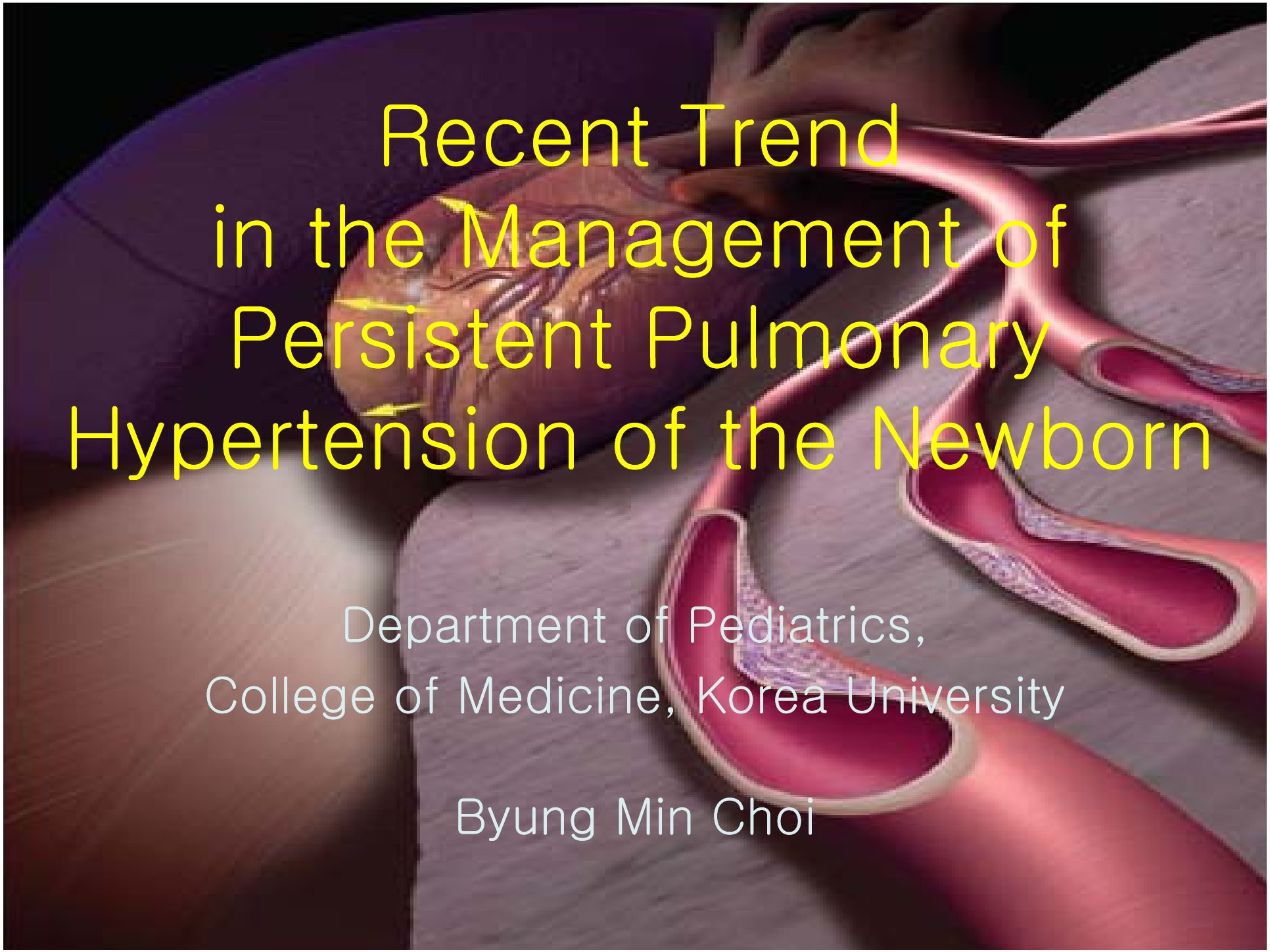

Recent Trend in the Management of Persistent Pulmonary Hypertension of the Newborn

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World Health Organization (WHO) 2003

I. Pulmonary Arterial Hypertension (PAH)

- Idiopathic (IPAH)
- Familial (FPAH)
- Associated with (APAH)
  Collagen vascular disease; congenital systemic to pulmonary shunts
  Portal hypertension; drugs and toxins
  Human immunodeficiency virus (HIV) infection
  Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, temoglobinopathies, myeloproliferative disorders, splenectomy)
- Associated with significant venous or capillary involvement
  Pulmonary veno-occlusive disease (PVO)
  Pulmonary capillary hemangiomatosis (PCH)
- Persistent pulmonary hypertension of the newborn

II. Pulmonary Venous Hypertension (PVH)

- Left-sided atrial or ventricular heart disease; left-sided valvular heart disease

III. Pulmonary Hypertension Associated with Hypoxemia

- Chronic obstructive pulmonary disease (COPD)
- Interstitial lung disease; sleep-disordered breathing
- Alveolar hypoventilation disorders; chronic exposure to high altitude
- Developmental abnormalities

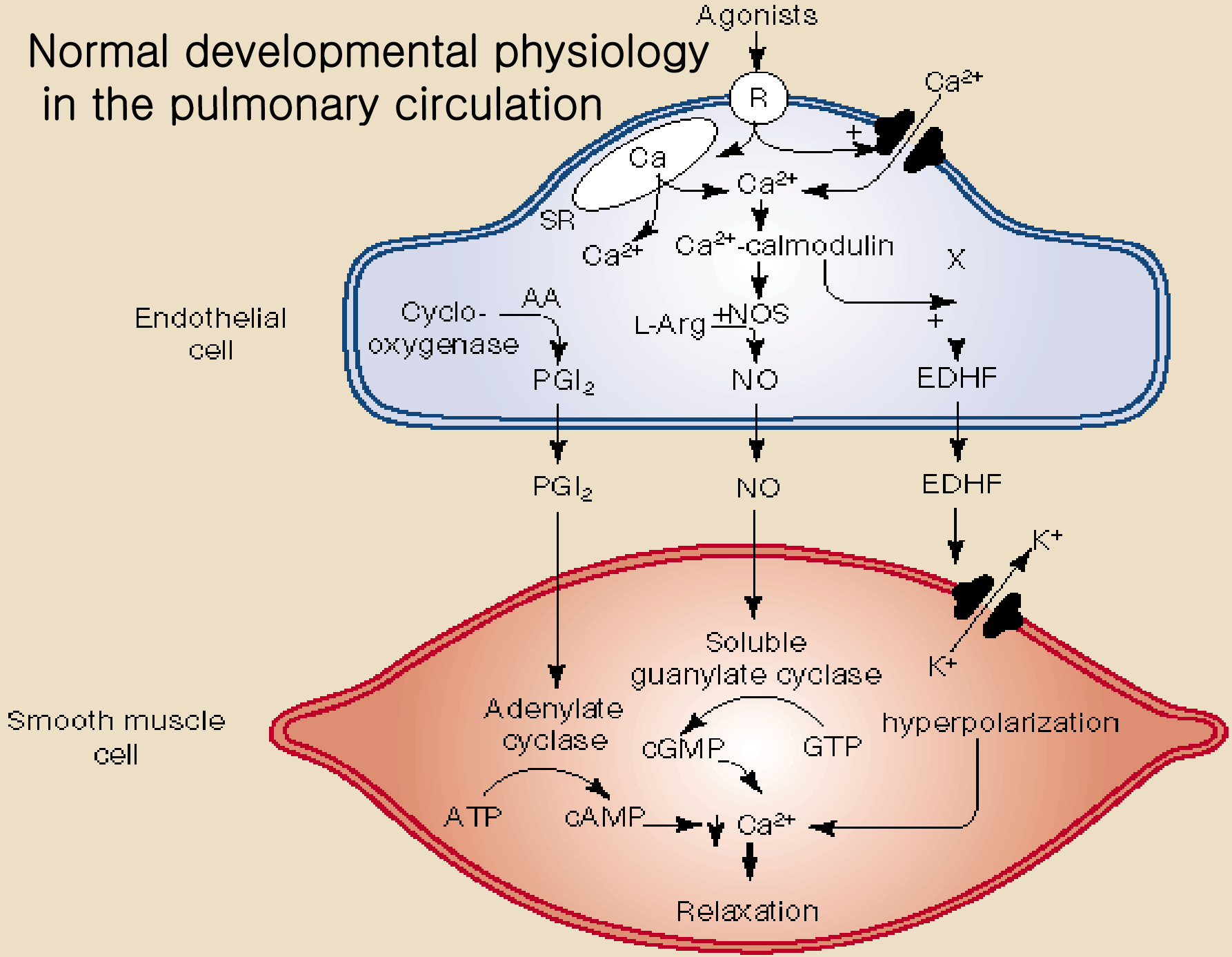
IV. Pulmonary Hypertension Due to Chronic Thrombotic and/or Embolic Disease

- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)

V. Miscellaneous

- Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Normal developmental physiology in the pulmonary circulation



Persistent Pulmonary Hypertension of the Newborn

- A failure of the pulmonary vasculature to relax at birth,

=> Unoxygenated blood to be shunted to the systemic circulation.

  - Right to left shunting => Hypoxemia & Res. Failure
    - Ductus arteriosus
    - Foramen ovale.

- Incidence: 1.9 (0.43 ~ 6.82) per 1000 live births
- Mortality: 11 (4 ~ 33) % of infant with PPHN

Causes of PPHN

- An event or illness during pregnancy or childbirth
  - Meconium aspiration syndrome
  - Severe pneumonia, Infection
  - Low blood sugar
  - Birth asphyxia
  - Respiratory distress syndorme
  - Maternal use of nonsteroidal anti-inflammatory medications and selective serotonin reuptake inhibitors
  - Amniotic fluid leak, Oligohydramnios
  - Abnormal lung development (Congenital Diaphragmatic Hernia)
- Stress during pregnancy
- Isolated condition with an unknown cause

General managements of PPHN

❖ Aim of treatment in PPHN

- Maximizing pulmonary blood flow
- Minimizing pulmonary vascular resistance
- Without compromising cardiac output.

- Oxygen theraphy
- Gentle handling and minimal interventions
- Use of sedation and paralysis

Aggressive therapy for systemic BP

- The size of the right-to-left shunt in PHN in part depends on systemic blood pressure, being higher if systemic vascular resistance is low.

- Volume expanders
- Inotropic drugs (Dopamine, dobutamine, milrinone)
- Transfusion (Hb 13 g/dl ~ Hct 70)
  - to maximize oxygen transport to the tissues.

Surfactant

- A multi-centre placebo-controlled trial
  - Infants with severe respiratory failure born at term,
  - Meconium aspiration syndrome, sepsis or PPHN.
  - Early use of surfactant significantly decreased the need for ECMO.

=> Consider surfactant therapy, particularly in infants with homogenous lung disease

Hyperventilation

- Uncontrolled small studies,
  - hyperventilation => Reduction in PAP
    Improvement in oxygenation.
- Recent study
  - Hypoxic pulmonary vasoconstriction was not attenuated during sustained alkalosis
  - PaCO2 19~26 mmHg => 50% reduction in cerebral BF.
  - Hypocarbia => Development of PVL & CP in preterm infants.
  - Barotrauma => Airleaks & Development of BPD

=> Aggressive hyperventilation is rarely used in PPHN.

Alkali infusion

- Preclinical studies
  - Beneficial effects of hyperventilation result from a raised pH rather than changes in PaCO2.

  => Alkali infusion would seem a logical treatment of PPHN for avoiding the barotrauma.

- Alkali infusion
  - not reduce mortality.
  - associated with an increased risk for the use of ECMO and prolonged O_2 dependency.
- Prolonged alkalaemia
  - increases the hypoxic reactivity of pulmonary vascular bed.

=> Routine alkali infusion is rarely used in PPHN.

High Frequency Oscillatory Ventilation

- A RCT in HFOV group
  - comparing the efficacy of conventional ventilation (CV) in infants with severe pulmonary dysfunction born at or near term
  - Incidence of airleak was reduced,
  - Incidence of IVH was higher.
- Cochrane review (2001)
  - HFOV could not be recommended in infants with severe pulmonary dysfunction born at or near term.
- If a high volume strategy is used, HFOV can improve oxygenation and carbon dioxide elimination.

Extracorporeal membrane oxygenation

- Randomized, UK collaborative trial,
  - Before the widespread use of HFOV, iNO and surfactant
  - 185 infants with severe hypoxic (OI ≥ 40), PPHN (62%)
  - Mortality rate: 32% in ECMO group & 59% in CV group.
  - conventional management group. Of

- Audits of current practice
  - Fewer infants are now referred for ECMO.

Inhaled NO therapy (iNO)

- iNo: in Meta-analysis (RCT) in near-term and term infants
  - improves in oxygenation.
  - reduces the requirement for ECMO (RR=0.63).

- iNO is more effective if given when a volume recruitment strategy has been used.

- HFOV + iNO: in Randomized multi-center trial
  - is more successful in severe PPHN than HFOV or iNO alone.

Inhaled NO therapy in preterm infants

iNO can improve oxygenation in preterm infants (<34 W GA)

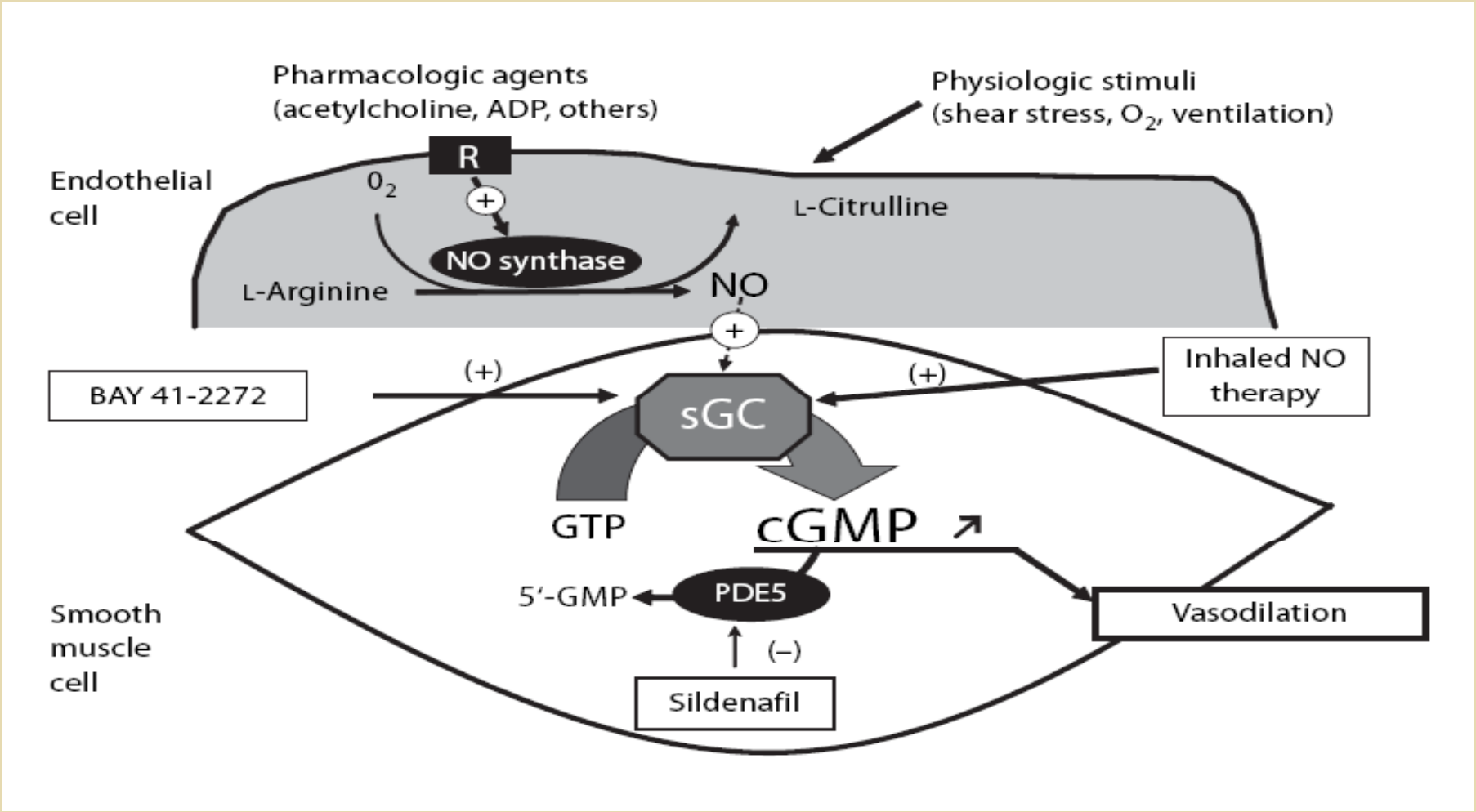
- Positive long-term effects in 1 RCT
- A significantly lower incidence of BPD and death in 1 center
- Side-effects:
  - ↑ Nitrogen dioxide: toxic to lung & ↑ bronchial hyperreactivity
  - ↑ Methemoglobin
  - ↑ Bleeding time
  - Surfactant dysfunction
  - Mutagenicity

=> iNO is not recommended for premature infants outside the context of a RCT.

Clinical variability in responsiveness to iNO therapy.

- An inability to deliver NO to the pulmonary circulation
  - Poor lung inflation
- Poor NO responsiveness
  - Myocardial dysfunction
  - Systemic hypotension
  - Severe pulmonary vascular structural disease
  - Unsuspected or missed anatomic cardiovascular lesions (TAPVR, COA, pulmonary venous stenosis or others)
  - Unsuspected anatomic lung lesions (alveolar capillary dysplasia, severe lung hypoplasia or dysplasia)
- Abnormalities in endothelial and smooth muscle cell function. => the need for additional approaches to severe PPHN.

NO-cGMP signaling pathway



soluble guanylate cyclase (sGC),
cyclic guanosin monophosphate (cGMP)
cGMP-specific (type 5) phosphodiesterase (PDE5)

Sildenafil

- Vasodilation are more specific to the lung.

- In an experimental model of PHN with MAS,
  - Sildenafil (IV) completely reversed the increased PVR without affecting systemic hemodynamics
  - Combinations with iNO => unacceptable deterioration in oxygenation. (systemic vasodilation, hypotension, ↑ shunting)
- Cochrane review in adults & children (Kanthapillai 2004)
  - The validity of the observed effects is undermined
  - The effects on long term outcome require further validation.
  - More studies of adequate size are required before the long term effects of sildenafil on clinically important outcomes can be established.

Sidenafil in neonates

- Uncontrolled studies
  - improves PVR and survival.
  - blunts the hypoxemia (following iNO withdrawal)
  - Severe retinopathy of prematurity
- Cochrane review (Shah 2007)
    - 2 studies including 37 patients
    - In resource-limited setting (iNO & HFOV are not available)
  - Improvement in oxygenation (reduction in oxygenation index)
  - Protective effect on mortality
  - No clinically important side effects

⇒ The safety & effectiveness has not yet been established.

⇒ Sidenafil should be restricted within the context of randomized controlled trials. (Combination with other pul. vasodilators ?)

Phosphodiesterase inhibitors

- cGMP-specific (type 5) PDE5 inhibitor
  - Dipyridamole
    - significant systemic vasodilation
  - Zaprinast
    - No adequate study.
  - Pentoxifylline
    - No adequate study.
- cGMP-specific (type 3) PDE3 inhibitor
  - Milrinone

Milrinone (PDE3 inhibitor)

- ↑ cAMP levels => ↑ myocardial contractility
  ↑ cardiac output.
- Retrospective case study
  - IV milrinone in combination with iNO (refractory to iNO)
  - produces early improvements in oxygenation without compromising systemic BP.

Combination therapy with iNO

- In an experimental model of pulmonary hypertension,
  - the addition of IV milrinone to iNO
  => further decreases in PAP and PVR, & increases in CO
- 3 cases of IVH in 4 infants with PPHN

Prostacyclin (PGI2)

- Vasodilation, through the production of cAMP
- Small, uncontrolled study,
  - **PGI_2 infusion** after volume correction and inotropic medication
  - resulted in a decrease in mean PAP
  - Side-effects (82%): systemic hypotension
- Preliminary data (4 infants)
  - **Nebulized PGI_2** may improve oxygenation without side-effects.

Tolazoline

- Potent non-specific vasodilator, competitive α-adrenergic antagonist.
- IV tolazoline in an early study
  - Oxygenation improved in only 67% of the infants with severe pulmonary disease
  - Side-effects (82%): systemic hypotension, GI hemorrhage and renal failure.

  => Slow bolus infusion with volume expander
- IT tolazoline via ET tube in small uncontrolled studies
  - improve oxygenation without side effects.
  - too large a dose => 'spill over' into the systemic circulation.

Magnesium sulphate ($MgSO_4$)

- Muscle relaxant and vasodilator at high serum concentrations
  - Antagonizes calcium ion entry into smooth muscle cells.
- Several reports
  - Infants with PPHN failed to respond to conventional therapy
  - Administration of $MgSO_4$ improves oxygenation
  - Less effective than iNO.
  - Hypermagnesemia => sedation, muscle relaxation, hypotension and calcium and potassium disturbances.
- Cochrane review (2007) – No RCT
  - On the basis of the current lack of evidence,
  - Use of $MgSO_4$ cannot be recommended in treatment of PPHN.

Calcium channel blockers

- Calcium channel blockers (diltiazem or nifedipine)
- Six children with BPD and PAH
  - Nifedipine administration compared with 95% O_2
  - resulted in a greater reduction in PVR.

- Further evidence is required before such therapy can be recommended for routine use in infants.

Endothelin-1

- ET-1: A potent vasoconstrictor & co-mitogen
  - produced by vascular endothelium.
  - play a key role in fetal pulmonary vasoregulation.
    - ET_A receptor in vascular smooth muscle
      - Vasoconstriction
    - ET_B receptor in endothelium
      - Vasodilator response through the release of NO

=> ET-1 plays an important role as a pulmonary vasoconstrictor in the normal fetus.

=> Upregulation of ET-1 contributes to the pathophysiology of PPHN.

Endothelin antagonists

- ET_A receptor antagonism
  - is potentially a strategy to treat infants with PHNN.
- Two randomised trials in adults with PAH

  Bosentan, a dual (ETA and ETB) receptor blocker,
  - improve the exercise capacity.
- The role of endothelin antagonists in infant with PPHN
  - needs investigation.

❖ **Endothelin systems:** plays important roles in the emergence and the main tenance of the functions of various organs in prenatal development.
- **Mitogen or co-mitogen** with other growth promoting factors
- **Regulator of apoptosis**

– Yoo KH, et al. J Korean Med Sci. 2008 in press.

Rho-Kinase Activity

- Rho-kinase in vascular smooth muscle cells
  - as key regulators of vascular tone and structure.
  - phosphorylates and inactivates myosin light chain phosphatase => promoting vasoconstriction.
- Rho-kinase inhibitors in animal studies
  - prevent the development of pulmonary hypertension
  - cause potent and sustained pulmonary vasodilation
  - prevent pulmonary vasoconstriction caused by inhibition of NO production,

=> may provide a future therapy for severe PPHN.

Vascular Endothelial Growth Factor (VEGF)

- Impaired VEGF signaling => Pathogenesis of PPHN.
- Experimental studies
  - Lung VEGF expression is markedly decreased in an experimental model of PPHN in sheep.
  - Inhibition of VEGF mimics the structural and functional abnormalities of PPHN.
  - Treatment with recombinant human VEGF protein increases eNOS expression and activity and improves pulmonary hypertensive remodeling in PPHN.
- Clinical studies in blood and tracheal fluid aspirates of ventilated infants
  - VEGF was decreased in human PPHN.

=> VEGF is a key modulator of pulmonary vascular function in PPHN.

Superoxide dismutase (SOD)

- Scavengers of reactive oxygen species

- **Hyperoxic ventilation** in the management of PPHN

  => Reactive oxygen species (superoxide anions)

  => Inactivate NO and cause vasoconstriction and oxidation.

  => to worsening of PHT in newborns.

- **Intratracheal recombinant human superoxide dismutase (rhSOD)** improves oxygenation and reduces pulmonary arterial contractility and oxidation in an ovine model of neonatal PHT.

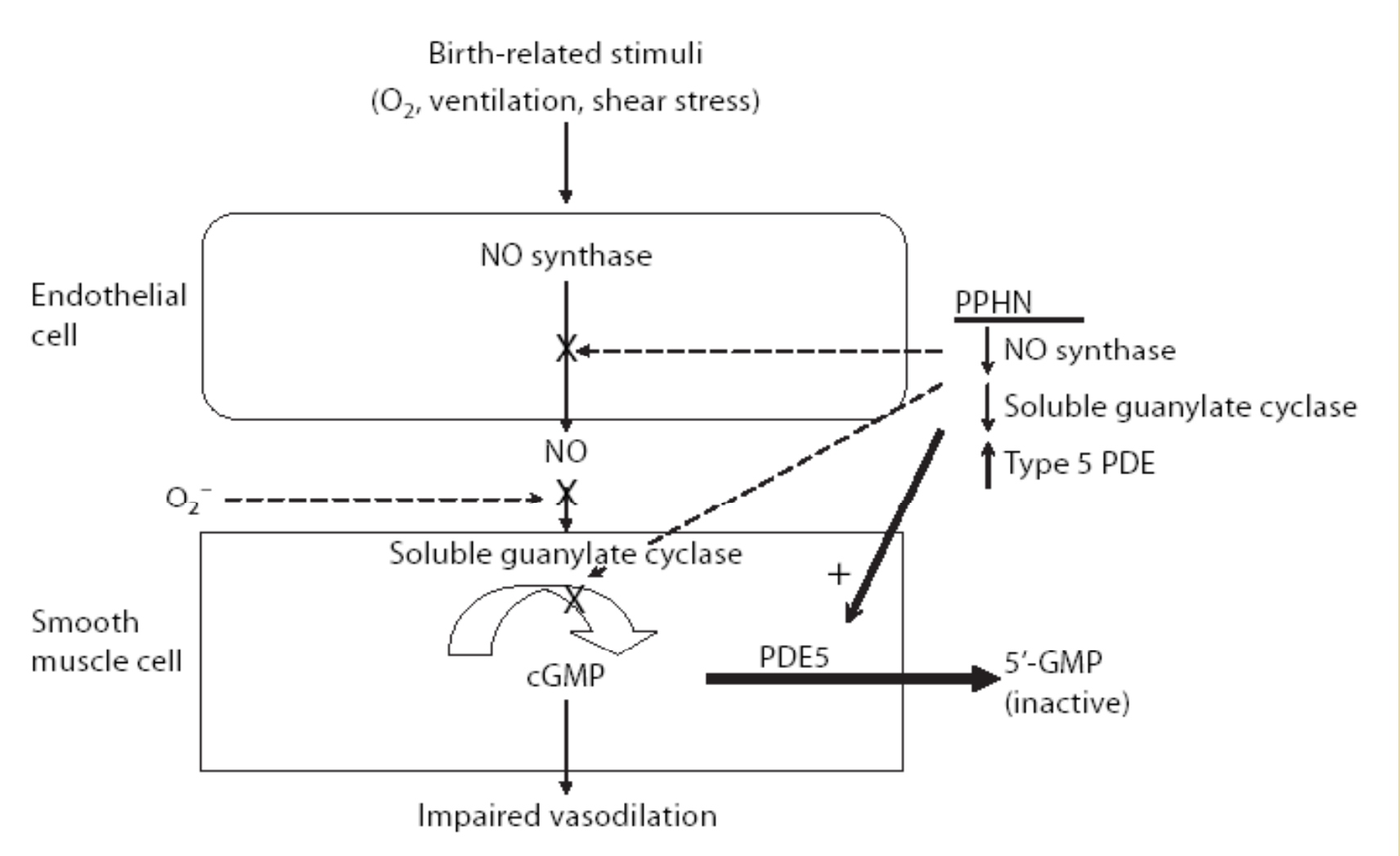
Conclusions

- iNO has improved the clinical course and outcomes of many infants.
- Novel therapeutic strategies for the treatment of refractory PPHN
  - To enhance NO-cGMP activity.
    - cGMP-specific PDE inhibitors: sildenafil
    - soluble guanylate cyclase activators: BAY 41-2272
    - superoxide scavengers: superoxide dismutase
    - rho-kinase inhibitors: fasudil
  - To enhance VEGF signaling.

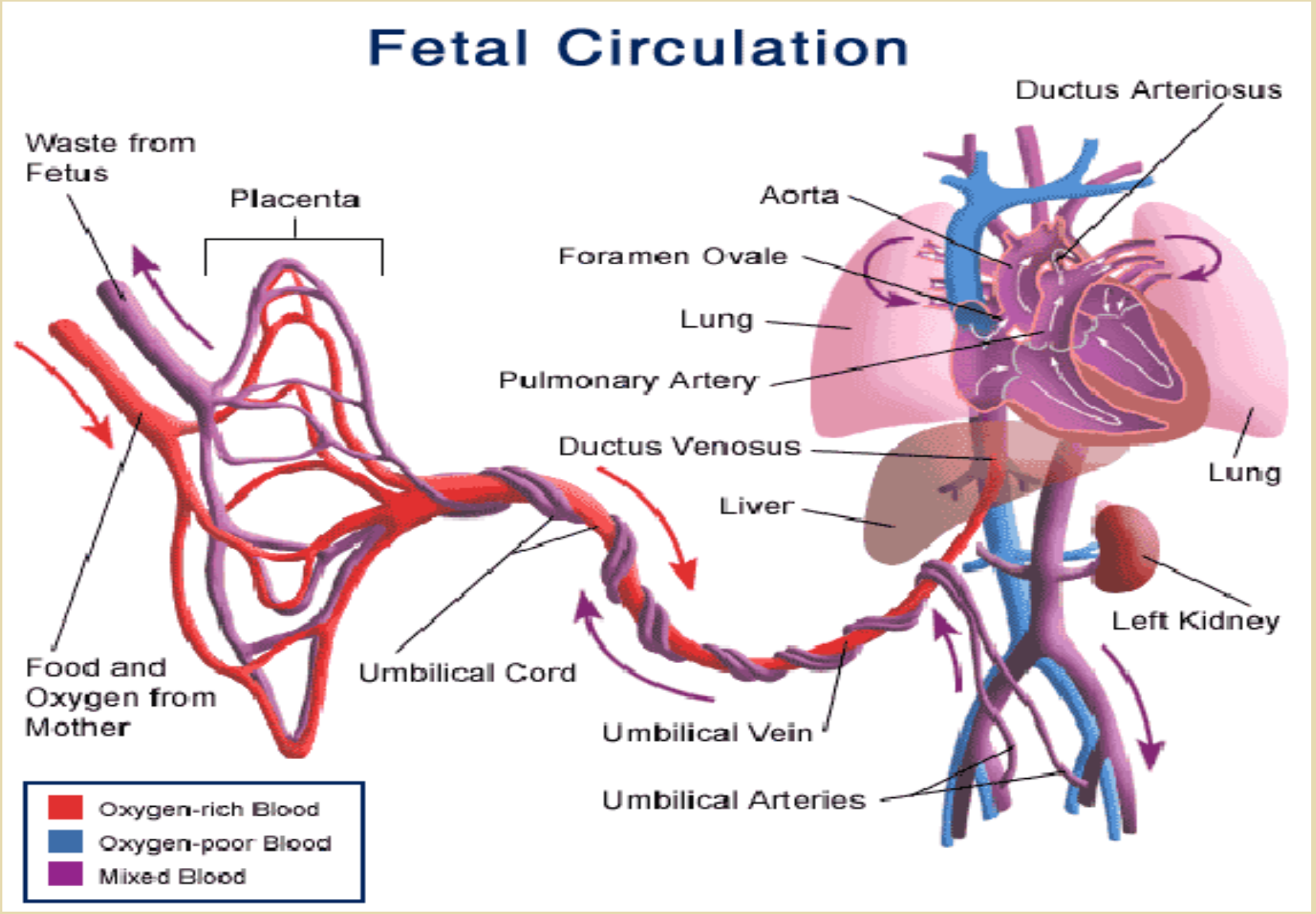
Speculations

- The efficacy and optimum use of iNO in preterm infants.
- The role of prophylactic iNO in preventing BPD.
- The safety and efficacy of vasodilators, such as prostacyclin or tolazoline, given by inhalation.
- The optimum combinations of various agents to use in PPHN to minimize PVR without deterioration in oxygenation or a fall in systemic BP.

NO-cGMP signaling pathway



Vasoconstrictors *(Maintain high fetal PVR)*	**Vasodilators** *(Decrease PVR during transition)*
Norepinephrine	PGI_2, PGD_2, PGE_2
a-adrenergic stimulation	Nitric oxide
Hypoxia	Cyclic GMP
Endothelin	Oxygen
Thromboxanes	Adenosine
Leukotrienes	ATP
Platelet activating factor	Bradykinin
PGF_{2a}	


Fetal Circulation
Ductus Arteriosus
Waste from Fetus
Placenta
Aorta
Foramen Ovale
Lung
Pulmonary Artery
Ductus Venosus
Lung
Liver
Left Kidney
Food and Oxygen from Mother
Umbilical Cord
Umbilical Vein
Umbilical Arteries
Oxygen-rich Blood
Oxygen-poor Blood
Mixed Blood