Persistent Pulmonary Hypertension of the Newborn (PPHN)

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No disclosures
What is PPHN?

PH: increased mean PAP (or resistance)

Adults: PAP >25 mm Hg

Potentially fatal condition

Incidence: 2-4 : 1000 newborns

Complex of symptoms

Transition from intra- to extra-uterine life

Origen already intra-uterine

Due to heterogeneous nature standardization of treatment is difficult
Failure to decrease PAP
or
Secondary progressive increase in PAP
PPHN

R-L shunt: hypoxaemia

Right heart failure
Classification PPHN; lungvascular pathology

• **Underdevelopment**

• **Maldevelopment**

• **Maladaptation**
1. Underdevelopment

Lunghypoplasia; CDH

Diminished cross sectional vascular area
2. Maldevelopment

Normal lung development

- normal bronchial branching
- normal alveolarisation
- normal number of pulmonary blood vessels
2. Maldevelopment 2

Abnormal vascular wall
- increased medial thickness
- increased adventitial thickness
- extension of muscularization
2. Maldevelopment 3

Aetiology: Chronic intra-uterine hypoxia
meconium aspiration syndrome
serotonin

Excessive longperfusion prenatally
NSAID-ductal closure

Total abnormal pulmonary venous return (TAPVR)
3. Maladaptation

Normal lung development
active vasoconstriction
elevated PAP

Aetiology
acidosis
hyperviscosity
cold-stress
sepsis, pneumonia
aspiration syndrome
RDS
‘wet lung’
Underdevelopment

Maldevelopment

Maladaptation

Pathophysiology

Therapeutic effectivity

PPHN
Therapeutic options

Pathways in PPHN

Endothelial cells

Smooth muscle cells

Pre-proendothelin → Proendothelin → Endothelin-1

L-arginine → eNOS → NO + L-citrulline

Arachidonic acid → Prostacyclin synthase → Prostacyclin

ET-A → ET-B

Vasoconstriction and proliferation

Guanylate cyclase

GTP → cGMP → Protein kinases

PDE5

GMP → Vasodilatation and anti-proliferation

PDE3/4

G → Adenylate cyclase

cAMP → ATP → AMP
Non selective vasodilator
NINOS trial (no CDH)  
N Eng J Med 97

n=235, GA > 34 wk, OI > 25

20 ppm NO vs controls

death or need for ecmo; 46 vs 64%

NO:

improves oxygenation and decreases ecmo need in (near) term infants
Death: 48 vs 43 % NS

ECMO need: 80 vs 54 % (p<0.05)

NO+CHD  NINOS trial in CDH; Pediatr 97
N=53, 20 ppm NO vs controls
Sildenafil

Endothelial cells

- Pre-proendothelin
  - Proendothelin
  - Endothelin-1
  - ET-A
  - ET-B
  - Vasoconstriction and proliferation

- L-arginine
  - eNOS
  - NO + L-citrulline

- Arachidonic acid
  - Prostacyclin synthase
  - Prostacyclin

Smooth muscle cells

- Guanylate cyclase
  - GTP → cGMP
  - Protein kinases
  - Vasodilatation and anti-proliferation

- cAMP → ATP
  - PDE3/4
  - AMP

- PDE5
  - GMP

Sildenafil
Oral sildenafil: 1 mg/kg b.w., every 6 hrs

Current status: interesting observations, no conclusion possible yet
Milrinone

Endothelial cells

Pre-proendothelin → Proendothelin → Endothelin-1

L-arginine → eNOS → NO + L-citrulline

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Smooth muscle cells

ET-A + ET-B

Vasoconstriction and proliferation

Guanylate cyclase

GTP → cGMP → Protein kinases → Vasodilatation and anti-proliferation

PDE5 → GMP

CAMP → ATP

PDE3/4 → AMP

milrinone
30% non-responder on NO!!

Current status: interesting observations, no conclusion possible yet

McNamara, Journal of Critical Care 2006
Endothelial cells

Prostacyclin synthase

Arachidonic acid

NO + L-citrulline

endothelium

Pre-proendothelin

Proendothelin

Protein kinases

GTP

cGMP

PDE5

GMP

Vasodilatation and anti-proliferation

G

Adenylate cyclase

PDE3/4

AMP

ET-A

ET-B

Vasoconstriction and proliferation

Guanylate cyclase

cAMP

ATP

Smooth muscle cells
**Prostacycline pathway**

**PGE₂/TXB₂** imbalance in plasma in neonatal hypoxemic respiratory failure

**Figure 1** Error bar graph showing mean plasma PGE₂/TXB₂ ratio and 95% confidence intervals for Control (n = 8) and NHRF (n = 6) subjects. The PGE₂/TXB₂ ratio was significantly higher in the Controls compared to NHRF subjects as evidenced by lack of overlap in the 95% confidence intervals of the mean. **p < 0.01** on univariate analysis and **p < 0.05** on linear regression analysis.
Prostaglandin Inhibition Prevents the Fall in Pulmonary Vascular Resistance as a Result of Rhythmic Distension of the Lungs in Fetal Lambs

HARM VELVIS, PHILLIP MOORE, AND MICHAEL A. HEYMANN
Fig. 1. – a) the arterial oxygen tension ($P_{aO_2}$)/inspiratory oxygen fraction ($FiO_2$) ratio, b) the oxygenation index and c) the mean arterial blood pressure are all shown before and after endotracheal instillation of a bolus of 50 ng·kg⁻¹ epoprostenol. Data are presented as mean and std.
Release of $\text{Ca}^{2+}$ from intracellular calcium stores
Endothelin

Nitrofen CDH rat model

ET-1 expression

ET-A receptor expression

Fig 1. Northern blot analysis of ET-1 expression in control and CDH lungs. (A) Filters were hybridized with ET-1 cDNA probe (upper panel) and GAPDH (lower panel) for reference purposes. Autoradiography shows enhanced expression of ET-1 mRNA in CDH lungs. (B) Bar graph shows relative levels of ET-1 mRNA. *significantly different from respective control lungs (both RL and LL, P < .05). RL, right lung; LL, left lung; C, control rats.

Elevated immunoreactive endothelin-1 levels in newborn infants with persistent pulmonary hypertension

Adam A. Rosenberg, MD, Jan Kennaugh, MD, Stacia L. Koppenhafer, Mary Loomis, RN, Barbara A. Chatfield, MD, and Steve H. Abman, MD

Table II. Plasma immunoreactive endothelin-1 levels

<table>
<thead>
<tr>
<th></th>
<th>Cord blood (n = 10)</th>
<th>HMD (n = 8)</th>
<th>PPHN, no ECMO (n = 12)</th>
<th>PPHN, with ECMO (n = 12)</th>
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<tbody>
<tr>
<td>irET-1 (pg/ml)</td>
<td>15.1 ± 4.1</td>
<td>11.8 ± 1.2</td>
<td>21.2 ± 2.0</td>
<td>31.0 ± 4.7*, †, ‡</td>
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Values are expressed as mean ± SEM.
* p < 0.003 compared with cord blood control.
† p < 0.002 compared with HMD.
‡ p < 0.05 compared with PPHN, no ECMO.
Figure. A, Immunoreactive endothelin-1 (irET-1) levels in ECMO-treated infants. Day 1 sample is before ECMO; day 3 sample is after 24 hours of ECMO; day 10 sample is after decannulation from ECMO. B, Levels of irET-1 in non-ECMO-treated patients with persistent pulmonary hypertension (*p <0.001 compared with day 1 value).
Fig. 3. RhoA and Rho kinase: pathways leading to vascular smooth muscle contraction. Solid lines refer to stimulation, dashed lines to inhibition; a query indicates uncertain physiological significance. Bold lines indicate pathways believed to be most physiological relevant. AA, arachidonic acid; CD, caldesmon; GEF, guanine nucleotide exchange factors; GDP, G protein coupled receptors; HSP27, heat shock protein 27; LCA, L-type Ca^{2+} channels; LIMK, LIM kinase; MBS, myosin binding subunit of MLCP; P38, p38 MAP kinase; iPLA2, Ca^{2+}-independent phospholipase A2; cPLA2, Ca^{2+}-dependent phospholipase A2; PLC, phospholipase C; ROC, receptor operated channels; ROK, Rho kinase; ROS, reactive oxygen species; SFK, Src family kinases.
Acute vasodilator effects of a Rho-kinase inhibitor, fasudil, in patients with severe pulmonary hypertension

Y Fukumoto, T Matoba, A Ito, H Tanaka, T Kishi, S Hayashidani, K Abe, A Takeshita, H Shimokawa

N=9; all on PGI$_2$ iv
Pathways involved in treatment of neonatal pulmonary hypertension

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Target</th>
<th>Drug</th>
<th>Status</th>
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<td>PGI2</td>
<td>Epoprostanol</td>
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<td>Nitric Oxide</td>
<td>NO</td>
<td>Inhaled NO</td>
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<td>Natriuretic Peptide</td>
<td>BNP</td>
<td>Nestiritide</td>
<td>ped case reports</td>
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**SMC membrane**

**Hypoxic potassium-channel inhibition**
- **Normoxia**
  - Extracellular
  - Intracellular

**Membrane depolarization**
- **Pulmonary-artery smooth-muscle cells**
  - Normoxia: -60 mV
  - Hypoxia: -20 mV

**Activation of L-type calcium channel**
- Extracellular
- Intracellular

**Calcium channel**
- Extracellular: 
- Intracellular: 

**Oxygen**
Is oxygen effective in treatment of PPHN?

No randomised studies

Also not for parachutes
Figure 3. Hyperoxia increases PDE5 activity in FPASMCs. FPASMCs were exposed to 21% O2-5% CO2, 50% O2-5% CO2, or 95% O2-5% CO2 for 24 hours, and total protein was harvested. PDE5 specific activity was measured as the sildenafil-inhibitable fraction of total cGMP hydrolysis, normalized for total milligrams of protein. Data are shown as means ± SEM (n=8; read in duplicate). *P<0.05 vs 21% O2, #P<0.05 vs 50% O2.
Figure 1. Exogenous NO induces less cGMP in FPASMCs exposed to hyperoxia. FPASMCs were exposed to 21% O₂–5% CO₂, 50% O₂–5% CO₂, or 95% O₂–5% CO₂ with or without DETANONate (100 μmol/L) for 24 hours. Cells were assayed for cGMP by enzyme-linked immunosassay, and cGMP was normalized for milligrams of total protein. Data are shown as means±SEM (n=6; read in triplicate). *P<0.05 vs cells not treated with DETANONate, #P<0.001 vs 21% O₂+NO.

PPHN: complex problem

Increasing knowledge about molecular aspects

New therapies will become available

It is more than oxygen, artificial ventilation, inotropics and vasopressors
And if you get into real trouble and nothing works