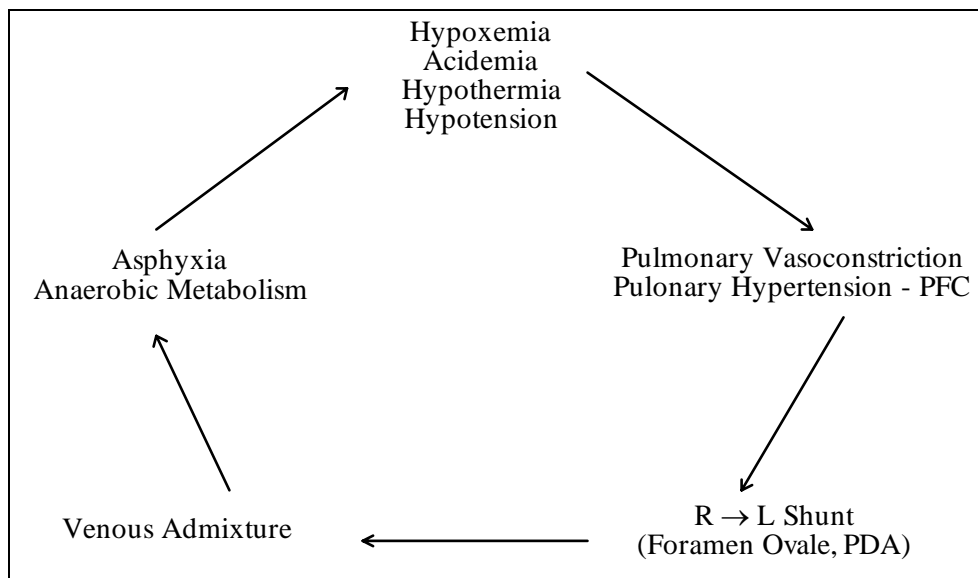

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)

Nitric Oxide Inhalation

DEFINITION

Severe hypoxemic respiratory failure associated with right-to-left shunting of blood across the foramen ovale and/or patent ductus arteriosus.

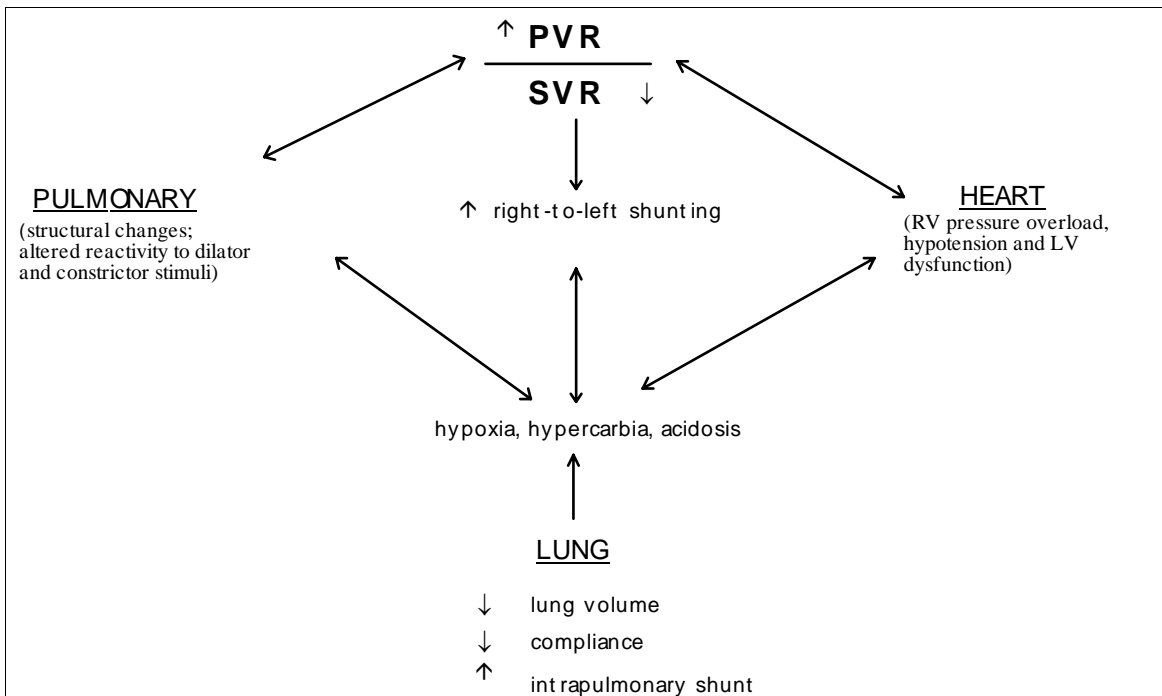
CYCLE OF EVENTS OFTEN PRESENT IN THE SICK NEWBORN INFANT



CLINICAL FACTORS ASSOCIATED WITH PULMONARY HYPERTENSION

- Hypoxia
 - Acidosis
 - Hypotension (systemic)
 - Hypoglycemia
 - Polycythemia
 - Atelectasis
 - Hyperinflation
 - Hypothermia
 - Hypocalcemia
-
-

CARDIOPULMONARY INTERACTIONS IN PPHN



PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; PDA = patent ductus arteriosus; FO = foramen ovale; RV = right ventricular; LV = left ventricular

CLASSIFICATION

- Primary or idiopathic
 - ❖ No parenchymal disease
 - ❖ Very responsive to nitric oxide inhalation
 - ❖ Avoid overdistention
- Secondary
 - ❖ Underlying lung disease (e.g., pneumonia, RDS, meconium)

and/or

 - ❖ Cardiac or hemodynamic disturbances - reduced left ventricular output

CLASSIFICATION - DESCRIPTIONS

- Underdevelopment of pulmonary circulation
 - ❖ Diaphragmatic hernia
 - ❖ Hypoplasia
- Maldevelopment with excessive muscularization of pulmonary arteries

- ❖ Diaphragmatic hernia
 - ❖ Meconium aspiration
 - Maladaptation or failure of reduction of pulmonary vascular resistance
 - ❖ Disorder associated with hypoxia, acidosis
-

CARDIOPULMONARY INTERACTIONS

- Extrapulmonary R → L shunt
 - ❖ Patent ductus arteriosus
 - and/or**
 - ❖ Foramen ovale
 - Intrapulmonary shunt
 - ❖ Adequate ventilation - optimal lung inflation
 - Cardiac disturbance - hemodynamic deterioration
 - ❖ Volume
 - ❖ Systemic vascular resistance - blood pressure
 - ❖ Left ventricular function
-

NITRIC OXIDE - CLINICAL CONDITIONS

- Persistent pulmonary hypertension
 - Perinatal distress
 - Congenital heart disease with pulmonary vascular disease
 - Respiratory distress syndrome
 - Meconium aspiration
 - Bronchopulmonary dysplasia
 - Diaphragmatic hernia - mass, pulmonary hypoplasia
-

SIGNS AND SYMPTOMS IN NEWBORN INFANTS

- Grunting, flaring and retractions, tachypnea
- Cyanosis
- Cardiomegaly uncommon (20-25%)

- Murmur of tricuspid and/or mitral insufficiency
- Hepatomegaly uncommon

DIAGNOSTIC EVALUATION OF THE NEWBORN INFANT WITH CYANOSIS

- History, physical examination
- Serum glucose, calcium; central hematocrit; WBC with differential; platelet count
- Arterial blood gases
 - ❖ 100% oxygen - PaO₂ above 770-100 mmHg (excludes most congenital heart defects)
 - ❖ Right radial, descending aorta (DA) - simultaneous PaO₂
 - Right radial exceeds DA PaO₂ by 10-20 mmHg in persistent pulmonary hypertension
 - ❖ Pulse oximetry: Preductal (right finger) oxygen saturation (SaO₂) exceeds postductal (toe) SaO₂ by ≥5%
 - ❖ Hyperventilation - usually PaO₂ increases with lung disease

Oxygen Concentration (%)	Ventilator Status	PaCO ₂ Goal	PaO ₂ Values		
			PPH	Lung Disease	R → L Cardiac
21% - Room Air	Spontaneous	40	40	40	40
100% - Hyperoxia	Spontaneous or MV ^a	40	40	>100	40
100% - Pre- and Post-ductal Shunt	Spontaneous or MV	40	>10-15 ^b	<5 ^c	<5
100% - Hyperoxia, Hyperventilation	MV	20-25	>100	>150	40
a MV - Mechanical Ventilation			b > Greater Than		c < Less Than

- Chest x-ray
- Electrocardiogram
- Echocardiogram - very important
- PGE1 infusion and possibly cardiac catheterization if congenital heart disease cannot be excluded

- Pulmonary vasodilator as nitric oxide inhalation if congenital heart disease excluded; monitor for toxicity

MANAGEMENT OF THE NEWBORN INFANT WITH PERSISTENT PULMONARY HYPERTENSION

- Avoid aspirin near delivery
 - ❖ Low-dose aspirin probably not a problem
- Indomethacin—preterm labor inhibitor
 - ❖ Monitor ductus arteriosus patency
- Prevent perinatal stress
- Immediate resuscitation, stabilization
- Correct metabolic, hematologic abnormalities
- Correct hypotension
 - ❖ Colloid
 - ❖ Inotropic agents
 - Dopamine (2-20 $\mu\text{g}/\text{kg}/\text{min}$)
 - Dobutamine (10-25 $\mu\text{g}/\text{kg}/\text{min}$)
- Maintain $\text{SaO}_2 \geq 95\%$, PaO_2 above 70
 - ❖ FIO_2 often 1.0
 - ❖ Hyperventilation to $\text{pH} > 7.50$
 - ❖ NaHCO_3 to $\uparrow \text{pH}$
- Surfactant administration
- Suggested initial ventilatory settings — conventional
 - ❖ $\text{FIO}_2 = 1.0$
 - ❖ Rate = 40-75
 - ❖ P-max = 25-50 cm H_2O
 - ❖ PEEP = 5-7 cm H_2O
 - ❖ Inspiratory time = 0.3-0.4
- High-frequency ventilation (oscillatory) - suggested initial settings
 - ❖ Hertz = 10-14
 - ❖ Amplitude = 45-50
 - ❖ $\text{FIO}_2 = 1.0$
 - ❖ MAP = 20-34
- Analgesia, sedation — Fentanyl (3-10 $\mu\text{g}/\text{kg}/\text{hour}$); neuromuscular blocking agent
- Pulmonary vasodilator — nitric oxide inhalation (10-20 ppm)
- Prostaglandin E1 — 0.05-0.1 $\mu\text{g}/\text{kg}/\text{min}$ (if cyanotic congenital heart disease is suspected)
- ECMO if failure to respond to 100% oxygen, alkalosis and nitric oxide

$$\text{Oxygenation Index } \frac{(\text{MAP} \times \text{FIO}_2 \times 100)}{\text{postductal PaO}_2} \geq 40-45$$

- Slowly wean oxygen, ventilatory support

IDEAL PULMONARY VASODILATOR

- Lower pulmonary vascular resistance
- No systemic vasodilation
 - ↓
 - Increase in cardiac output
 - Increase in pulmonary blood flow
 - Increase in oxygenation

FACTORS THAT MODULATE PULMONARY VASCULAR RESISTANCE (PVR)

<u>Lowers PVR</u>	<u>Increases PVR</u>
Endogenous mediators and mechanisms	Endogenous mediators and mechanisms
Oxygen	Hypoxia
Nitric oxide	Acidosis
Prostaglandin I ₂ , E ₂ , D ₂	Endothelin-1
Adenosine, adenosine triphosphate, magnesium	Leukotrienes
Bradykinin	Thromboxanes
Atrial natriuretic factor	Platelet activating factor
Alkalosis	Ca ⁺⁺ channel activation
K ⁺ channel activation	α-adrenergic stimulation
Histamine	Prostaglandin F _{2α}
Vagal nerve stimulation	Mechanical factors
Acetylcholine	Overinflation or underinflation
β-adrenergic stimulation	Excessive muscularization, vascular remodeling
Mechanical factors	Altered mechanical properties of smooth muscle
Lung inflation	— Pulmonary hypoplasia
Vascular cell structural changes	Alveolar capillary dysplasia
Interstitial fluid and pressure changes	Pulmonary thromboemboli
Shear stress	Main pulmonary artery distention
	Ventricular dysfunction, venous hypertension

NITRIC OXIDE OR ENDOTHELIUM DERIVED RELAXATION FACTOR

RAPID and **SELECTIVE** for Pulmonary Vasculature

- L-arginine Nitric oxide synthase → nitric oxide
- Nitric oxide diffuses into adjacent smooth muscle and stimulates guanylate cyclase to produce cyclic GMP
- Nitric oxide then diffuses into vascular space
- Inactivated upon binding with hemoglobin
- Inhibits platelet aggregation, adhesion
- T 1/2 < 1 second
- Final denominator for action of local vasodilators

STIMULI FOR RELEASE OF NITRIC OXIDE (NO)

- Shear stress*
- Oxygen
- Ventilation inflation
- Adenosine diphosphate*
- Bradykinin*

*↑ intracellular Ca⁺⁺ → ↑NO synthase

NITRIC OXIDE INSUFFICIENCY

Pulmonary Hypertension - Endothelial Dysfunction

- Vasoconstriction*
- In situ thrombosis*
- Proliferation of vascular smooth muscle*
- Thrombosis
- Microvascular permeability (↑)
- Adhesion of leukocytes

* ↓ NO, ↓ prostacyclin, ↑ endothelin - 1

POTENTIAL BENEFITS OF NITRIC OXIDE

- Reduced inspired oxygen
 - Reduced ventilator requirements
 - Reduced need for high-frequency ventilation
 - Reduced need for ECMO support
 - Reduced air leak syndrome
 - Reduced morbidity (PBD, CNS, hearing)
 - Improved survival
-

NITRIC OXIDE THERAPY

- Dosage: 5→10→20→40 ppm (?)
 - Ventilation: Ensure optimal ventilation - lung inflation
 - ❖ Optimize ventilation - perfusion matching
 - ❖ High-frequency ventilation - oscillation, jet
 - Length: 2 days - 21 days
 - ❖ 0.3-1 ppm may be needed for several days
 - Down regulation of endogenous NO synthesis?
 - Responses (O₂): None - gradual - rapid (full- or near-term infants)
 - ❖ Suboptimal - transient, optimal - sustained
 - ❖ No response - severe parenchymal disease without extrapulmonary shunt
 - Premature infant: Trials underway
 - ❖ Extrapulmonary shunting
 - ❖ Deterioration after surfactant
 - ❖ Low-dose inhalation
-

NITRIC OXIDE TOXICITY

- Monitor NO₂, methemoglobin levels

- Inhibition of DNA synthesis ?
 - Prolongation of bleeding time (30-300 ppm)
 - ❖ Inhibition of platelet adhesion
 - ❖ Effect on preterm infants
 - Surfactant inactivation ?
 - Pulmonary inflammatory cell dysfunction ?
-

QUESTIONS ABOUT NITRIC OXIDE (NO)

- Effect of NO in specific neonatal lung disorders (e.g., BPD, meconium aspiration, pneumonia, diaphragmatic hernia) ?
 - Effect of chronic NO exposure on damaged airways of newborn infants ?
 - Effect of NO on hyperoxic lung damage from hyperoxia ?
 - Effect of superoxide dismutase on action of NO (prolongation ?)
 - Effect of NO on WBC endothelial cell adhesion in sepsis ?
 - Inherited or acquired defect in NO production (like pyloric stenosis) /
 - Can NO be induced ?
 - Does inhaled NO reduce endogenous NO ?
 - Best methods to administer NO, eliminate nitrogen dioxide ?
 - Optimum concentration of inhaled NO ?
-

OTHER POTENTIAL AGENTS TO USE WITH NITRIC OXIDE

- Phosphodiesterase inhibitor (e.g., dipyridamole)
 - Prostacyclin I₂ - aerosol ?
 - Tolazoline (ET tube) - ?
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REFERENCES

- Abman S, et al. Inhaled nitric oxide in the management of a premature newborn with severe respiratory distress and pulmonary hypertension. *Pediatrics* 92:606, 1993.
- Abman SH, Kinsella JP. Nitric oxide in the pathophysiology and treatment of neonatal pulmonary hypertension. *Neonatal Respir Dis* 4(2), 1994

- Abu-Osba YK. Treatment of persistent pulmonary hypertension of the newborn: update. *Arch Dis Child* 66:74, 1991.
- Abu-Osba YK, et al. Treatment of severe persistent pulmonary hypertension of the newborn with magnesium sulphate. *Arch Dis Child* 67:31, 1992.
- Baumgart S, et al. Diagnosis-related criteria in the consideration of extracorporeal membrane oxygenation in neonates previously treated with high-frequency jet ventilation. *Pediatrics* 89:491, 1992.
- Benitz WU, et al. Use of sodium nitroprusside in neonates: Efficacy and safety. *J Pediatr* 106:102, 1985.
- Bifano EM, Pfannestiel A. Duration of hyperventilation and outcome in infants with persistent pulmonary hypertension. *Pediatrics* 81:657, 1988.
- Bohn D, et al. Ventilatory predictors of pulmonary hypoplasia in congenital diaphragmatic hernia, confirmed by morphologic assessment. *J Pediatr* 111:423, 1987.
- Bucciarelli RL, et al. Persistence of fetal cardiopulmonary circulation: One manifestation of transient tachypnea of the newborn. *Pediatrics* 58:192, 1976.
- Carter JM, et al. High-frequency oscillatory ventilation and extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure. *Pediatrics* 85:159, 1990.
- Castillo L, et al. Whole body arginine metabolism and nitric oxide synthesis in newborns with persistent pulmonary hypertension. *Pediatr Res* 38:17, 1995.
- Davidson D. NO bandwagon, yet. Inhaled nitric oxide (NO) for neonatal pulmonary hypertension. *Am Rev Respir Dis* 147:1078, 1993.
- Day RW, et al. Acute response to inhaled nitric oxide in newborns with respiratory failure and pulmonary hypertension. *Pediatrics* 98:698, 1996.
- Donn SM. Alternatives to ECMO. *Arch Dis Child* 70:F81, 1994.
- Drummond WH, et al. The independent effects of hyperventilation, tolazoline, and dopamine on infants with persistent pulmonary hypertension. *J Pediatr* 98:603, 1981.
- Dworetz AR, et al. Survival of infants with persistent pulmonary hypertension without extracorporeal membrane oxygenation. *Pediatrics* 84:1, 1989.
- Ferrara TB, et al. Efficacy and neurologic outcome of profound hypocapneic alkalosis for the treatment of persistent pulmonary hypertension in infancy. *J Pediatr* 105:457, 1984.
- Finer NN, et al. Inhaled nitric oxide in infants referred for extracorporeal membrane oxygenation: Dose response. *J Pediatr* 124:302, 1994.
- Fox WW, Duara S. Persistent pulmonary hypertension in the neonate: Diagnosis and management. *J Pediatr* 103:505, 1983.
- Fratacci MD, et al. Inhaled nitric oxide: a selective pulmonary vasodilator of heparin-protamine vasoconstriction in sheep. *Anesthesiology* 75:927, 1991.
- Frostell CG, et al. Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 83:2038, 1991.
- Galantowicz ME, et al. Differential effects of alveolar and arterial oxygen tension on pulmonary vasomotor tone in ECMO-perfused, isolated piglet lungs. *J Pediatr Surg* 26:312, 1991.
- Geggel RL. Inhalational nitric oxide: A selective pulmonary vasodilator for treatment of persistent pulmonary hypertension of the newborn. *J Pediatr* 123:76, 1993.
- Gersony WM. Persistence of the fetal circulation: A commentary. *J Pediatr* 82:1103, 1973.
- Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* 333:214, 1995.
- Goetzman BW, et al. Neonatal hypoxia and pulmonary vasospasm: Response to tolazoline. *J Pediatr* 89:617, 1976.
- Goldman AP, et al. Four patterns of response to inhaled nitric oxide for persistent pulmonary hypertension of the newborn. *Pediatrics* 98:706, 1996.
- Haworth SG. Normal structural and functional adaptation to extrauterine life. *J Pediatr* 98:915, 1981.
- Haworth SG, Reed L. Persistent fetal circulation. newly recognized structural features. *J Pediatr* 88:614, 1976.
- Hendricks-Muñoz KD, Walton JP. Hearing loss in infants with persistent fetal circulation. *Pediatrics* 81:650, 1988.
- Henneberg SW, et al. Inhalation of nitric oxide as a treatment of pulmonary hypertension in congenital diaphragmatic hernia. *J Pediatr Surg* 30:853, 1995.
- Heritage CK, Cunningham MD. Association of elective repeat Cesarean delivery in persistent pulmonary hypertension of the newborn. *Am J Obstet Gynecol* 152:627, 1985.
- Karamanoukian HL, et al. Inhaled nitric oxide in congenital hypoplasia of the lungs due to diaphragmatic hernia or oligohydramnios. *Pediatrics* 94:715, 1994.

Keszler M, et al. Severe respiratory failure after elective repeat cesarean delivery: A potentially preventable condition leading to extracorporeal membrane oxygenation. *Pediatrics* 89:670, 1992.

Kinsella JP, Abman SH. Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn. *J Pediatr* 126:853, 1995.

Kinsella JP, et al. Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of inhaled nitric oxide. *J Pediatr* 123:103, 1993.

Konduri GG, Woodard LL. Selective pulmonary vasodilation by low-dose infusion of adenosine triphosphate in newborn lambs. *J Pediatr* 119:94, 1991.

Levin DL. Primary pulmonary hypoplasia. *J Pediatr* 95:550, 1979.

Levin DL, et al. Persistent pulmonary hypertension of the newborn infant. *J Pediatr* 89:626, 1976.

Levin DL, et al. Fetal hypertension and the development of increased pulmonary vascular smooth muscle: A possible mechanism for persistent pulmonary hypertension of the newborn infant. *J Pediatr* 92:265, 1976.

Loscalzo J. Nitric oxide and vascular disease. *N Engl J Med* 333:251, 1995.

Macdonald PD, Yu VYH. Simultaneous measurement of preductal and postductal oxygen saturation by pulse oximetry in hyaline membrane disease. *Arch Dis Child* 6;7:1166, 1992.

Malik AB, Kidd BSC. Independent effects of changes in H⁺ and CO₂ concentrations on hypoxic pulmonary vasoconstriction. *J Appl Physiol* 34:318, 1973.

Maron MJ, et al. Hearing and neurodevelopmental outcome in survivors of persistent pulmonary hypertension of the newborn. *Pediatrics* 90:392, 1992.

Mupanemunda RH, Edwards AD. Treatment of newborn infants with inhaled nitric oxide. *Arch Dis Child* 72:F131, 1995.

Murphy JD, et al. The structural basis of persistent pulmonary hypertension of the newborn infant. *J Pediatr* 98:962, 1981.

O'Rourke PP, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: A prospective study. *Pediatrics* 84:957, 1989

Pearl G. Inhaled nitric oxide. The past, the present, and the future. *Anesthesiology* 78:413, 1993.

Peckham GJ, Fox WW. Physiologic factors affecting pulmonary artery pressure in infants with persistent pulmonary hypertension. *J Pediatr* 93:1005, 1978.

Perkin RM, Anas NG. Pulmonary hypertension in pediatric patients. *J Pediatr* 105:511, 1984.

Reimenschneider TA, et al. Disturbances of the transitional circulation: Spectrum of pulmonary hypertension and myocardial dysfunction. *J Pediatr* 89:622, 1976.

Roberts JD, et al. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 340:818, 1992.

Roberts JD, Shaul PW. Advances in the treatment of persistent pulmonary hypertension of the newborn. *Ped Clin North Am* 40:983, 1993.

Rosenberg A. Response of the cerebral circulation to hypocarbia in postasphyxia newborn lambs. *Pediatr Res* 32:537, 1992.

Rowe RD. Abnormal pulmonary vasoconstriction in the newborn. *Pediatrics* 59:318, 1977.

Rudolph AM. High pulmonary vascular resistance after birth. *Clin Pediatr* 19:585, 1980.

Rudolph AM, Yuan S. Response of the pulmonary vasculature to hypoxia and H⁺ ion concentration changes. *J Clin Invest* 45:399, 1966.

Segall ML, et al. Thrombocytopenia and pulmonary hypertension in the perinatal aspiration syndromes. *J Pediatr* 96:727, 1980

Sell EJ, et al. Persistent fetal circulation: Neurodevelopmental outcome. *Am J Dis Child* 139:25, 1985.

Shah N, et al. Inhaled nitric oxide in congenital diaphragmatic hernia. *J Pediatr Surg* 29:1010, 1994.

Soifer SJ, et al. Prostaglandin D₂ reverses induced pulmonary hypertension in the newborn lamb. *J Pediatr* 100:458, 1982.

Spitzer AR, et al. Pulmonary hypertension and persistent fetal circulation in the newborn. *Clin Perinatol* 15:389, 1988.

Stevenson DK, et al. Refractory hypoxemia associated with neonatal pulmonary disease: The use and limitations of tolazoline. *J Pediatr* 95:595, 1979.

Walsh-Sukys MC. Persistent pulmonary hypertension of the newborn. The black box revisited. *Clin Perinatol* 20:127, 1993.

Walsh-Sukys MC, et al. Severe respiratory failure in neonates: Mortality and morbidity rates and neurodevelopmental outcomes. *J Pediatr* 125:104, 1994.

- Walther FJ, et al. Persistent pulmonary hypertension in premature neonates with severe respiratory distress syndrome. *Pediatrics* 90:899, 1992.
- Whitelaw A, et al. Hypocapnia and cerebral ischaemia in hypotensive newborn piglets. *Arch Dis Child* 66:1110, 1991.
- Wiswell TE, et al. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. *Pediatrics* 98:918, 1996.
- Wu, T-J, et al. Persistent pulmonary hypertension of the newborn treated with magnesium sulfate in premature neonates. *Pediatrics* 96:472-1995.
- Wung J-T, et al. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. *Pediatrics* 76:488, 1985.

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