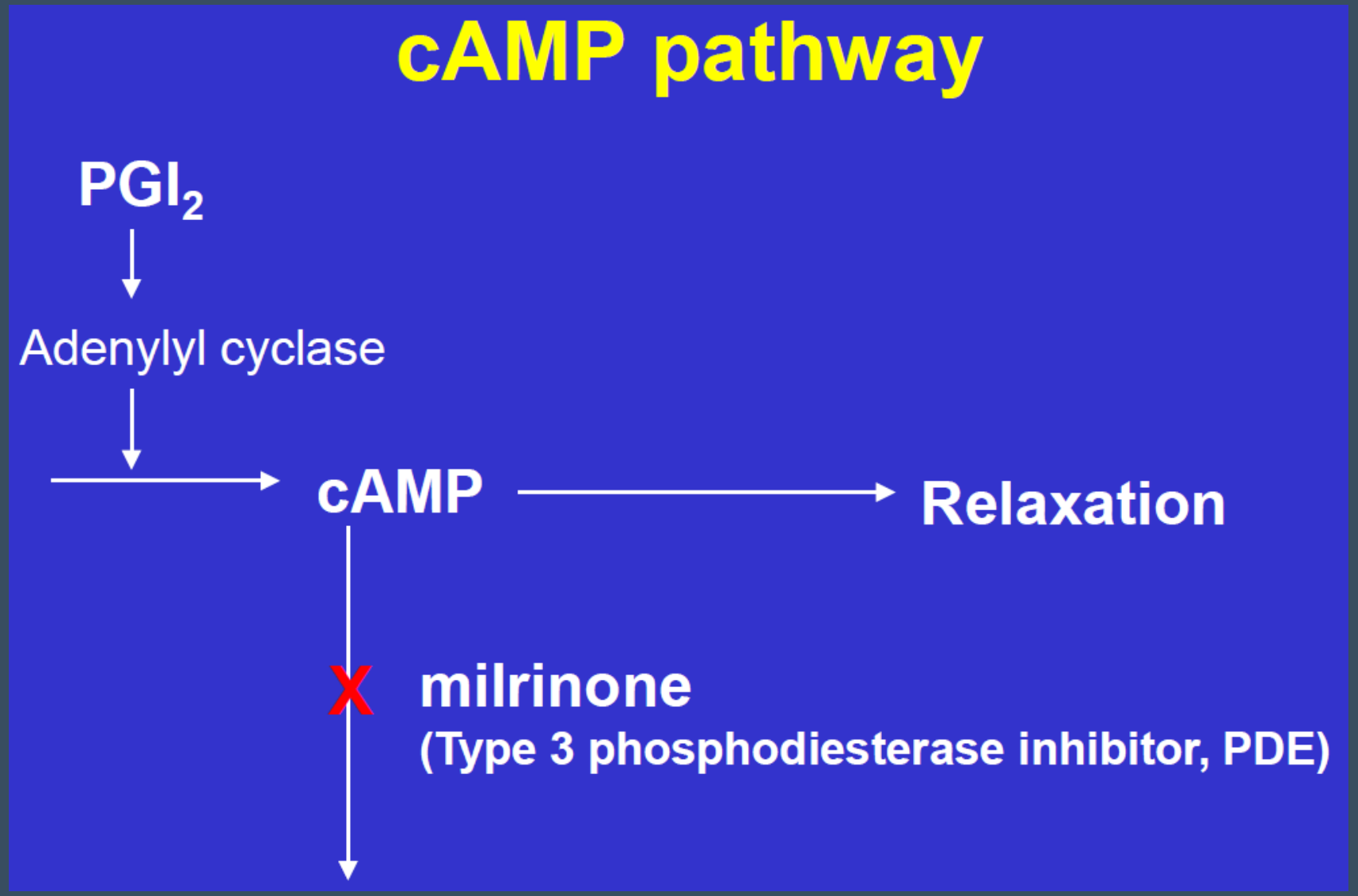
Acute deterioration of mean blood pressure, heart rate, and SPO_2 with the same FiO2 followed the initial attempt at weaning. FiO2 was increased and the weaning was successful. Note how quickly FiO2 was reduced following successful weaning.

Aly H, Sahni R, Wung JT Arch Dis Child 1997;76:

Inhaled NO and Sildenafil



Prostacyclin and Milrinone



Vasodilatory Options

1. Nitric Oxide Pathway (cGMP)
   - Inhaled Nitric Oxide
   - Phosphodiesterase type 5 inhibitor (PDE5): sildenafil

2. Prostacycline Pathway:
   - Prostacyclines: ventavis (iloprost) inhalation
     - treprostinil (remodulin) I.V. or S.C.
     - (tyvaso) oral inhalation (>18 yr. old)
     - epoprostenol (flolan) I.V.2ng/kg/min, ↑2 ng q8h
   - Phosphodiesterase type 3 inhibitor (PDE3): milrinone

3. Endothelin receptor antagonist:
   - bosentan, Ambrisentan

Sedation

- Should be used judiciously
- Spontaneous breathing should not be compromised
- A more individualized approach will find the cause of agitation and reduce the need of sedatives
- NICU environment is of extreme importance

Heller et al, J Perinatol; 1997

Sedation

- Addiction to opiates is a known NICU complication
- Long-term outcomes are not studied
- Continuous infusion of sedatives prolongs the duration of mechanical ventilation

Kollef MH et al, Chest 1998;114

Dexmedetomidine (Precedex)

- It is a non-opioid sedative
- It is a highly selective α2-adrenergic agonist
- It is able to achieve its effects without causing respiratory depression
- It however causes bradycardia & hypotension

Avoid Paralytic Agents

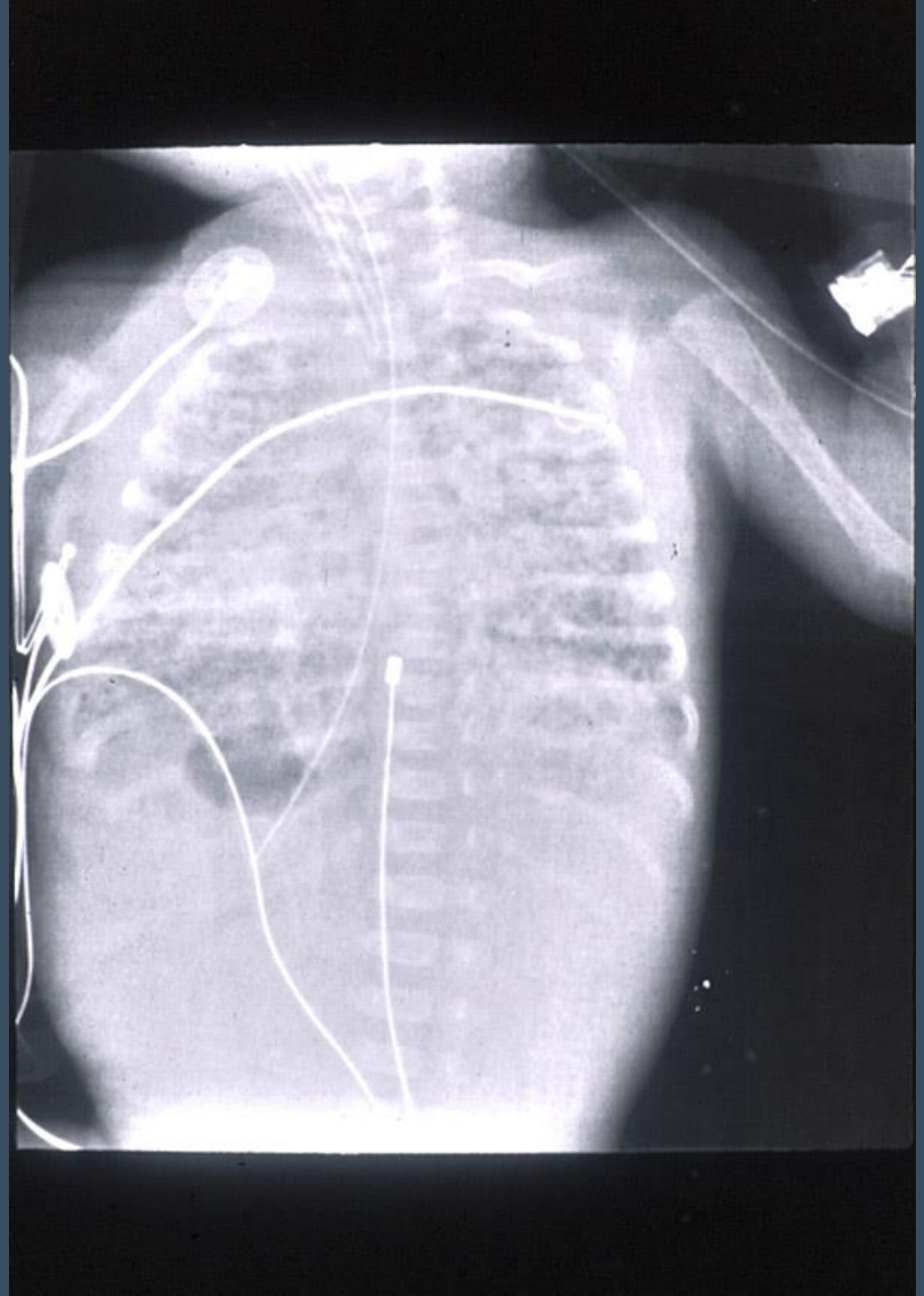
- Have no place in NICUs adopting gentle ventilation
- No single randomized trial to support its use
- Was used in NICUs based on a few hours' observation of blood gases

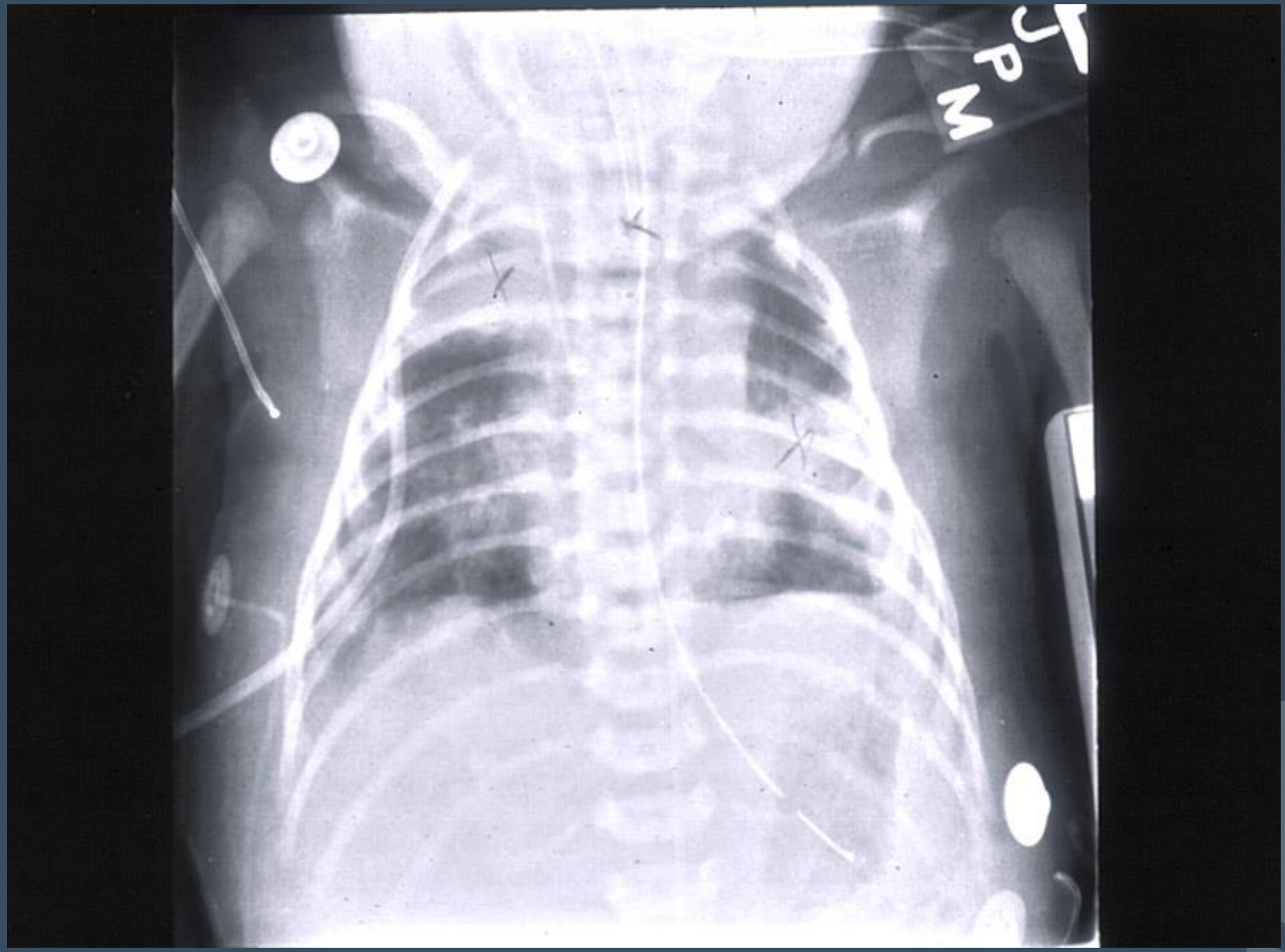
Avoid Paralytic Agents

- While being paralyzed, infants are completely dependent on the ventilator, without any spontaneous breathing
- Thus, the number of breaths given by the ventilator are substantially increased
- Providers lose contact with patients, and are unable to interpret chest x-rays

Avoid Paralytic Agents

- Other known side effects:
  - Suppression of cough reflex with retention of secretions and atelectasis
  - Peripheral edema
  - Autonomic and cardiovascular changes
  - inappropriate use of sedatives and analgesics
  - Myopathy and joint complications




PM

Ventilation Strategies

- Hyperventilation
- pH ≥ 7.5
- $PaCO_2$ ≤ 25 mmHg
- PaO_2 >100 mmHg
- Paralytic agents
- Sedation (drips)

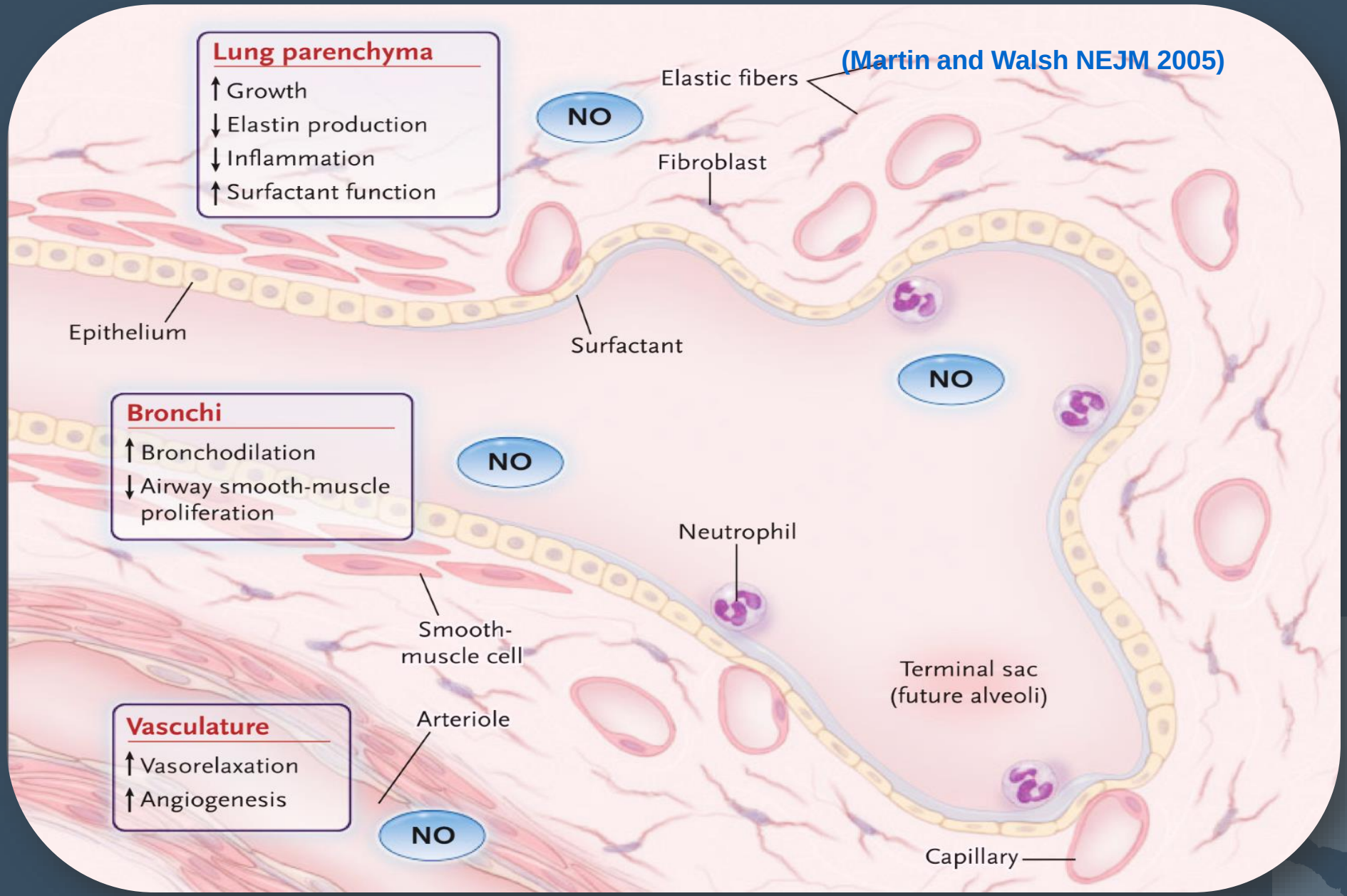
- Gentle Strategy
- pH ≥ 7.25
- $PaCO_2$=50-60 mmHg
- PaO_2 =40-60 mmHg
- No paralytic agents
- Judicious sedation

Conclusions on Management

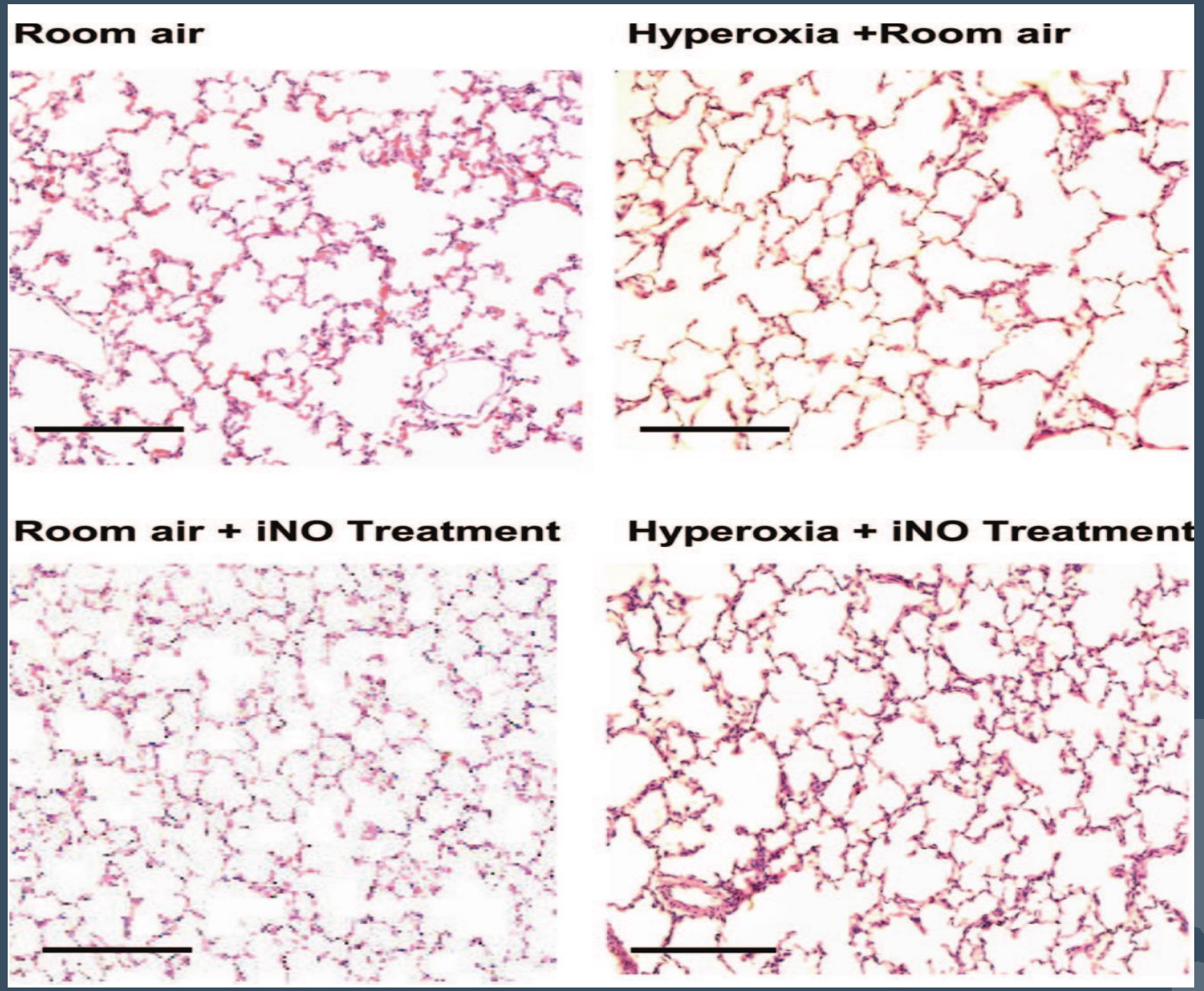
- Use gentle ventilation
- Avoid paralytic agents and excessive sedation
- Stepwise use of systemic pressors and pulmonary vasodilators

Inhaled Nitric Oxide for Preterm Infants

Role of NO in The Developing Lung



(Martin and Walsh NEJM 2005)


Room air
Hyperoxia +Room air
Room air + iNO Treatment
Hyperoxia + iNO Treatment

Clinical Trials of iNO in Preterm Infants

- More than 3000 preterm infants in at least 11 clinical trials
- Used for:
  - Early respiratory failure ≤ 3 days:
    - rescue iNO for sick infants ---------- 7 trials
    - routine iNO for intubated infants ---- 2 trials
  - Late iNO (>3 days)
    - To prevent CLD ---------- 2 trials

Measured Outcomes in These Trials

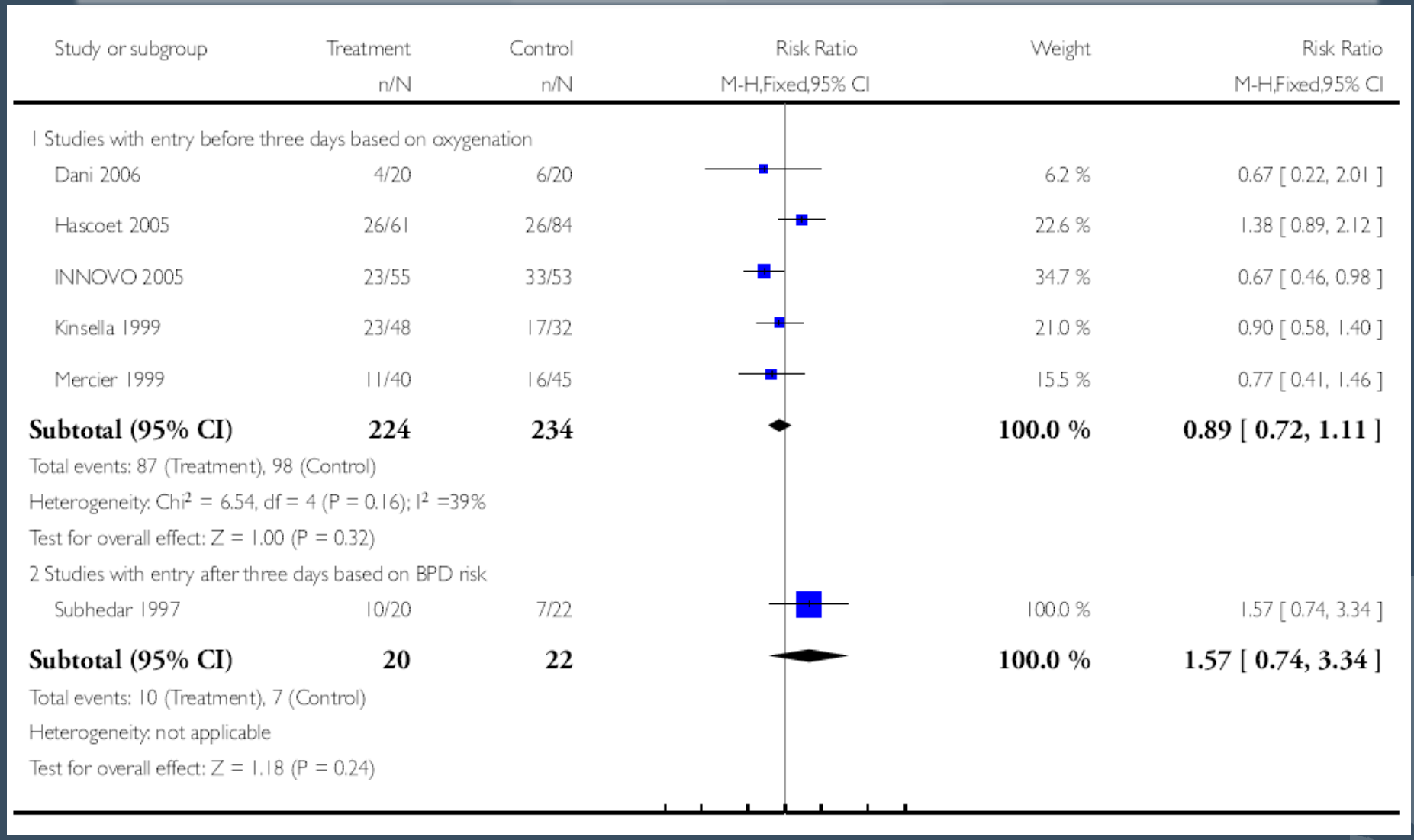
- Mortality
- BPD
- Mortality + BPD
- IVH
- NDO

Outcomes: Survival

- None of the 11 trials has any improvement in survival
- None of the trials reported any improvement in survival at 36 weeks (6 trials)
- Only when combining the 2 trials on early routine iNO, there is a marginal improvement in survival: RR=0.71 (95%CI= 0.6 – 0.98), NTT= 9 - 100

Finer et al, 2009

Mortality



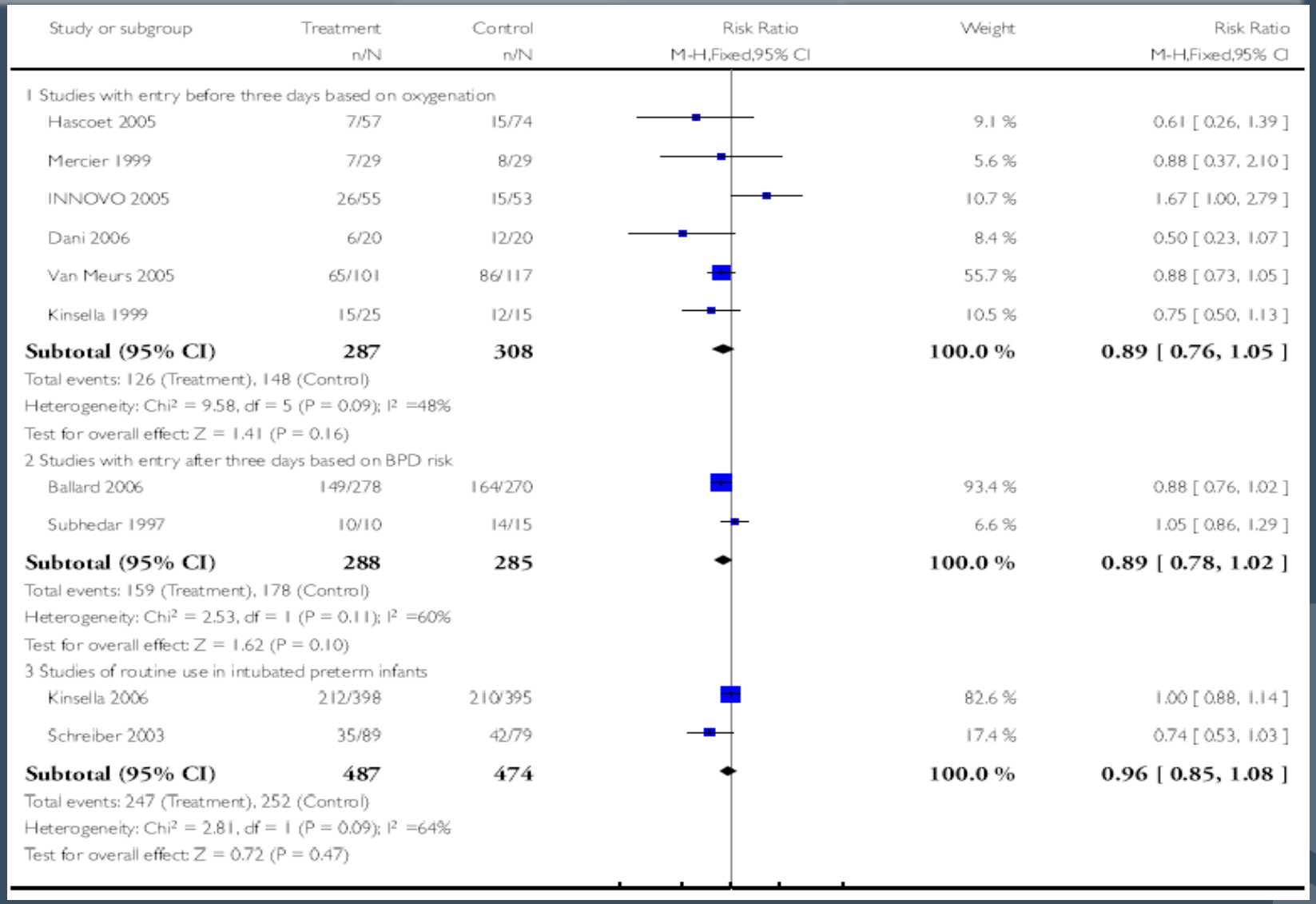
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Studies with entry before three days based on oxygenation					
Dani 2006	4/20	6/20		6.2 %	0.67 [0.22, 2.01]
Hascoet 2005	26/61	26/84		22.6 %	1.38 [0.89, 2.12]
INNOVO 2005	23/55	33/53		34.7 %	0.67 [0.46, 0.98]
Kinsella 1999	23/48	17/32		21.0 %	0.90 [0.58, 1.40]
Mercier 1999	11/40	16/45		15.5 %	0.77 [0.41, 1.46]
Subtotal (95% CI)	**224**	**234**		**100.0 %**	**0.89 [0.72, 1.11]**
Total events: 87 (Treatment), 98 (Control)					
Heterogeneity: Chi^2 = 6.54, df = 4 (P = 0.16); I^2 =39%					
Test for overall effect: Z = 1.00 (P = 0.32)					
2 Studies with entry after three days based on BPD risk					
Subhedar 1997	10/20	7/22		100.0 %	1.57 [0.74, 3.34]
Subtotal (95% CI)	**20**	**22**		**100.0 %**	**1.57 [0.74, 3.34]**
Total events: 10 (Treatment), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.18 (P = 0.24)					

Outcomes: BPD at 36 Weeks

- None of the individual trials showed any improvement of BPD by 36 weeks PMA
- There was a substantial heterogeneity of the BPD rate among trials

Finer et al, 2009

BPD at 36 Weeks PMA



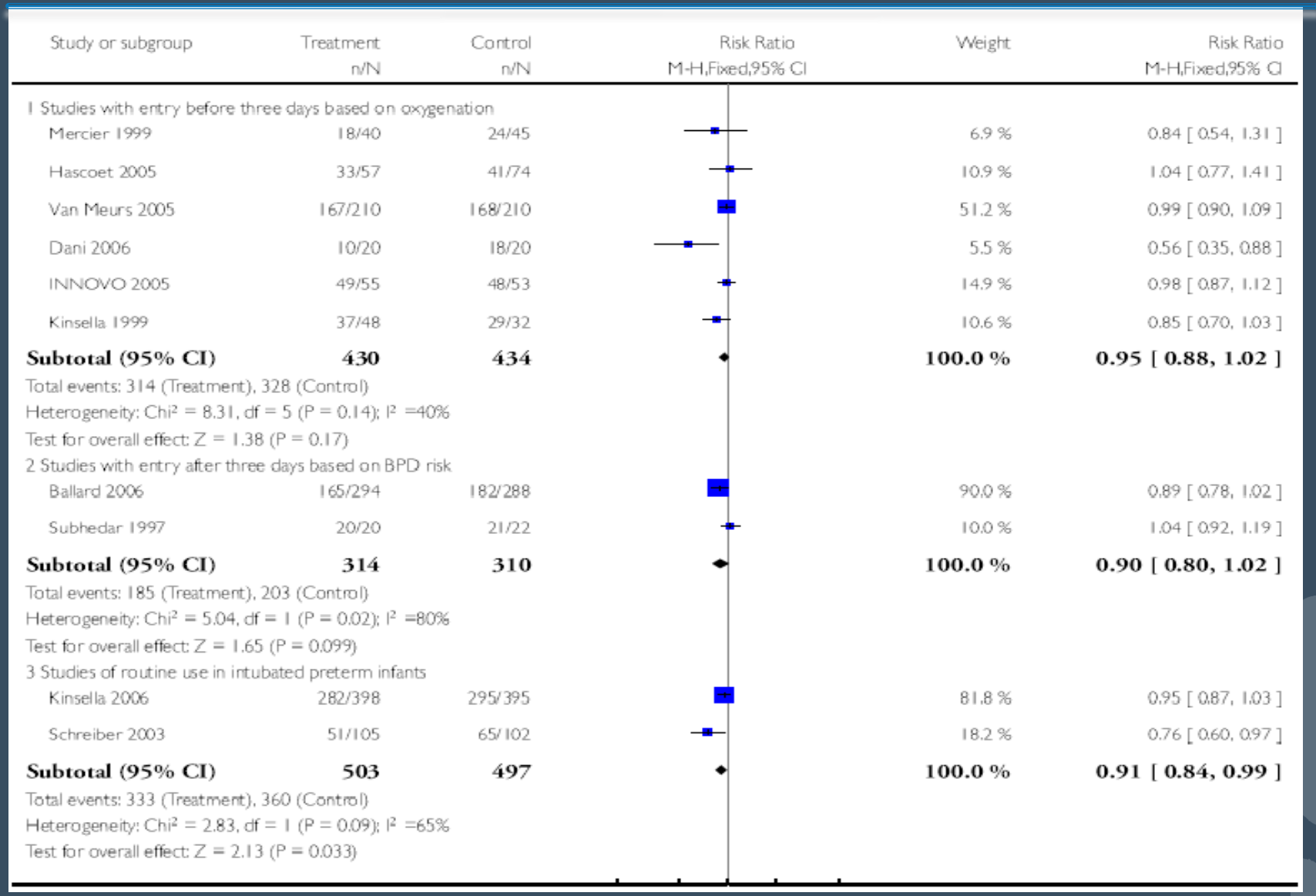
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Studies with entry before three days based on oxygenation					
Hascoet 2005	7/57	15/74		9.1 %	0.61 [0.26, 1.39]
Mercier 1999	7/29	8/29		5.6 %	0.88 [0.37, 2.10]
INNOVO 2005	26/55	15/53		10.7 %	1.67 [1.00, 2.79]
Dani 2006	6/20	12/20		8.4 %	0.50 [0.23, 1.07]
Van Meurs 2005	65/101	86/117		55.7 %	0.88 [0.73, 1.05]
Kinsella 1999	15/25	12/15		10.5 %	0.75 [0.50, 1.13]
Subtotal (95% CI)	**287**	**308**		**100.0 %**	**0.89 [0.76, 1.05]**
Total events: 126 (Treatment), 148 (Control)					
Heterogeneity: Chi² = 9.58, df = 5 (P = 0.09); I² =48%					
Test for overall effect: Z = 1.41 (P = 0.16)					
2 Studies with entry after three days based on BPD risk					
Ballard 2006	149/278	164/270		93.4 %	0.88 [0.76, 1.02]
Subhedar 1997	10/10	14/15		6.6 %	1.05 [0.86, 1.29]
Subtotal (95% CI)	**288**	**285**		**100.0 %**	**0.89 [0.78, 1.02]**
Total events: 159 (Treatment), 178 (Control)					
Heterogeneity: Chi² = 2.53, df = 1 (P = 0.11); I² =60%					
Test for overall effect: Z = 1.62 (P = 0.10)					
3 Studies of routine use in intubated preterm infants					
Kinsella 2006	212/398	210/395		82.6 %	1.00 [0.88, 1.14]
Schreiber 2003	35/89	42/79		17.4 %	0.74 [0.53, 1.03]
Subtotal (95% CI)	**487**	**474**		**100.0 %**	**0.96 [0.85, 1.08]**
Total events: 247 (Treatment), 252 (Control)					
Heterogeneity: Chi² = 2.81, df = 1 (P = 0.09); I² =64%					
Test for overall effect: Z = 0.72 (P = 0.47)					

Mortality + BPD

- None of the studies for early rescue iNO showed any significance
- None of the studies on late iNO showed any significance
- Early routine iNO for intubated infants barely showed some significance
  - RR=0.91 (95% CI= 0.84 - 0.99)
  - Number to treat =17 (8- 100)

Finer et al, 2009

Death or BPD at 36 Weeks PMA

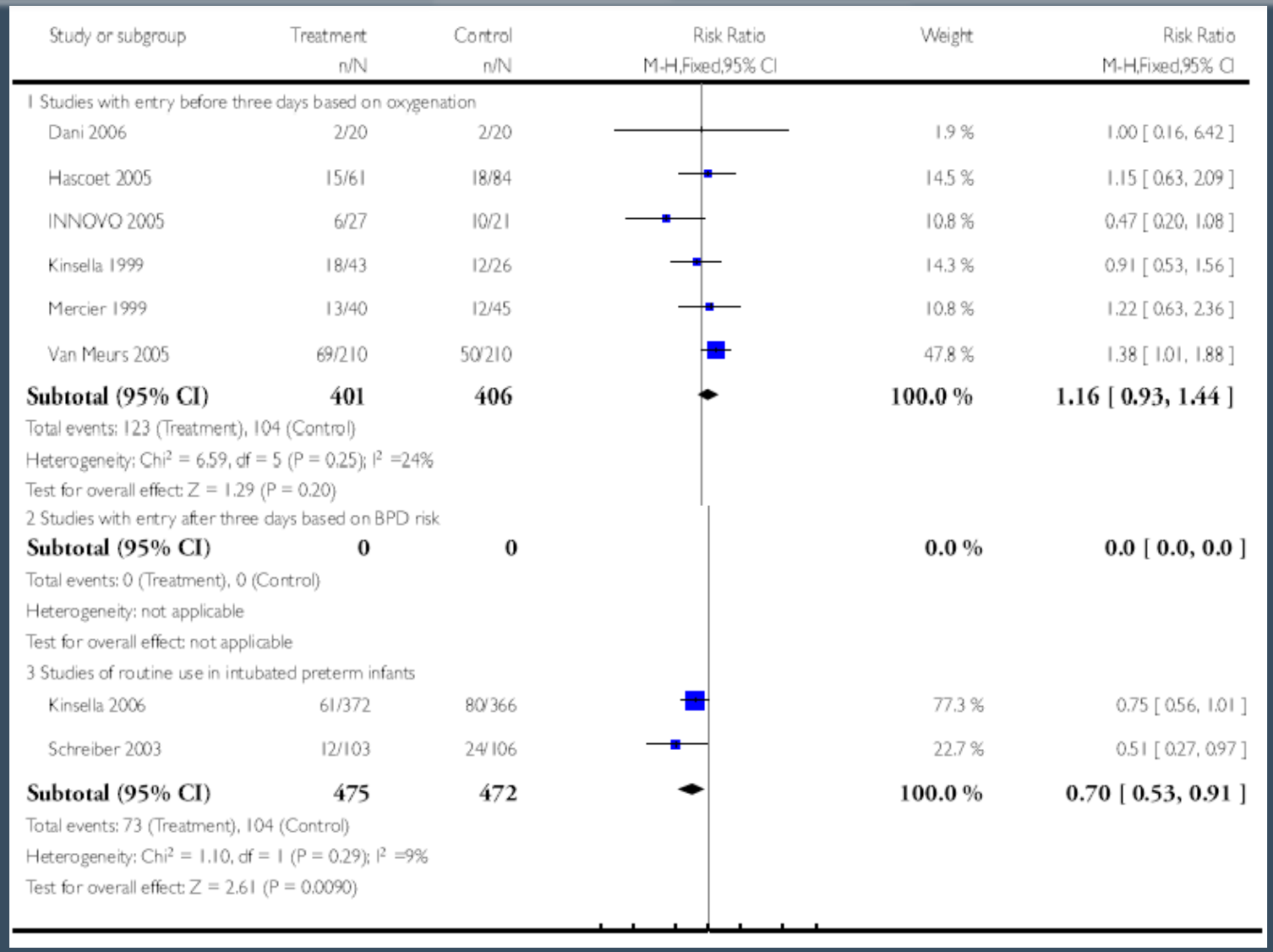


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Studies with entry before three days based on oxygenation					
Mercier 1999	18/40	24/45		6.9 %	0.84 [0.54, 1.31]
Hascoet 2005	33/57	41/74		10.9 %	1.04 [0.77, 1.41]
Van Meurs 2005	167/210	168/210		51.2 %	0.99 [0.90, 1.09]
Dani 2006	10/20	18/20		5.5 %	0.56 [0.35, 0.88]
INNOVO 2005	49/55	48/53		14.9 %	0.98 [0.87, 1.12]
Kinsella 1999	37/48	29/32		10.6 %	0.85 [0.70, 1.03]
Subtotal (95% CI)	**430**	**434**		**100.0 %**	**0.95 [0.88, 1.02]**
Total events: 314 (Treatment), 328 (Control)					
Heterogeneity: Chi^2 = 8.31, df = 5 (P = 0.14); I^2 =40%					
Test for overall effect: Z = 1.38 (P = 0.17)					
2 Studies with entry after three days based on BPD risk					
Ballard 2006	165/294	182/288		90.0 %	0.89 [0.78, 1.02]
Subhedar 1997	20/20	21/22		10.0 %	1.04 [0.92, 1.19]
Subtotal (95% CI)	**314**	**310**		**100.0 %**	**0.90 [0.80, 1.02]**
Total events: 185 (Treatment), 203 (Control)					
Heterogeneity: Chi^2 = 5.04, df = 1 (P = 0.02); I^2 =80%					
Test for overall effect: Z = 1.65 (P = 0.099)					
3 Studies of routine use in intubated preterm infants					
Kinsella 2006	282/398	295/395		81.8 %	0.95 [0.87, 1.03]
Schreiber 2003	51/105	65/102		18.2 %	0.76 [0.60, 0.97]
Subtotal (95% CI)	**503**	**497**		**100.0 %**	**0.91 [0.84, 0.99]**
Total events: 333 (Treatment), 360 (Control)					
Heterogeneity: Chi^2 = 2.83, df = 1 (P = 0.09); I^2 =65%					
Test for overall effect: Z = 2.13 (P = 0.033)					

Intraventricular Hemorrhage

- Any IVH: none of the studies showed any difference (3 studies reported this outcome)
- Severe IVH:
  - Early rescue iNO:
    - A non-significant trend for increase: RR=1.27 (95% CI= 0.99 – 1.62)
    - A non-significant trend for increased IVH/PVL
  - Early routine iNO:
    - no difference in severe IVH
    - Reduced IVH/PVL (Number to treat = 14)

Severe IVH or PVL

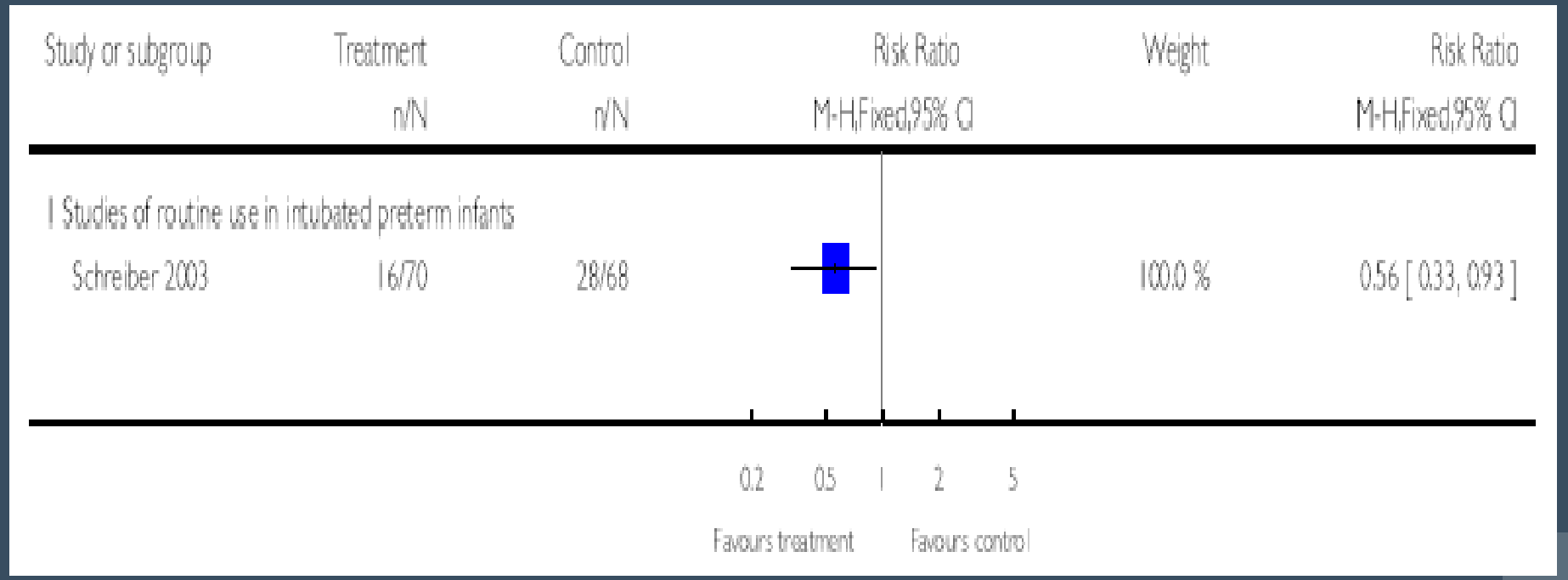


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Studies with entry before three days based on oxygenation					
Dani 2006	2/20	2/20		1.9 %	1.00 [0.16, 6.42]
Hascoet 2005	15/61	18/84		14.5 %	1.15 [0.63, 2.09]
INNOVO 2005	6/27	10/21		10.8 %	0.47 [0.20, 1.08]
Kinsella 1999	18/43	12/26		14.3 %	0.91 [0.53, 1.56]
Mercier 1999	13/40	12/45		10.8 %	1.22 [0.63, 2.36]
Van Meurs 2005	69/210	50/210		47.8 %	1.38 [1.01, 1.88]
Subtotal (95% CI)	**401**	**406**		**100.0 %**	**1.16 [0.93, 1.44]**
Total events: 123 (Treatment), 104 (Control)					
Heterogeneity: Chi^2 = 6.59, df = 5 (P = 0.25); I^2 =24%					
Test for overall effect: Z = 1.29 (P = 0.20)					
2 Studies with entry after three days based on BPD risk					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Studies of routine use in intubated preterm infants					
Kinsella 2006	61/372	80/366		77.3 %	0.75 [0.56, 1.01]
Schreiber 2003	12/103	24/106		22.7 %	0.51 [0.27, 0.97]
Subtotal (95% CI)	**475**	**472**		**100.0 %**	**0.70 [0.53, 0.91]**
Total events: 73 (Treatment), 104 (Control)					
Heterogeneity: Chi^2 = 1.10, df = 1 (P = 0.29); I^2 =9%					
Test for overall effect: Z = 2.61 (P = 0.0090)					

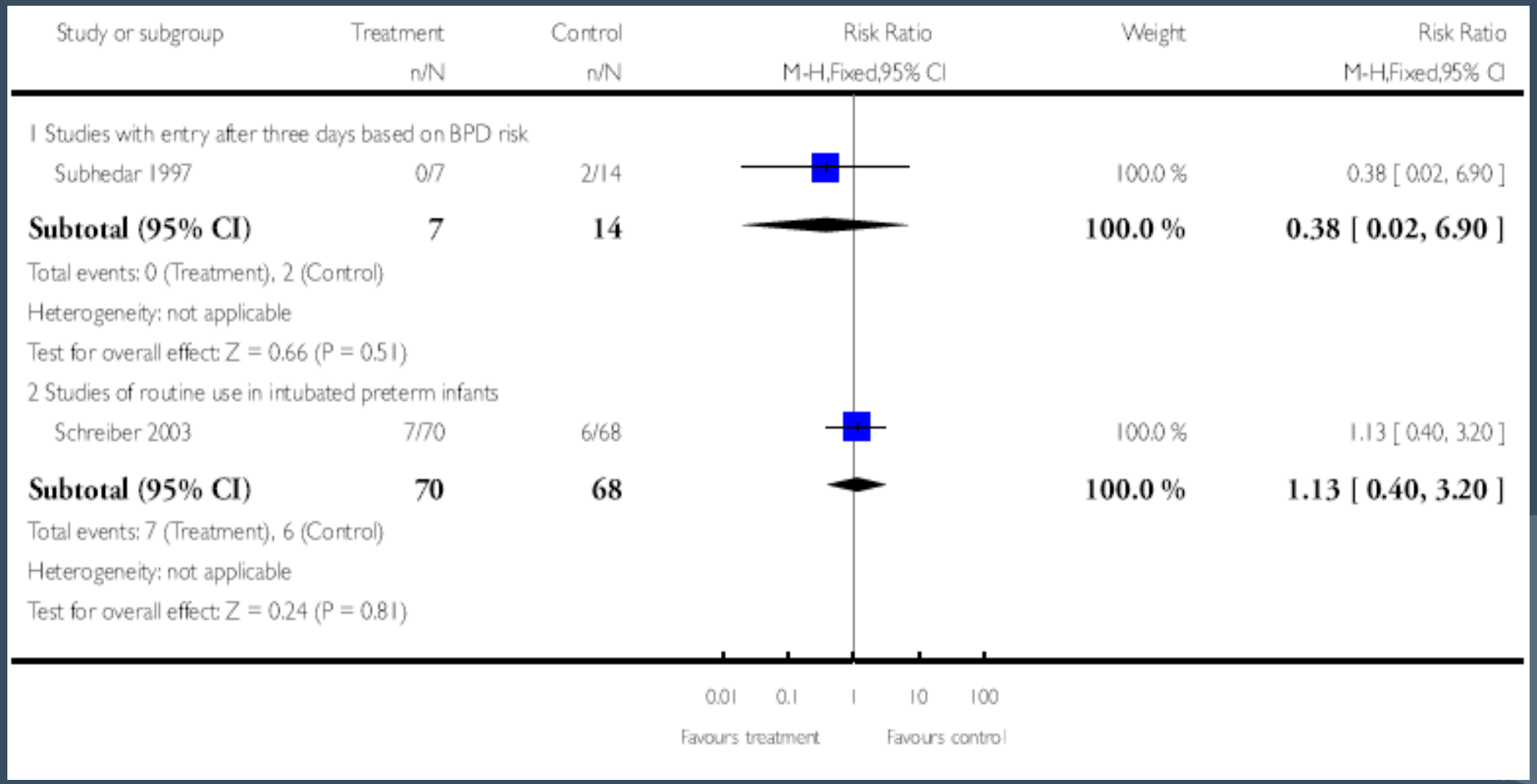
Neurodevelopmental Outcomes

- Only 3 trials reported NDO:
  - 2 trials showed no difference
  - The trial by Schreiber (early routine iNO) showed significant improvement in NDO examination (but not CP)

Adverse NDO


Study or subgroup
Treatment
n/N
Control
n/N
Risk Ratio
M-H,Fixed,95% CI
Weight
Risk Ratio
M-H,Fixed,95% CI
1 Studies of routine use in intubated preterm infants
Schreiber 2003
16/70
28/68
100.0 %
0.56 [0.33, 0.93]
0.2
0.5
1
2
5
Favours treatment
Favours control

Cerebral Palsy at 9 Months



Finer et al, 2009

Non-Invasive iNO for Preemies

- Kinsella 2014, N=124
- BW= 500-1250g, on CPAP or NC receives 10 ppm until 30 wks

- Outcome:
  - No Difference in BPD or death
  - No difference in mechanical ventilation or ventilator days

Kinsella JP, et al. *J Pediatr* (2014)

Pulmonary Outcome at 1 Year

MEDICAL HISTORY:	iNO (%)	Placebo (%)	RR (95% CI)	NNT (95% CI)
Wheezing or whistling in chest	49.6	56.4	0.70 (0.48-1.03)	---
Bronchodilators	40.1	54.1	0.53 (0.36-0.78)	6.3 (4.0-15.6)
Inhaled Steroids	19.8	32.4	0.50 (0.32-0.77)	7.5 (4.6-19.6)
Systemic Steroids	11.0	17.7	0.56 (0.32-0.97)	14.1 (7.3-250.0)

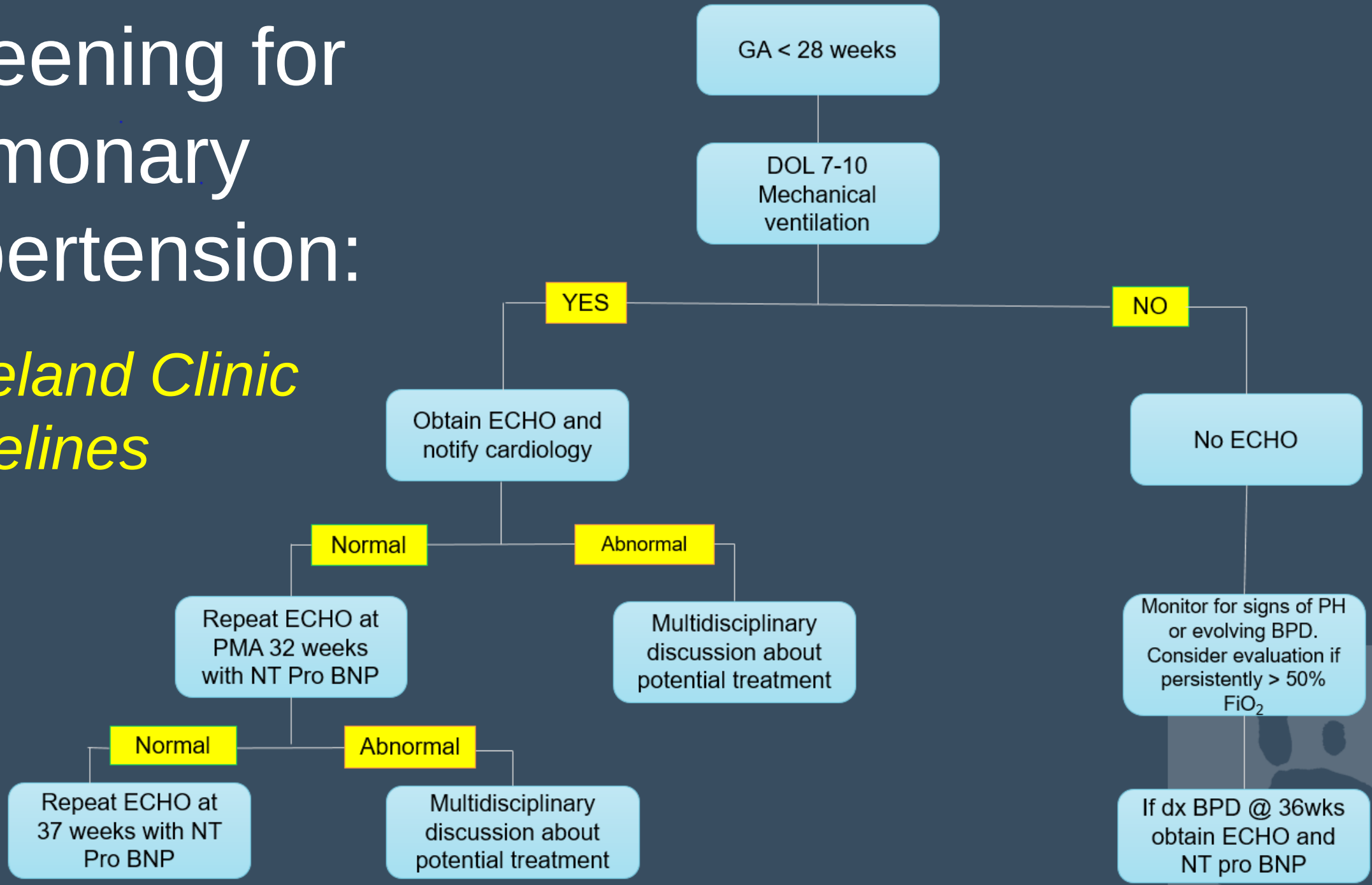
Hibbs, J Peds, 2008

Pulmonary Outcome at 1 Year

MEDICAL HISTORY:	iNO (%)	Placebo (%)	RR	NNT
Any hospitalization	46.5%	50.4%	0.83 (0.57-1.21)	---
Respiratory hospitalization	22.6%	21.9%	1.03 (0.65-1.62)	---
Diuretic use	18.6%	28.4%	0.54 (0.34-0.85)	9 (5.2-33.3)
Any home O_2 use	38.4%	49.5%	0.65 (0.44-0.95)	9.4 (5.0-76.9)
Persistent O_2 at follow-up	3.0%	9.4%	0.30 (0.13-0.73)	15.9 (9.4-52.6)

Screening for Pulmonary Hypertension:

Cleveland Clinic Guidelines



Inhaled NO in Premature Infants

- Pros. No real short term side effects
- Cons. Long term risks are unknown and significant expense
- iNO may be beneficial in:
  - certain sub-category of premature infants
  - who had specific underlying pathology
  - when therapy is used for certain duration

Inhaled NO in Premature Infants

CONCLUSIONS:

- An individualized, at the bed-side evaluation is recommended to clarify:
- Who (how severely immature)?
- Why (exact underlying lung pathology)?
- How long (duration of use)?

"If you do not have an exit strategy do not enter"

Thank You