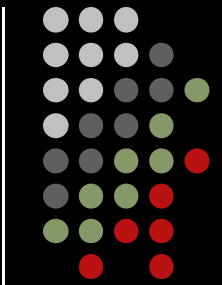
TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER™

Department of Neonatology
Persistent Pulmonary Hypertension of the Newborn

Jesus Peinado PGY2

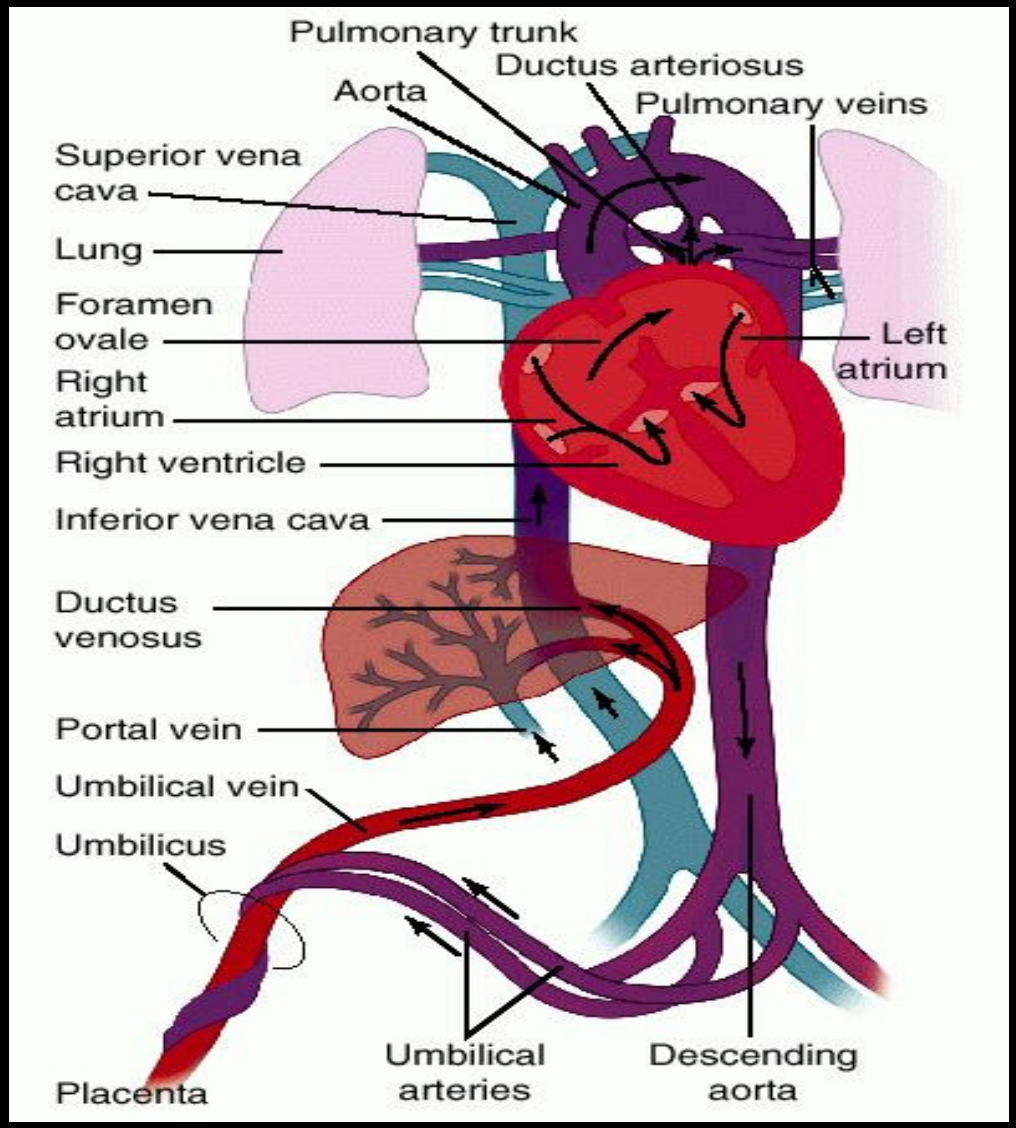
Feb 2009

Transitional Physiology

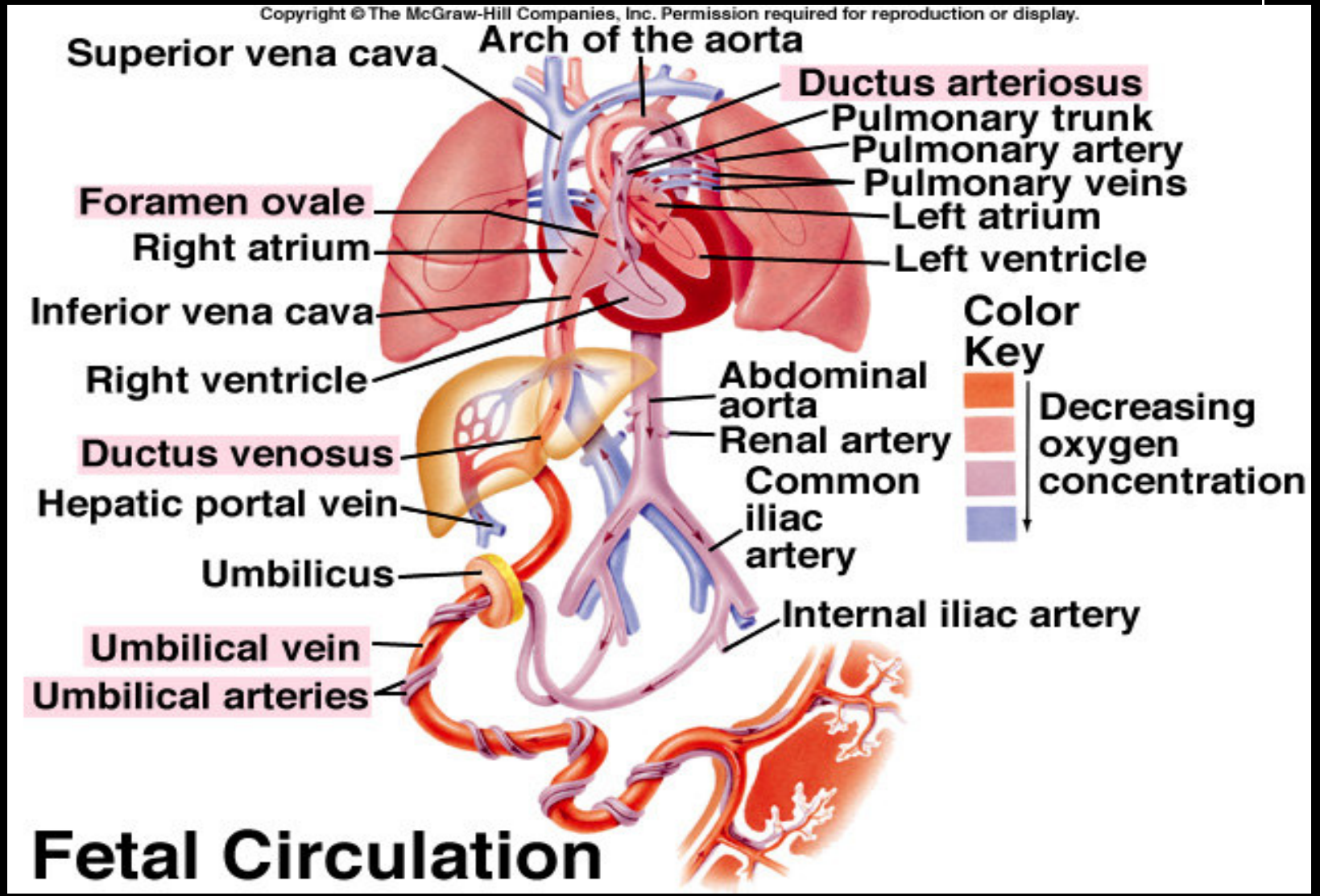


- The process of postnatal circulatory adjustments made by the newborn
- It is the most dramatic event in human physiology
- Converts high PVR to low PVR of the postnatal lung
- 8-10 fold increase in pulmonary blood flow

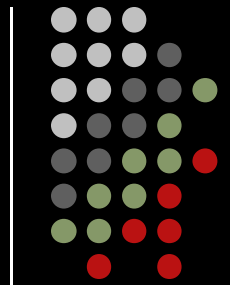
Fetal Circulatory Anatomy



Fetal Circulation

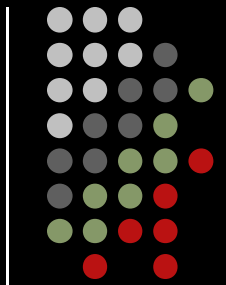


Events Critical to Postnatal Circulation



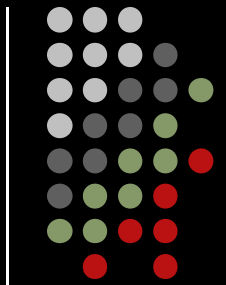
- Ventilation
- Oxygenation
- Cord clamping

Ventilation



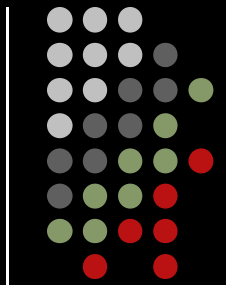
- Clears fetal lung fluid
- Establishes functional residual capacity
- Creates a fluid-gas interface w/in the alveolus
- Reduces pressure on pulmonary capillary beds
- Stimulates surfactant production
- Increases pulmonary blood flow

Ventilation



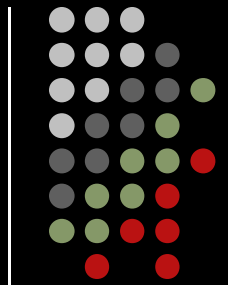
- Increases pulmonary venous return
- Increases left ventricular output
- Increases oxygen tension
- Stimulates pulmonary stretch receptors
- Produces reflex vasodilatation of the peripheral vascular beds

Oxygenation



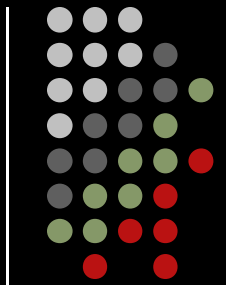
- Increases oxygen tension
- Further reduces pulmonary vascular resistance
- Increases pulmonary blood flow
- Increases venous return
- Increases left atrial pressure
- Functionally closes the foramen ovale
- Decreases ductal level shunting

Cord Clamping



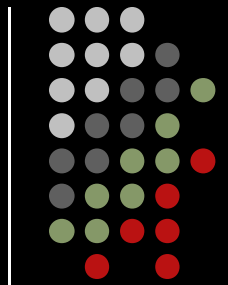
- Removes low resistance placenta
- Increases systemic vascular resistance

Mediators of fetal Pulmonary Vasoconstriction



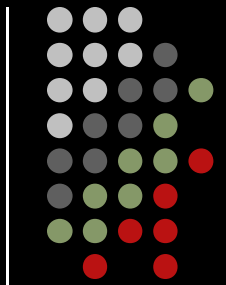
- Vasoconstrictors maintain elevated PVR
- Cyclooxygenase products of Arachidonic acid
- Leukotrienes
- Cytochrome P450 metabolites
- Isoprostanes
- Endothelins
- Rho/Rho Kinase

Mediators of Fetal Pulmonary Vasodilatation



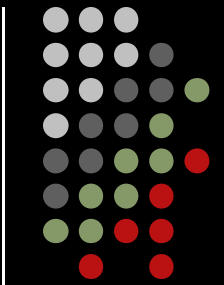
- Cyclooxygenase-dependent Vasodilators
- Nitric Oxide

Factors Involved in Failed Circulatory Adaptation



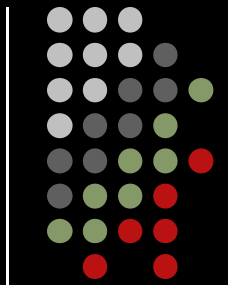
- Hypoxia
- pH
- Hypothermia and polycythemia
- Atelectasis
- Pulmonary hypoplasia/structural changes
- Impact of postnatal age

Epidemiology



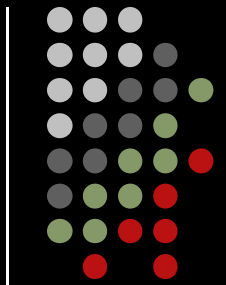
- Respiratory failure is a common reason for admission to NICU
- Accounts for 30-50% of neonatal mortality
- Severe respiratory failure occurs in 2% of NB
- 30% are born at or near full-term
- 50% of infants 34 wks requiring ventilation will display ECHO findings of elevated pulmonary artery pressure

Epidemiology



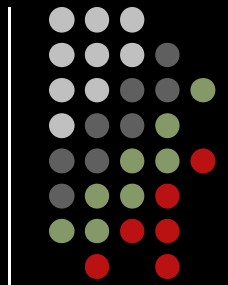
- PPHN occurs in 2-6/1000 live births
- Accounts for up to 10% of NICU admissions
- PPHN carries a mortality rate of 11%
- Results in > 900 deaths each year

Presentation



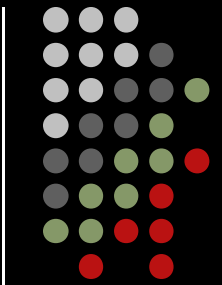
- Any infant manifesting hypoxemia
- A single, loud 2nd heart sound
- 5% or more in pre- and post-ductal sats
- Clinical assessment w/ hyperoxia test

Etiology



- Underdevelopment
- Maldevelopment
- Maladaptation

Underdevelopment



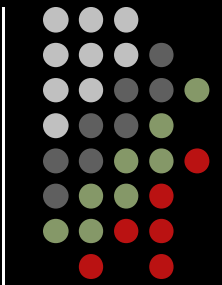
- The cross sectional area of the pulmonary vasculature is reduced
- There is fixed elevation of PVR

Examples

CDH, cystic adenomatoid malformation of the lung, renal agenesis, oligohydramnios w/ obstructive uropathy and IUGR

- The adaptive mechanism is limited: high mortality

Maldevelopment

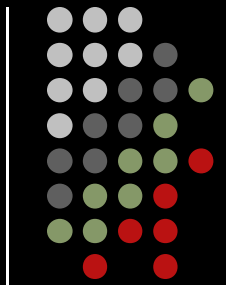


- Normal development of the lung
- Normal branching and alveolar differentiation
- Normal number of pulmonary vessels

BUT

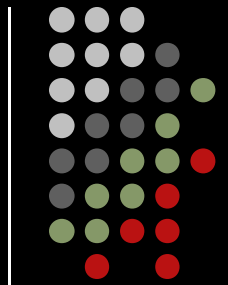
- Muscle layer and arterioles abnormally thick
- Extends into small vessels w/ thin walls and no muscle cells
- Extracellular matrix is excessive

Mechanisms



- Higher concentrations of endothelin-1
- Lower concentrations of cGMP
- Genetic predisposition
- Post-term delivery
- MAS
- Premature closure of the ductus arteriosus

Maladaptation

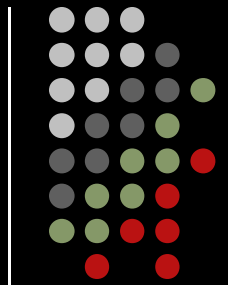


- The pulmonary vascular bed is normally developed

However

- Adverse perinatal conditions lead to vasoconstriction
- Interference with normal postnatal fall in PVR

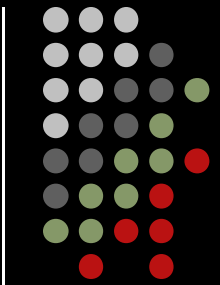
Maladaptation



Conditions

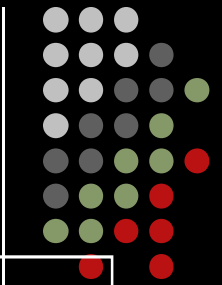
- Perinatal depression
- Pulmonary parenchymal diseases
- Bacterial infections

Clinical Management / Therapeutic Interventions



- Oxygen therapy
- Hyperventilation and alkaline infusion
- Sedation and paralysis
- Tolazoline
- Magnesium sulfate

Evidence-based Therapies

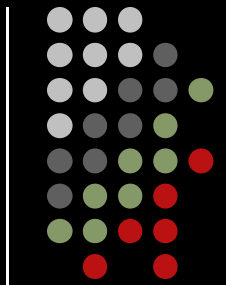


- Inhaled Nitric Oxide
- Surfactant therapy

Novel and Experimental Therapies

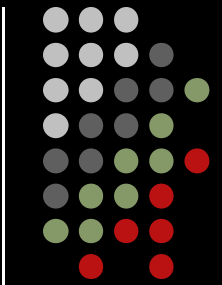
- Alternative means of delivering NO
- Phosphodiesterase inhibitors
- L-Arginine therapy/L Citrulline therapy
- Antioxidant therapy

Surfactant Therapy



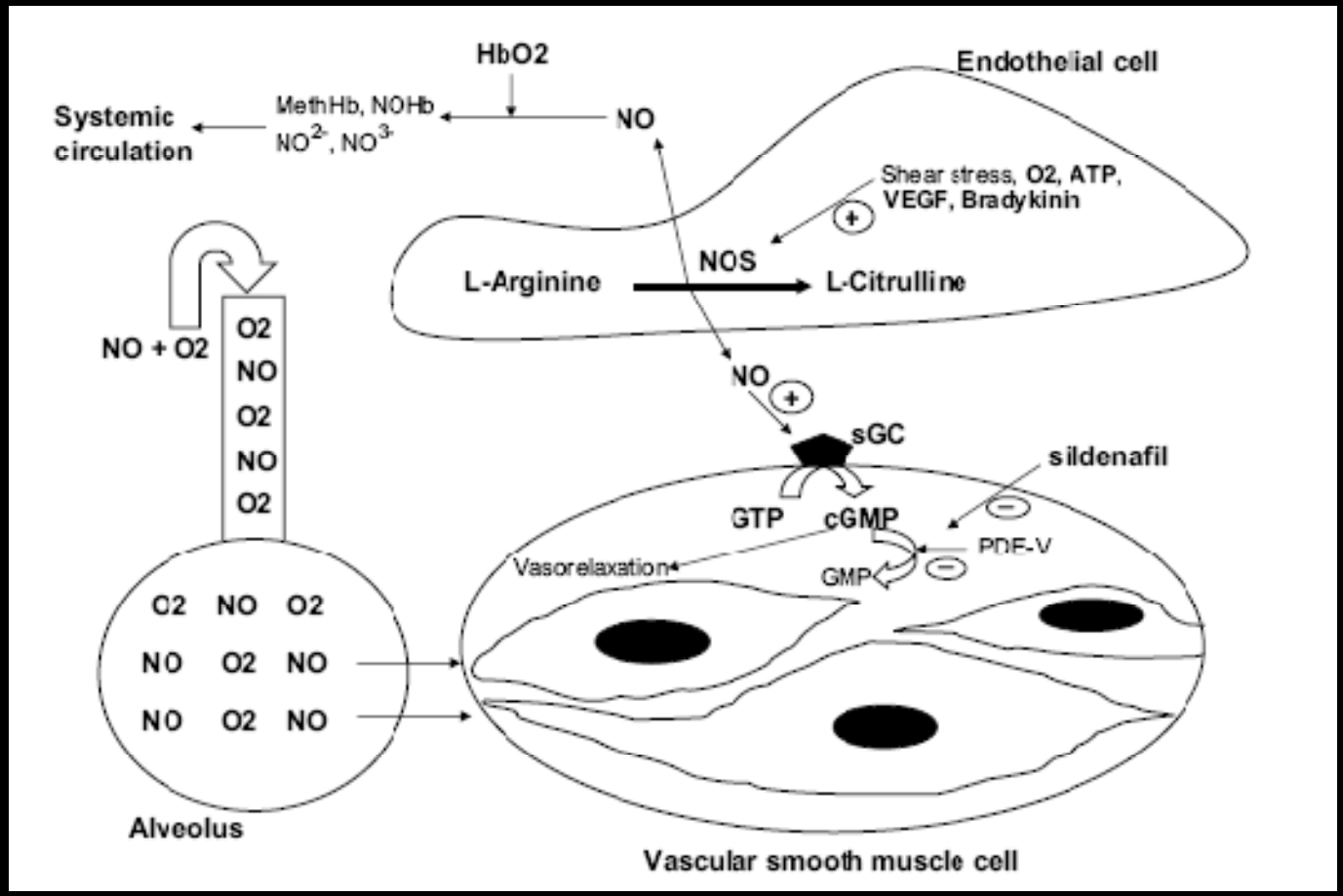
- As adjunctive treatment for severe hypoxemic respiratory failure
- Associated with improvement in infants w/ MAS and pneumonia
- Reduces the duration of ECMO

Nitric Oxide

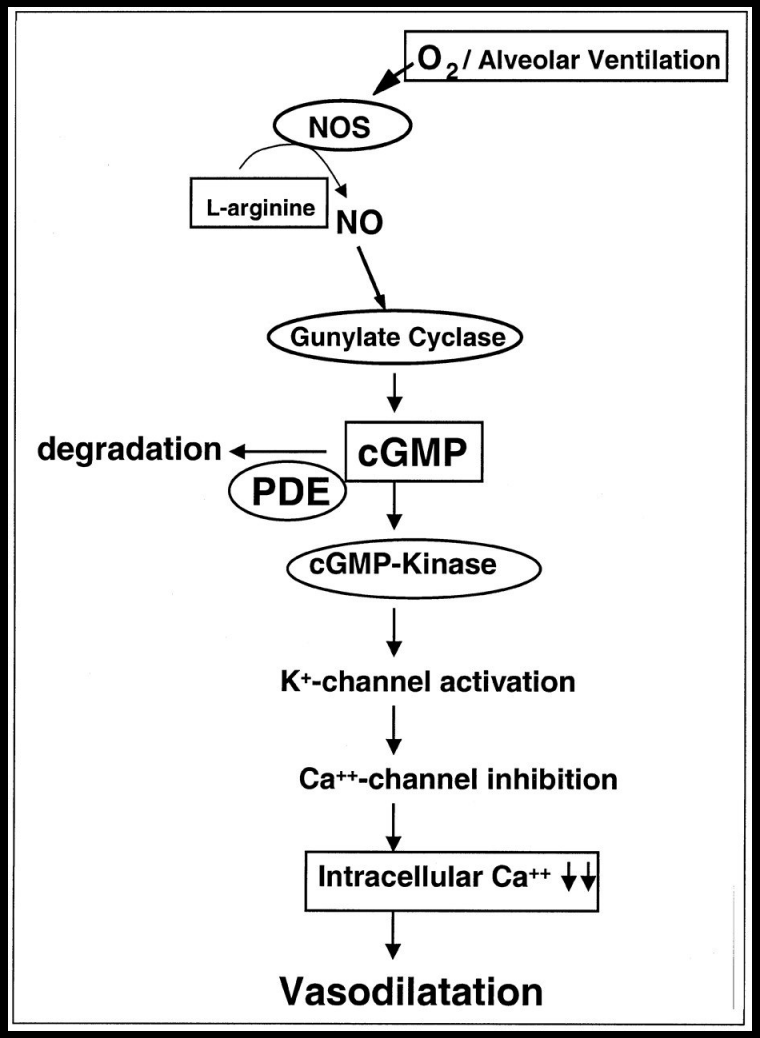


- FDA approved in 1999 iNO for treatment
- The first evidence-based medical therapy
- Criteria for eligibility OI
- OI of 25 → 50% risk of ECMO or dying
- OI of 40 → ECMO therapy
- MAP, pneumonia, HMD and idiopathic PPHN >65 % of patients will respond
- CDH < 35% will respond to iNO

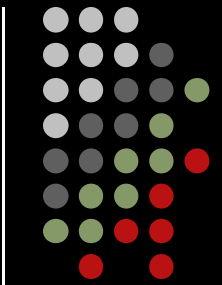
Biology of Nitric Oxide



Scheme of nitric oxide (NO) metabolism pathway

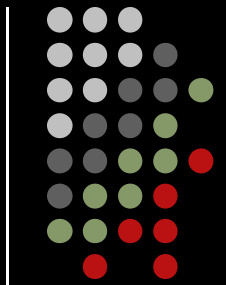


Isoforms



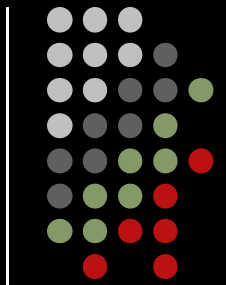
- Neuronal NOS (NOS-1) → Expressed in the airway epithelium → calcium dependent
- Inducible NOS (NOS-2) → in the airway, vascular smooth muscle and macrophages → calcium independent
- Endothelial NOS (NOS-3) → in the vascular endothelium and airway epithelial cells → calcium dependent

Short Term Benefits of NO



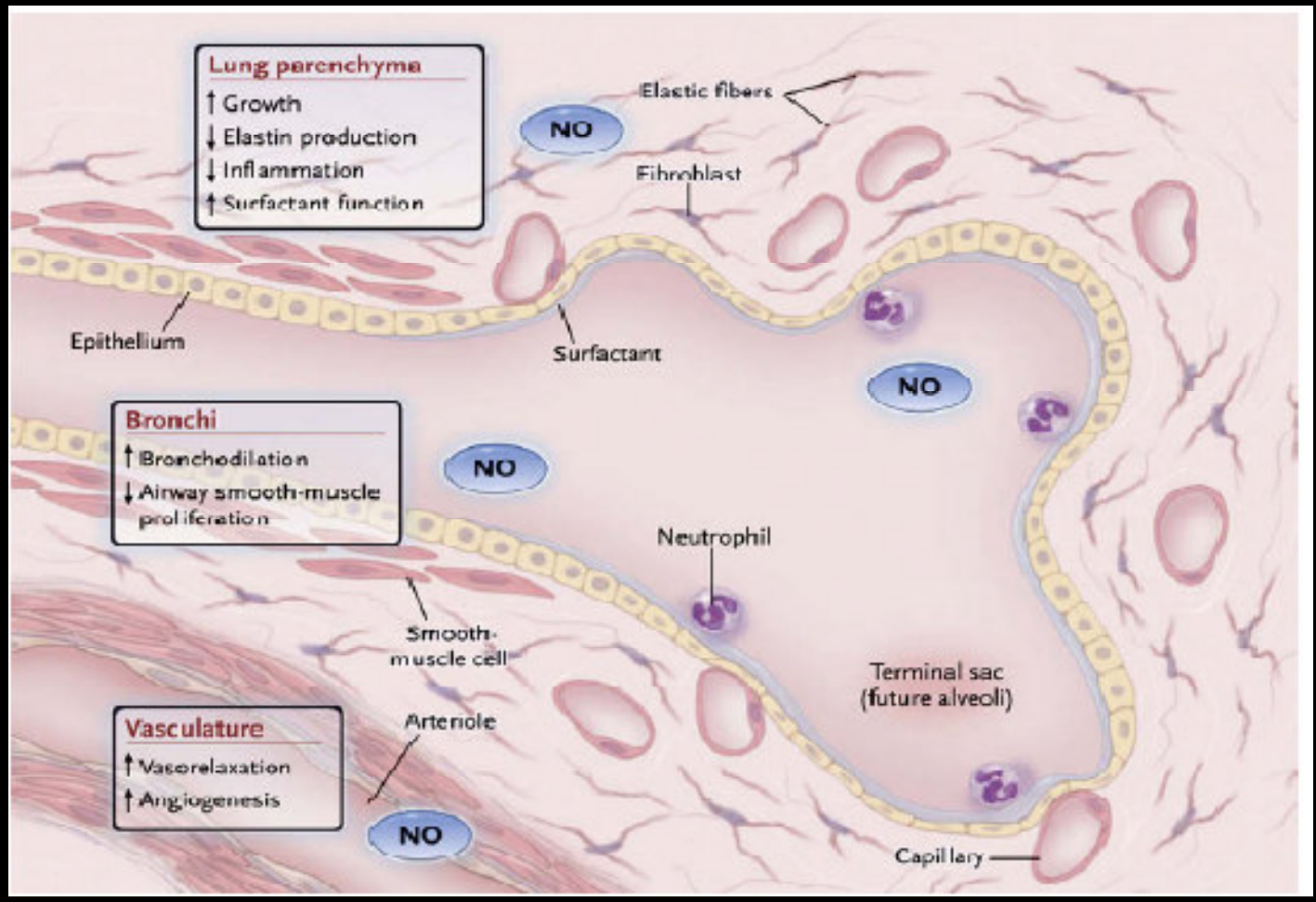
- Selective pulmonary vasodilatation
- Improvement in V/Q matching
- Decreased neutrophil accumulation and activation
- Improvement in oxygenation in hypoxic respiratory failure

Long-term Benefits of NO



- Reduced need for oxygen
- Decrease in oxidant stress
- Improved surfactant function
- Decreased airway resistance
- Improved growth attributable to stimulation of angiogenesis and alveolarization

NO on The Developing Lung

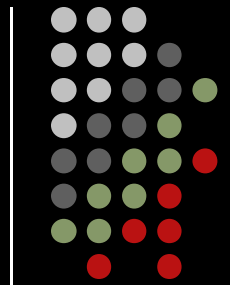


Toxicities

Methemoglobinemia

- When NO reacts with hemoglobin
- Methemoglobin has low affinity for oxygen
- Impedes tissue oxygen delivery
- > 5 to 10% associated w/ cyanosis/hypoxia

Toxicities



Platelets

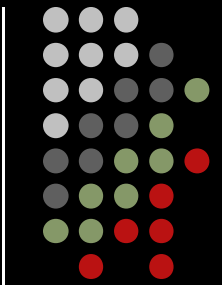
- NO mediates thrombotic balance
- Decreases platelet aggregation
- Bleeding times are prolonged

Toxicities

Nitrogen Dioxide and Peroxynitrite

- NO combining w/ O2 forms a toxic gas
- Implicated in oxidant stress injury to lungs
- Peroxynitrite is formed when NO combines w/ superoxide anion
- Can induce surfactant dysfunction
- Can cause membrane damage by lipid peroxydation and contribute to BPD

Alternative Means of Delivering Nitric Oxide

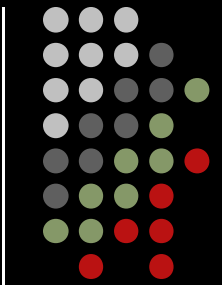


- O-nitroethanol designed to replete S-nitro sothiols (SNOs)
- NO is bound to SNO which do not react w/ O2 or superoxide to produce toxic metabolites
- SNOs are involved in V/Q matching

However

- Methemoglobinemia

Phosphodiesterase Inhibitors



- Prolong half-life of cGMP
- Enhances the biological actions of exogenous and endogenous NO
- Lower the PVR
- Augment the response to inhaled NO
- It is an adjunct to I NO

References

- Inhaled Nitric Oxide for Preterm Neonates, Nandini Arul et al, Clin Perinatol 36 (2009) 43–61.
- Pulmonary Hypertension in the Critical Care Setting: Classification, Pathophysiology, Diagnosis, and Management, Rubenfire Melvyn, Crit Care Clin 23 (2007) 801–834
- Hypoxic Respiratory Failure in the Late Preterm Infant, Dudell Golde G. Clin Perinatol 33 (2006) 803–830,
- Persistent pulmonary hypertension in premature neonates with severe respiratory distress syndrome. Walther FJ, Benders MJ, Leighton JO. Pediatrics 1992;90:899–904.
- Pathogenesis and management of neonatal pulmonary hypertension, Bancari Eduardo, The Newborn Lung 2008: 241-293.