INHALED NITRIC OXIDE FOR TREATMENT PERSISTENT PULMONARY HYPERTENSION IN THE NEWBORN

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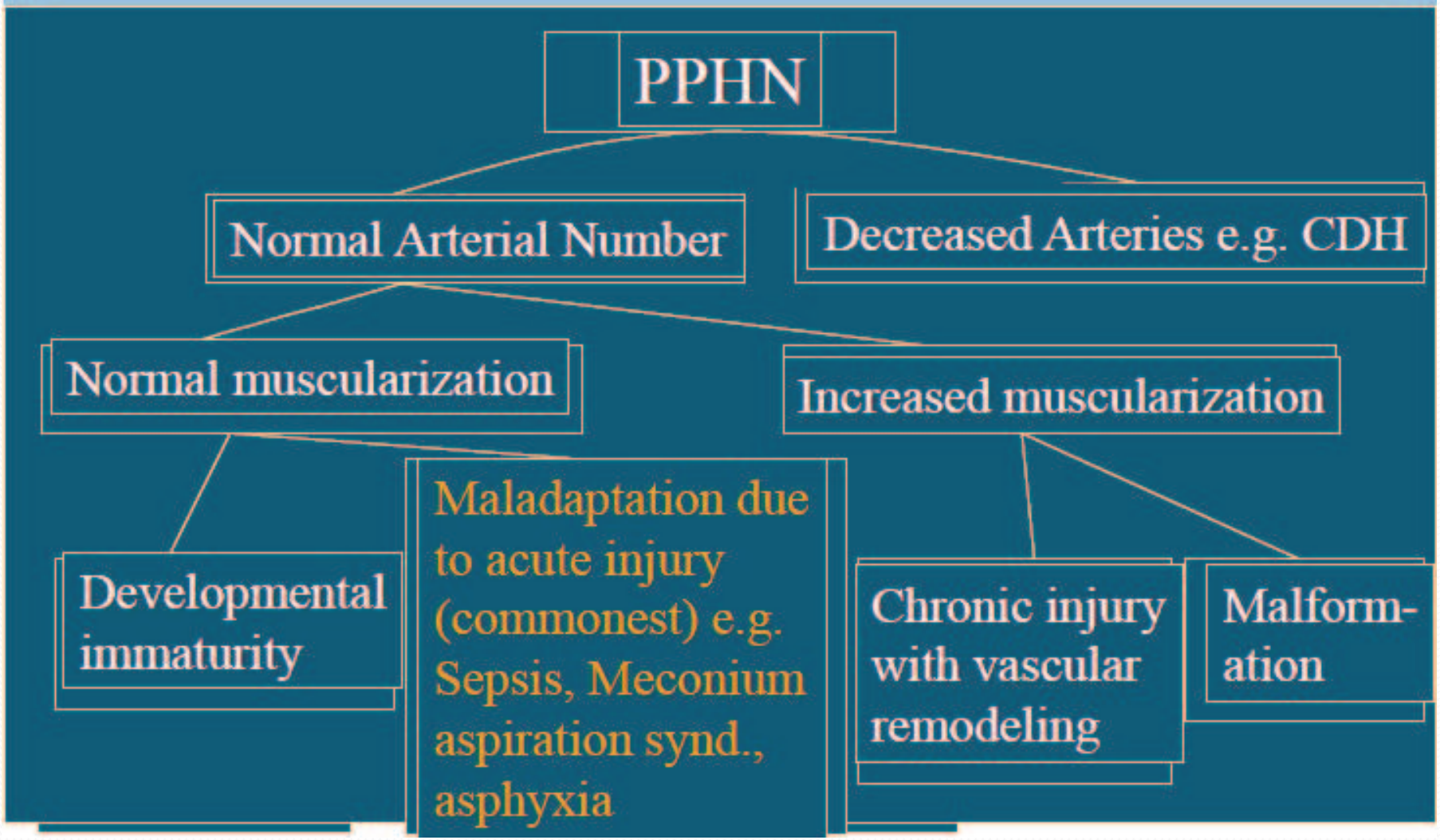
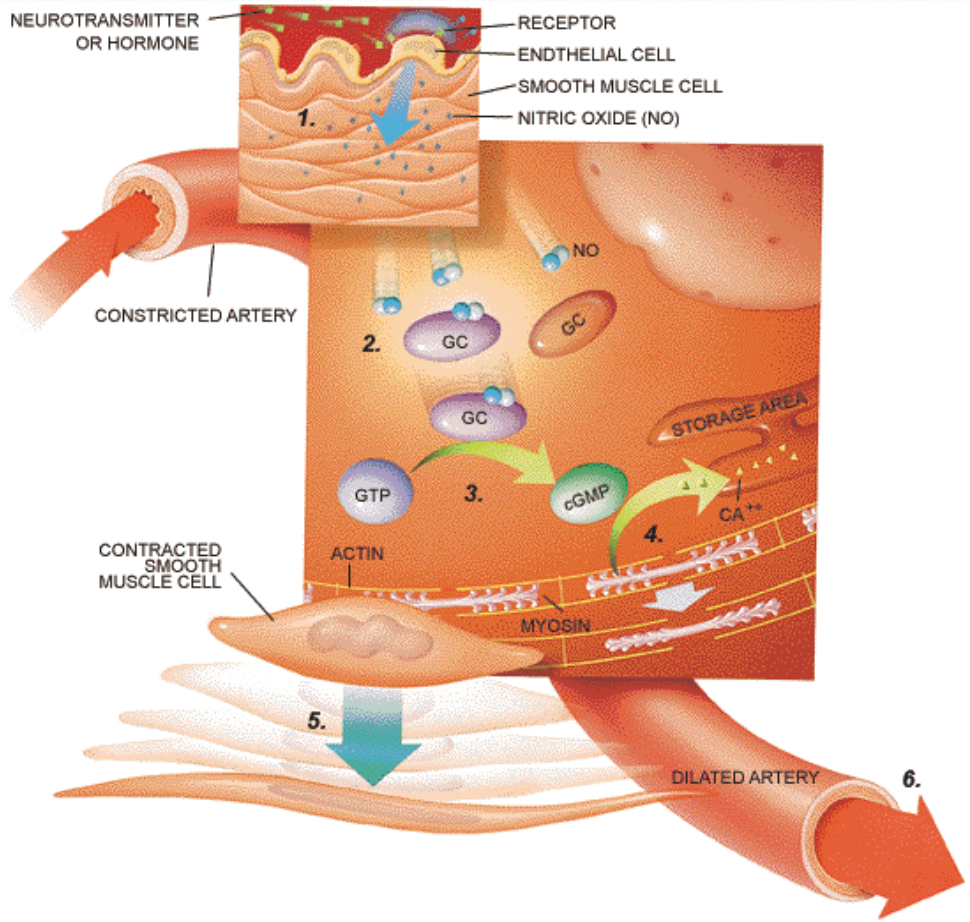
PERSISTENT PULMORNARY HYPERTENSION OF THE NEWBORN (PPHN)

- PPHN : pulmonary vascular resistance (PVR) remains elevated after birth, resulting in right-to-left shunting of blood through fetal circulatory pathways
- Three types of abnormalities of the pulmonary vasculature : underdevelopment, maldevelopment, and maladaptation
- 1.9/ 1000 live births

Causes of PPHN



NITRIC OXIDE



Does Inhaled NO effect in PPHN ?

Nitric oxide for respiratory failure in infants born at or near term : Systematic Review And Meta-Analysis

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

- Methods :
  - 14 RCTs
  - 735 term and near-term infants (> 34 weeks gestation)
  - Newborn infants :hypoxemia cause by lung disease, pulmonary hypertension with right to left shunting, or both
  - Exclude : intracardiac shunting due to structural congenital heart disease

iNO / PPHN

outcome	iNO (N)	Control(N)	mean difference	RR , 95% CI
1. Death or requirement of ECMO	418	335		0.65 (0,55-0,76)
2. Change Oxygenation index **after treatment**	114	119	-15.1[-20.52;-9,68]	
3. Change PaO_2 **after treatment**	114	119	50.4 [32.14; 68,66] mmHg	

iNO/PPHN

Outcome	iNO (N)	Control (N)	RR , 95% CI
4.Neurodevelopmental disability	120	181	0.97(0.66;1.84)
5.Hearing impairment in at least one ear among survivors	75	82	1.14(0.71;1.84)
6.Cerebral palsy among survivors	120	179	1.02(0.49; 2.14)

iNO / Congenital diaphragmatic hernia

Outcome	iNO (N)	Control (N)	Mean Difference	RR , 95% CI
1. Death or requirement of ECMO	38	46		1.09(0.95; 1.26)
2. Change Oxygenation index after treatment	21	23	-6.7[-18.39;4.99]	
3. Change PaO_2 after treatment	21	23	6.7[-2.32; 15.72] mmHg	

CONCLUSIONS(1)

- Near-term and terminfants with hypoxic respiratory failure unresponsive to other therapy, excluding infants with diaphragmatic hernia, should have a trial of inhaled nitric oxide.

Low dose or high dose iNO ?

5 ppm or 20 ppm or 80 ppm

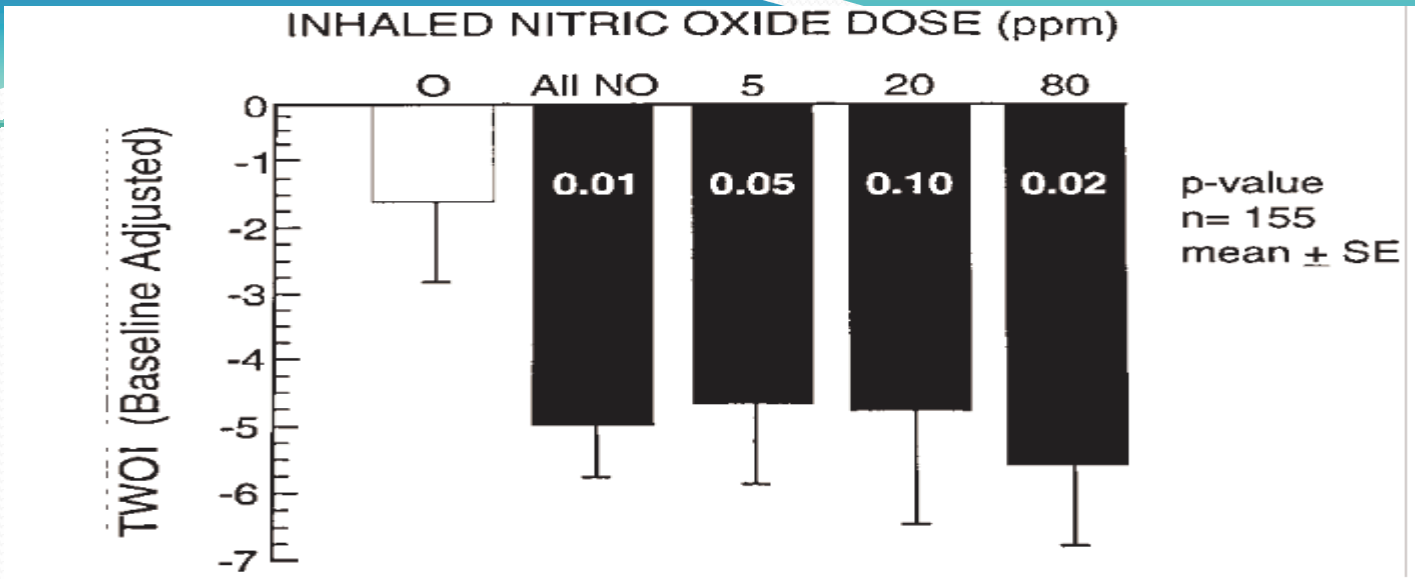


Fig 3. The time-weighted oxygenation index (TWOI) over 24 hours or duration of the treatment gas (control = NO at 0 ppm) whichever came first, for term infants with PPHN. A negative TWOI indicates a sustained improvement in oxygenation from the baseline OI of each treatment group.

- **Efficacy results were similar among NO doses**

Davidson D, Barefield ES, Kattwinkel J, Dudell G, Damask M, Straube R, Rhines J, Chang CT . **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. The I-NO/PPHN Study Group.** Pediatrics. 1998;101(3 Pt 1):325

Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group.

N Engl J Med. 2000;342(7):469

- Methods
  - 248 neonates who were born after 34 weeks' gestation
  - PPHN with OI ≥ 25
  - Low dose iNO : 20 ppm for a maximum of 24 hours, followed by 5 ppm for no more than 96 hours
  - Control : not using iNO

outcome	iNO	Control	P
Need ECMO	48/126(38%)	78/122(64%)	0.001
Mortality after 30 days	similar		
Chronic lung disease developed	7%	20%	0.02

CONCLUSIONS (2) :iNO reduces the extent to which ECMO is needed in neonates with hypoxemic respiratory failure and pulmonary hypertension

Methaemoglobinaemia risk factors with inhaled nitric oxide therapy in newborn infants

Acta Paediatr. 2010;99(10):1467

Methods :

Neonates who were treated with iNO and had at least one MetHb measurement were included.

Demographic characteristics and methods of iNO administration (dosage, duration) at the time of each MetHb measurement were analysed

RESULT

- 442 MetHb measurements from 81 premature and 82 term and near-term infants
- Higher maximum dose of iNO (22.7 vs 17.7 p.p.m) was a significant risk factor for elevated MetHb
- Higher oxygen levels (FiO_2 = 75.5% vs 51.7%) were associated with higher MetHb in term infants
- Preterm infants had no risk for high MetHb when iNO was kept below **8 p.p.m**

- CONCLUSION (3) : High MetHb is exceptional in neonates treated with low dose iNO. Associated risk factors are related to **high iNO dose** and the simultaneous use of **high concentrations of oxygen**

Early versus standard iNO ?

A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure

Pediatrics. **2004**;113(3 Pt 1):559

- Methods :
  - >or =34 weeks' gestation
  - Early iNO : OI 15 -25 on any 2 measurements in a 12-hour interval (150 patients)
  - Control (standard therapy) :OI ≥ 25 were given iNO as (149 paitients)

outcome	Early iNO	Standard iNO
PaO_2 increase > 20 mmHg	73%	37%
Death	6.7%	9.4%
Need ECMO	10.7%	12.1%

CONCLUSION (4) :iNO improves oxygenation but does not reducethe 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

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

J Perinatol. 2010 Jun;30(6):420-4. Epub **2009** Nov 5

- Methods :
  - 56 patients
  - early iNO with 20 ppm (OI 10 – 30, 48h after birth)
  - control (CMV with FiO_2 = 100%)

RESULT

outcome	Early iNO	Control	P
OI > 40	7/28 (25%)	17/28 (61%)	0.05
Mean OI (base 22)	19(4h) 18(24h) 16(48h)	29(4h) 35(12h) 32(24h) 23(48h)	

CONCLUSION (5) :Early use of iNO in newborns with moderate respiratory failure improves oxygenation and decreases the probability of developing severe hypoxemic respiratory failure

CONCLUSION

- iNO effect in PPHN
- Efficacy results were similar among NO doses
- High dose iNO , high concentrations of oxygen : high risk MetHb
- Early use of iNO : improves oxygenation and decreases the probability of developing severe hypoxemic respiratory failure