Inhaled Nitric Oxide in Infants

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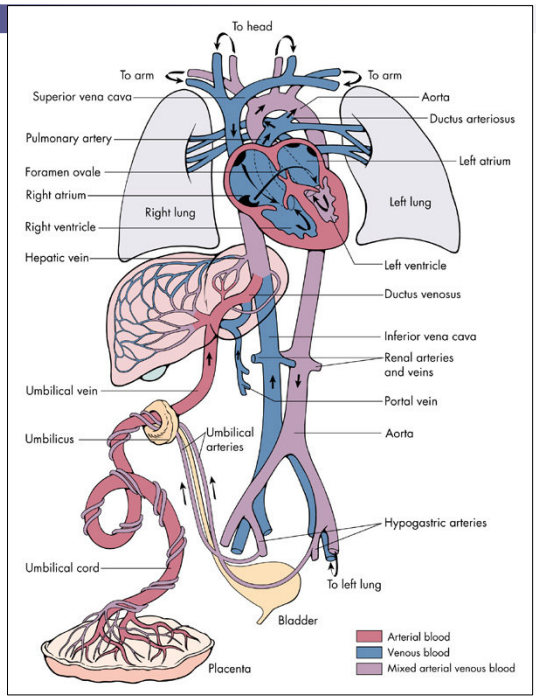
Objectives

- Review neonatal transition to extrauterine life
- Describe Hypoxic Respiratory Failure (HRF)/Persistent Pulmonary Hypertension (PPHN)
- Discuss use of inhaled Nitric Oxide (iNO).



Fetal Oxygenation

Maternal Circulation			
	paO2	SaO2	pCO2
Uterine Artery	100 mmHg	98%	32 mmHg
Uterine Vein	40 mmHg	75%	45 mmHg
Fetal Circulation			
	paO2	SaO2	pCO2
Umbilical Artery	18 mmHg	45%	55 mmHg
Umbilical Vein	28 mmHg	70%	40 mmHg

Fetal Hemoglobin Dissociation Curve

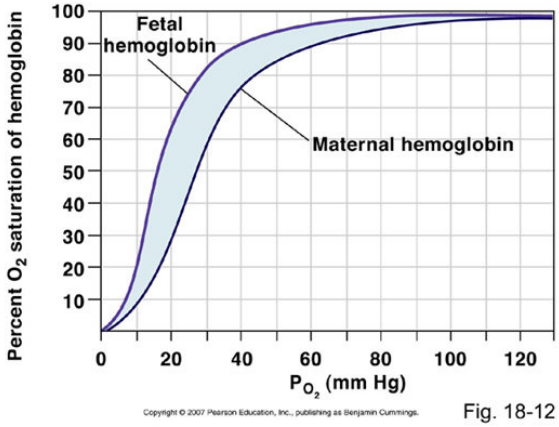


Fig. 18-12

5 Major Events to Breath Air

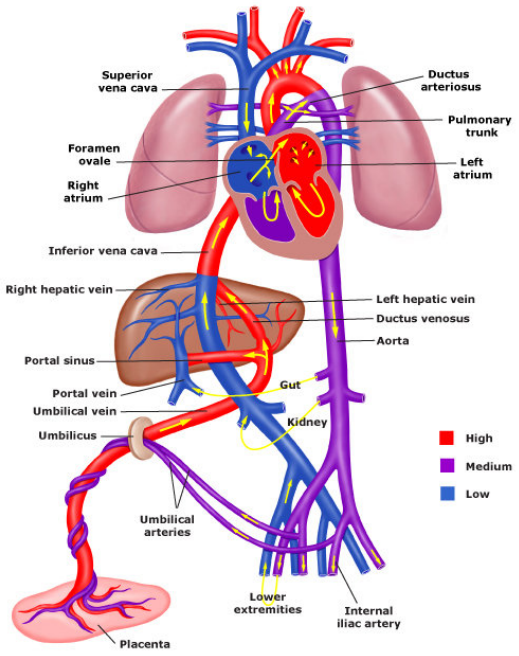
- Clearance of fetal lung fluid
- Establishment of spontaneous breathing
- Surfactant release
- Decrease in PVR
- Cessation of R>L shunt of blood returning to heart

Neonatal Transition

- Absorption of fetal lung fluid
- Increase in SVR
  - Placenta is extremely low resistance
- Inflation of lungs
- Increase in PaO2
  - In utero – 20-30 mmHg
- Increase pulmonary blood flow
- PFO and PDA close

Circulatory Changes

- In utero, circulation is maintained as massive R->L shunt
- High pulmonary vascular resistance
- Low systemic vascular resistance



Circulatory Changes

- Decrease in PVR
  - Air replaces fluid in lungs
  - Results in mechanical distention of pulmonary vasculature
  - Increased oxygenation (↑PaO2) results in further decrease of PVR
    - Oxygen is best pulmonary vasodilator

Circulatory Changes

- Increase in SVR
  - Clamping umbilical cord causes immediate, drastic increase in SVR

Circulatory Changes

- Stopping R->L Shunt
  - No more umbilical vessel flow
    - Ductus venosus
    - Umbilical arteries
      - Further constricted by increased PaO2
  - Decrease in PVR and increase in SVR
    - Closing of PFO from increase in pulmonary blood flow and blood return to left atrium
    - Decreased flow through ductus arteriosus
    - Oxygen causes vasoconstriction in ductus

Hypoxic Respiratory Failure
Persistent Pulmonary Hypertension

PPHN

- Persistent Pulmonary Hypertension of the Newborn
  - Previously known as Persistent Fetal Circulation (PFC)
- 1-2 per 1000 births
- Full-term Infants

PPHN

- Failure of normal circulatory transition postnatally
- Elevated pulmonary vascular resistance
  - Left-to-right shunt
  - Severe hypoxemia
  - May be normal CO2 exchange

Pathophysiology & Causes

- Maladaption – normal structure
  - Hypoxia, acidosis
  - Asphyxia, hypothermia, hyperviscosity
  - Pneumonia, Meconium Aspiration Syndrome
- Maldevelopment – abnormal structure with vascular smooth muscle hypertrophy
  - Premature PDA Closure
  - Pulmonary hypoplasia, CDH
  - Alveolar capillary dysplasia
- Cardiac Dysfunction

Clinical Presentation

- Severe hypoxemia and respiratory distress
  - Labile oxygen saturations
- Evidence of shunting (right arm and leg)
  - Differential O2 sats - >5% difference
  - Differential PaO2 - >20 mmHg
- Cardiac exam
  - Single S2, Loud
  - TR murmur
- CXR – depends on etiology
  - “Black lung disease,” MAS, pneumonia

Diagnosis

- Hyperoxia Test – 10 minutes of 100%
  - PaO2
    - <100 mmHg – Cardiac/PPHN
    - 100-150 mmHg – Suggestive of PPHN
    - >150 mmHg – Primary Airspace Disease
  - May add hyperventilation if abnormal

Diagnosis - ECHO

- Tricuspid Regurgitation
  - Elevated Pulmonary Pressures
- RVH/Decreased RV function
- Bowing of Ventricular Septum into LV
- Right-to-left shunt at PDA/PFO

Physiology Review

- A-a Gradient

$$AaD_{O2} = Fi_{O2}\,(P_{atm}-47) - \frac{Pa_{CO2}}{R} - Pa_{O2}$$

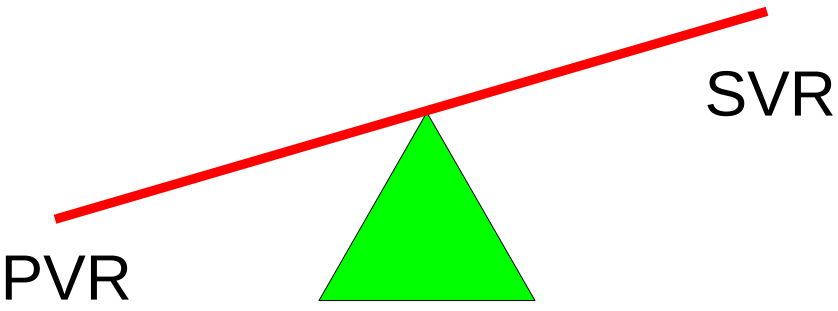
- Oxygen Index

$$OI = \frac{\text{Mean Airway Pressure} \times Fi_{O2} \times 100}{Pa_{O2}}$$

Treatment of PPHN

- Blood flows downhill

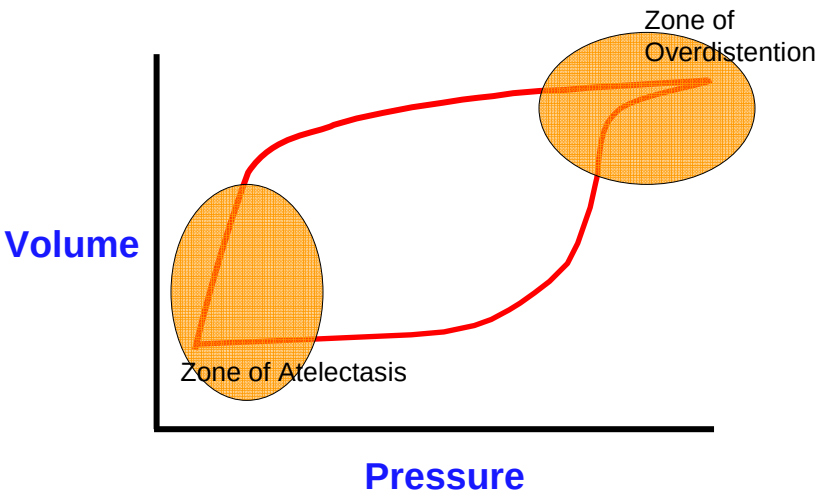
Treatment of PPHN



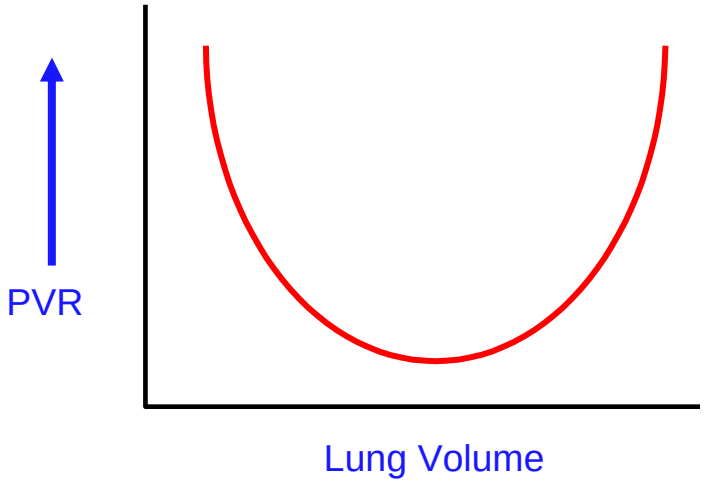
Treatment of PPHN

- Antibiotics
- 100% Oxygen
- Volume
- PRBCs
- Sedation, Low Stimulation Environment
- Correct Acidosis
- Pressors, Hydrocortisone
- Optimize Ventilation
  - Hyperventilation, High Frequency
  - Goal PaO2 – 60-80
  - Keep pH normal (7.35-7.45), PaCO2 35-45
  - Consider Surfactant

Optimal Lung Volume

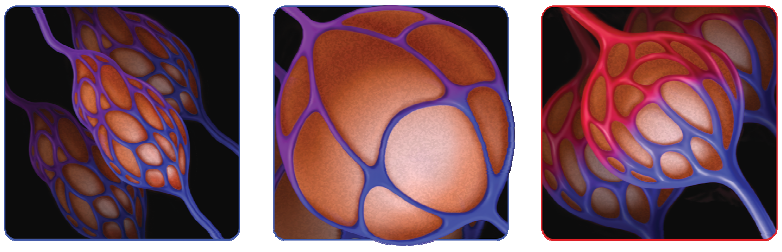


Optimal Lung Volume



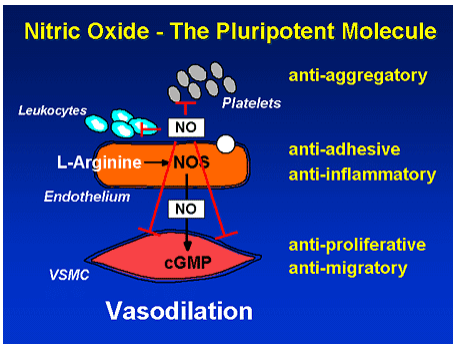
Optimal Lung Volume - Optimize V/Q Matching

V/Q <<<1 V/Q >>>1 V/Q = 1



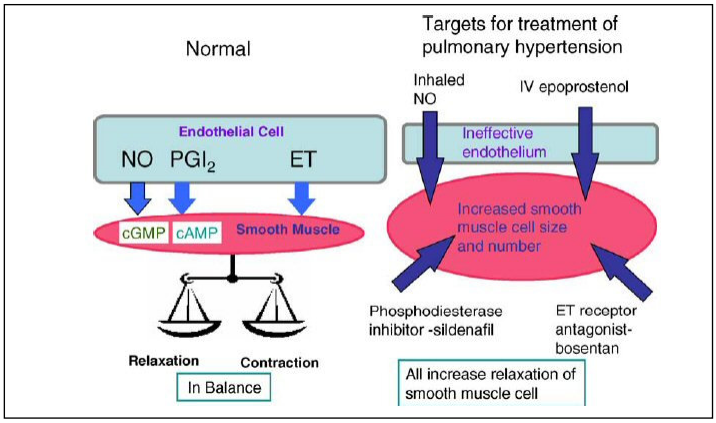
Treatment of PPHN

- Historical
  - Alkalinization
  - Nitroprusside, Tolazoline
- Current
  - iNO
  - PGI2 (Epoprostanol, Flolan)
  - ECMO
- Other
  - PDE inhibitors: sildenafil, dipyridamol, zaprinast- effect same pathway as iNO
  - Endothelin antagonist: bosentan
  - PGE1: Alprostadil



Inhaled Nitric Oxide

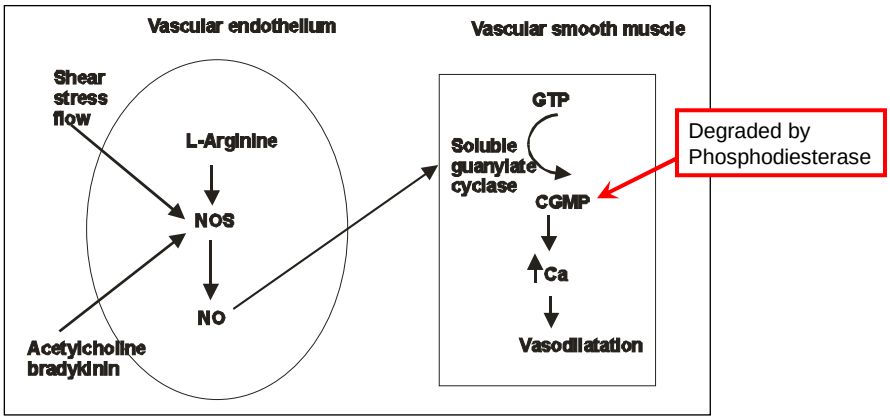
Treatment of PPHN



How it works

- Nitric Oxide (NO) is a naturally occuring molecule derived from oxidation of L-arginine by NO Synthase (NOS) in vascular endothelium
- NO diffuses from the endothelium to act on vascular smooth muscle cells
- NO is a potent vasodilator that induces vascular smooth muscle relaxation by increasing cGMP production

Inhaled Nitric Oxide



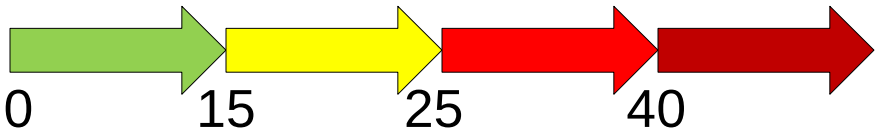
Indications

NO is indicated in infants with ECHO documented PPHN **after lung inflation and hemodynamics are optimized** (consider hydrocortisone, high frequency ventilation, surfactant first) and:

- gestational age >34 weeks
- OI >25 (15)

Indications

- Oxygen Index in PPHN



Inhaled Nitric Oxide

- Side Effects
  - rebound pulmonary hypertension
  - methemoglobinemia
  - NO2 production
- Contraindications
  - ductal dependent cardiac defect
  - congenital methemoglobinemia
  - fatal congenital disease

iNO Dosing

- starting and maximum dose=20ppm
- wean to 5ppm by 4-24h
- usual duration <5d, exceptions- CDH, pulmonary hypoplasia
- if no response in <1 hour, can D/C quickly, otherwise need to wean

Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the Term Newborn: A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study

Davidson, et al. Pediatrics, 101(3) 1998.

- Multi-center, randomized, blinded, placebo controlled study
- 155 infants >36 weeks (of 320 planned)
- Primary outcome – decrease PPHN Major Sequelae Index
- Dose 5, 20 and 80 ppm
- Unable to prove primary outcome

Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the Term Newborn: A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study

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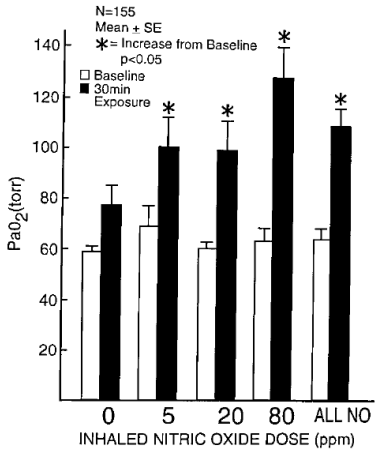

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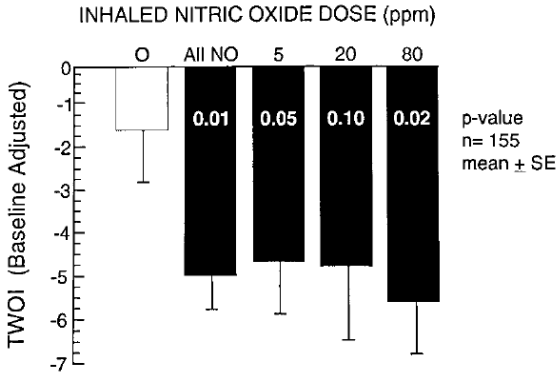

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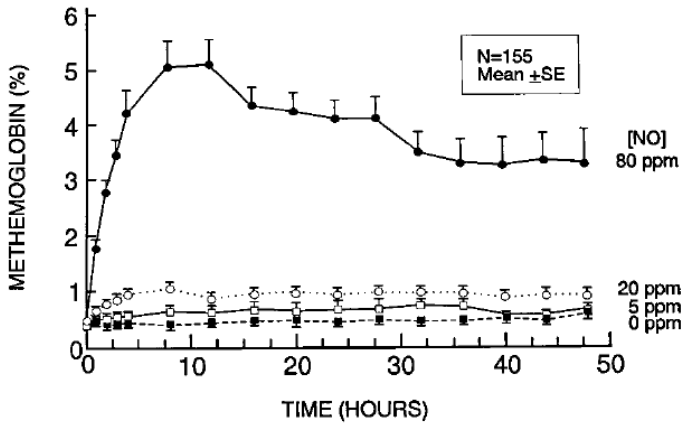

INHALED NITRIC OXIDE IN FULL-TERM AND NEARLY FULL-TERM INFANTS WITH HYPOXIC RESPIRATORY FAILURE

Ehrenkranz, et al. The Neonatal Inhaled Nitric Oxide Study Group. NEJM. 336(9) 1007.

- Multi-center, randomized, blinded, placebo controlled study
- 235 infants >34 weeks
- Primary outcome – reduce death/ECMO by DOL 120
- Infants with HRF with OI>25 x2

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TABLE 3. OUTCOMES OF ADMINISTRATION OF THE STUDY GAS, ACCORDING TO GROUP.*

OUTCOME	CONTROL GROUP (N = 121)	NITRIC OXIDE GROUP (N = 114)	P VALUE
Death by day 120 or ECMO — no. (%)	77 (63.6)	52 (45.6)	0.006
Death — no. (%)	20 (16.5)	16 (14.0)	0.60
ECMO — no. (%)	66 (54.5)	44 (38.6)	0.014
Change in PaO_2 — mm Hg	9.7±51.7	58.2±85.2	<0.001
Change in oxygenation index	0.8±21.1	−14.1±21.1	<0.001
Change in alveolar–arterial oxygen gradient — mm Hg	−6.7±57.5	−60.0±85.1	<0.001
Outcomes in surviving infants			
Length of hospitalization — days	29.5±22.6	36.4±44.8	0.17
Duration of assisted ventilation — days	11.7±13.0	11.6±7.0	0.97
Air leak after randomization — no. (%)	5 (5.1)	5 (5.2)	0.96
Bronchopulmonary dysplasia — no. (%)†	12 (11.9)	15 (15.3)	0.48

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TABLE 4. RESPONSES TO THE INITIAL ADMINISTRATION OF 20-ppm NITRIC OXIDE OR OXYGEN, AND SUBSEQUENT RESPONSES TO 80-ppm CONCENTRATIONS OF STUDY GAS BY INFANTS WHOSE RESPONSES TO THE INITIAL TREATMENT WERE LESS THAN COMPLETE.*

VARIABLE	CONTROL GROUP	NITRIC OXIDE GROUP	P VALUE†
	no. of patients (%)		
Response to treatment at 20 ppm			
No. of infants	117	112	
None	87 (74.4)	38 (33.9)	<0.001
Partial	13 (11.1)	17 (15.2)	
Complete	17 (14.5)	57 (50.9)	
Subsequent response to treatment at 80 ppm			
Infants with no response at 20 ppm			
None	64 (73.6)	29 (76.3)	0.30
Partial	5 (5.7)	5 (13.2)	
Complete	12 (13.8)	2 (5.3)	
80 ppm not tried	6 (6.9)	2 (5.3)	
Infants with partial responses at 20 ppm			
None	11 (84.6)	12 (70.6)	0.34
Partial	1 (7.7)	4 (23.5)	
Complete	0	1 (5.9)	
80 ppm not tried	1 (7.7)	0	

LOW-DOSE NITRIC OXIDE THERAPY FOR PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Clark, et al. NEJM. 342(7) 2000.

- Multi-center, randomized, blinded, placebo controlled study
- 248 infants >34 weeks
- Primary outcome – reduce need for ECMO
- Infants with HRF with OI>25
  - Clinical or ECHO evidence of PPHN
  - 5% difference in sats or 2 serious desaturation events

LOW-DOSE NITRIC OXIDE THERAPY FOR PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

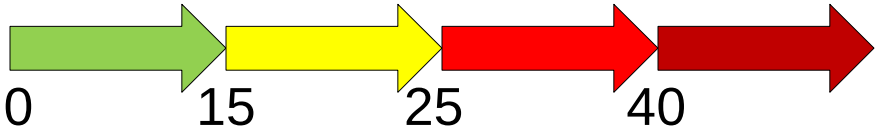
Clark, et al. NEJM. 342(7) 2000.

TABLE 3. OUTCOME ANALYSIS.*

OUTCOME	CONTROL GROUP (N=122)	NITRIC OXIDE GROUP (N=126)	P VALUE
Received extracorporeal membrane oxygenation			
Intention-to-treat analysis — no./total no. (%)	78/122 (64)	48/126 (38)	0.001
Neonates with no protocol violations — no./total no. (%)	74/116 (64)	43/111 (39)	0.001
Died before 30 days of age — no. (%)	10 (8)	9 (7)	0.40
Died before discharge — no. (%)	13 (11)	10 (8)	0.82
Died before discharge or received extracorporeal membrane oxygenation — no. (%)	80 (66)	50 (40)	0.001
Length of stay in the hospital for survivors			
Neonates assessed — no. (%)	104 (85)	113 (90)	0.09
Mean no. of days	29±23	25±15	
Duration of assisted ventilation for survivors			
Neonates assessed — no. (%)	109 (89)	116 (92)	0.40
Mean no. of days	12±10	11±7	
Pulmonary outcome in survivors			
Were receiving supplemental oxygen at 30 days — no./total no. (%)†	22/110 (20)	8/114 (7)	0.02
Received supplemental oxygen after discharge — no./total no. (%)†	12/107 (11)	6/113 (5)	0.14
Intraventricular hemorrhages (more than two) or infarct — no. (%)	8 (7)	4 (3)	0.34
Seizures — no. (%)	1 (1)	1 (1)	0.49

Indications

- Oxygen Index in PPHN



A Randomized Trial of Early Versus Standard Inhaled Nitric Oxide Therapy in Term and Near-Term Newborn Infants With Hypoxic Respiratory Failure

Konduri, et al. Pediatrics 113(3) 2004.

- Multi-center, randomized, blinded, placebo controlled study
- 299 infants >33 weeks (stopped early)
- Primary outcome – reduce death/ECMO
- Infants with HRF with OI between 15 and 25
- Started at 5 ppm and increased to 20 ppm
- "iNO improves oxygenation but does not reduce the incidence of ECMO/mortality when initiated at an OI of 15 to 25 compared with initiation at >25 in term and near-term neonates with respiratory failure."

A Randomized Trial of Early Versus Standard Inhaled Nitric Oxide Therapy in Term and Near-Term Newborn Infants With Hypoxic Respiratory Failure

Konduri, et al. Pediatrics 113(3) 2004.

TABLE 3. Outcome of the Early Administration of Study Gas by Group

Event	Early iNO Group (N = 150)	Control Group (N = 149)	P Value
Death by day 120 or ECMO, *n* (%)	25 (16.7)	29 (19.5)	.530
Death, *n* (%)	10 (6.7)	14 (9.4)	.385
ECMO, *n* (%)*	16 (10.7)	18 (12.1)	.700
Outcomes in surviving infants			
Length of hospitalization, d*	17 (12–27)	18 (12–30)	.51
Duration of assisted ventilation, d*	8 (6–12)	8 (6–13)	.76
Duration of oxygen therapy, d*	13 (9–19)	13 (9–19)	.58
Chronic lung disease, *n* (%)	16 (10.7)	13 (8.7)	.58

* Data are medians with first to third quartile ranges shown in parentheses.

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Konduri, et al. Pediatrics 113(3) 2004.

TABLE 4. Oxygenation Responses to Initial Administration of Study Gas

Variable	Early iNO Group	Control Group	P Value
Response to 5 ppm, *n* (%)			
No. of infants	145	147	
Complete	84 (58)	36 (24)	.001*
Partial	12 (8)	13 (9)	
None	49 (34)	98 (67)	
Change in Pao_2 (mm Hg)†	44 (6 to 111)	8.5 (−8 to 54)	<.0001
Change in OI†	−6.1 (−12 to −1)	−2.2 (−8 to 3)	.0001
Response to 20 ppm, *n* (%)‡			
No. of infants	50	105	
Complete	18 (36)	19 (18)	.002*
Partial	12 (24)	15 (14)	
None	20 (40)	71 (68)	
Change in Pao_2 (mm Hg)†	11 (−3 to 39)	4 (−16 to 28)	.17
Change in OI†	−2.7 (−7 to 1)	−1.6 (−5 to 7)	.17

A Randomized Trial of Early Versus Standard Inhaled Nitric Oxide Therapy in Term and Near-Term Newborn Infants With Hypoxic Respiratory Failure

Konduri, et al. Pediatrics 113(3) 2004.

TABLE 5. Secondary Outcomes of the Study

Variable	Early iNO Group (N = 150)	Control Group (N = 149)	P Value
Duration of study gas administration, h*	57 ± 48	39 ± 38	<.003
Initiation of standard iNO therapy, n (%)*	61 (41)	81 (54)	<.02
Duration of standard iNO therapy, h†	121 (41–175)	100 (56–158)	.52
Progression to OI >40, n (%)	11 (7)	21 (14)	.056

Randomized controlled trial of early compared with delayed use of inhaled nitric oxide in newborns with a moderate respiratory failure and pulmonary hypertension

Gonzalez et al. Journal of Perinatology, 30, 2010

- Multi-center, randomized, open label,study
- 56 infants >34 weeks
- Primary outcome – reduce number of infants who reached OI of 40
- Infants with HRF with OI between 10-30

Randomized controlled trial of early compared with delayed use of inhaled nitric oxide in newborns with a moderate respiratory failure and pulmonary hypertension

Gonzalez et al. Journal of Perinatology, 30, 2010

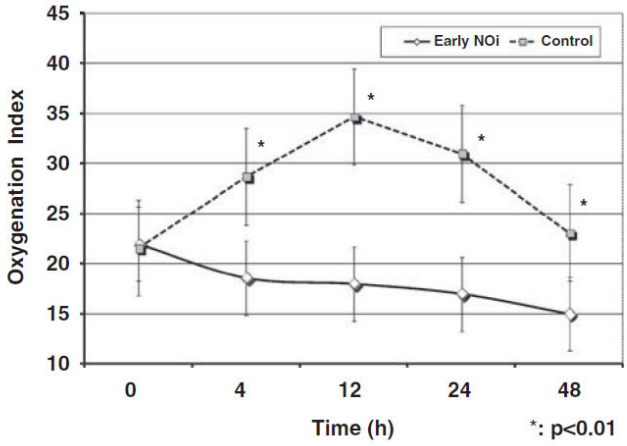

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Table 3 Respiratory outcomes

	Early iNO (n = *28*)	*Controls* (n = *28*)	P-*value*
Treatment failure (OI ⩾40), *n* (%)	7 (25)	17 (61)	<0.05
Deaths (*n*)	1	2	NS
Mech. ventilation days, median (range)	6 (3–28)	8 (4–37)	NS
Oxygen therapy days, median (range)	11.5 (5–90)	18 (6–142)	<0.03
Chronic lung disease, *n* (%)	4/27 (15)	7/26 (27)	NS

Abbreviations: iNO, inhaled nitric oxide; NS, not significant; OI, oxygenation index.

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